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Clinical manifestations of diabetic microangiopathy

B. Angelkort and V. Wienhausen

Medical Clinic North, Municipal Hospital, Dortmund, Germany

The development and extent of diabetic microangiopathy is dependent on duration and tight control of hyperglycemia in diabetic patients. Between 15 and 20% of all diabetics do not develop any clinical signs of microangiopathy, thus one must assume a genetically determined susceptibility for increased blood glucose levels. Improvements in the regulation of blood glucose levels correspond with slower progression of microangiopathic complications (DCCT, Kumamoto-study).

The most significant clinical manifestations are the diabetic nephropathy (NP), the diabetic retinopathy (RP) and the diabetic neuropathy (PNP). One main neuropathic complication is the development of a neuropathic and bacterially infected foot lesion, which may require major surgical intervention (incidence under optimal conditions: 3.6/100,000 diabetics per year. The NP shows different progression patterns in IDDM and NIDDM patients depending on HbA1 and hypertension. The cumulative incidence is 35% 20 years after onset of diabetes. The manifestation of renal insufficiency follows the stages of microalbuminuria and macroalbuminuria and may lead to terminal kidney failure, requiring regular dialysis treatment. Up to 50% of all dialysis-dependent patients are diabetics.

The RP can be divided into the proliferative and non-proliferative retinopathy. 20 years after onset of diabetes 95% of all IDDM patients have developed signs of RP, 50% of these diabetics suffer from proliferative retinopathy, during which the incidence correlates with the extent of HbA1 and blood pressure. In patients with NIDDM the prevalence of proliferative retinopathy is lower. Thirty years after an early onset of diabetes the overall prevalence of blindness is 12%. Depending on the criteria one finds signs of PNP in up to 100% of all diabetic patients. In a prospective study Pirort found a PNP prevalence of 7.5% in newly diagnosed diabetics. 25 years after onset of PNP prevalence reached 50%. One major complication of PNP is the neuropathic foot lesion, leading to the diabetic foot syndrome. The most important therapeutic options are the tight control of hyperglycemia, treatment of hypertension, abstinence from noxious agents (e.g., alcohol and smoking) and early local treatment (e.g., laser coagulation). *In vitro* experiments show that N-Phenaceylthiazolium Bromide (PTB) can break down protein glucose aggregates (AGE) and might prove to be an effective new principle.

Morphology and three-dimensional architecture of vessels in circumscribed scleroderma and Psoriasis vulgaris

M. Bacharach-Buhles, B. Panz, S. el Gammal and P. Altmeyer

Dermatological Clinic of the Ruhr-University, Bochum, Germany

The characteristic features of circumscribed scleroderma (cs) are white atrophic plaques, those of psoriasis (ps) are erythematosquamous hypertrophic plaques. We investigated whether clinical sclerosis and hypertrophy are associated with vascular alterations.

By means of computer-supported three-dimensional reconstruction technique the superficial vessels of cs and ps were reconstructed three-dimensionally. A total of 17 biopsies, eight from patients with cs in the area of the sclerotic centre and the lilac ring, one from clinically uninvolved skin and eight biopsies from patients suffering from ps were examined.

In the central part of the sclerotic plaque of cs papillary capillaries are missing completely, focally some blind ending capillaries can be observed. The superficial horizontal venous plexus is focally interrupted. In the area of the lilac ring intrapapillary vessels are intact. In ps the elongated tortuated intrapapillary capillaries consist of the original capillary of the papillary body and parts of the superficial horizontal venous plexus.

Sclerosis in cs is combined with a reduction of vessels in the area of the papillary bodies and the superficial plexus. The erythematous plaques of psoriasis exhibit an increase of intrapapillary capillaries caused by the inclusion of the preexisting subepidermal venous plexus, not by angiogenesis. Thus sclerosis of cs correlates with a structural vessel reduction, hypertrophy in ps with a functional, reversible inclusion of preexisting vessels.

The changes of red cell deformability in normal pregnancy and gestational hypertension

C. Berg, G.-F. v. Tempelhoff and L. Heilmann

Department of Obstetrics and Gynecology, City Hospital Rüsselsheim, August-Bebelstr. 59, 65428 Rüsselsheim, Germany

The parameters plasma viscosity, erythrocyte aggregation, erythrocyte deformability and hematocrit are changed by a lot of facts. The differences of these changes in normal pregnancy and pregnancy-induced hypertension should be the subject of this study. We determined hematocrit, plasma viscosity and erythrocyte aggregation by mother and fetus. Fibrinogen, leukocytes, thrombocytes, cholesterin, triglycerides, MCHC, MCV, haptoglobin and the deformability of the erythrocytes were measured in all women.

The plasma viscosity is in all groups nearly the same. Erythrocyte aggregation is higher during pregnancy (21.4 vs. 17.9) especially in preeclampsia (23.8 vs. 17.9). The decrease of the hematocrit (40% in the nonpregnant group vs. 36% by pregnant women) is caused by the hemodilution. The increase of MCHC is not significant and (32.1 in the normal nonpregnant group vs. 34.3 in pregnant women) the MCV does not change. The increase of cholesterin (237 mg/dl vs. 254 mg/dl) and triglycerides (187 mg/dl vs. 277 mg/dl) during pregnancy and preeclampsia is not significant. There is no significant change in red cell deformability parameters between nonpregnant and women with normal pregnancy. We found a marked decrease of the red cell deformability in patients with gestational hypertension compared with normal pregnant women associated with a decrease of haptoglobin. We found no significant correlations between red cell deformability and MCHC, MCV, cholesterin and triglycerides.

Missing volume expansion in the second trimester of pregnancy: a higher risk for gestational hypertension?

C. Berg, B. Herrle, G.-F. v. Tempelhoff, A. Bozer and L. Heilmann

Department of Obstetrics and Gynecology, City Hospital Rüsselsheim, 65468 Rüsselsheim, Germany

In many studies (Murphy et al., Steer et al.) a high maternal hemoglobin $\geqslant 13$ g/dl during the second trimester of pregnancy is described as a parameter which could be one factor for developing preeclampsia. In our retrospective study we wanted to investigate this parameter on a large collective of patients. We collected risks of pregnancies, maternal and fetal clinical data extended by rheological (hemoglobin, hemoglobin second trimester, hematocrit, erythrocyte aggregation, plasma viscosity) parameters of mother and fetus.

We studied 2963 patients delivered during the years 1990 to 1993 in the City Hospital of Rüsselsheim. These patients were devided into two subgroups; 441 patients with a hemoglobin $\geqslant 13$ g/dl and 2512 women with a hemoglobin < 13 g/dl.

In the group with a hemoglobin $\geqslant 13$ g/dl we found a higher rate of IUGR (10.7% vs. 3.7%), newborn weight < 2500 g (11.8% vs. 5.4%), pregnancy induced hypertension (16% vs. 9.7%) preeclampsia (3.4% vs. 1.4%) and preterm deliveries < 37 weeks (15% vs. 12.8%).

A hemoglobin $\geqslant 13$ g/dl in the second trimester of pregnancy is a prognostic adverse sign for developing IUGR and pregnancy induced hypertension.

Comparison of two different cold-exposure tests in regard to circulation in the nailfold capillaries

A. Büchtemann, A. Einspanier, U.Huhn, A. Steins and M. Jünger

Universitäts-Hautklinik, Liebermeisterstr. 25, D-72076 Tübingen, Germany

Introduction: Local cooling-tests are of major importance in the diagnosis and therapy of acral circulatory diseases. They are used in order to provoke acral vasospasm. Cold-exposure tests combined with capillary microscopy are particularly helpfull for the quantification of spasmolytical therapeutical procedures. Aim of the following study therefore was to compare the cooling-test method based on decompressing CO_2 gas (according to Mahler) with a recently developed cooling-test using a thermoelectric Peltier-element. Sixteen healthy control persons (mean age: 38; range 23–53) and 15 patients suffering from systemic sclerosis (mean age: 53; range 27–69) were included in the study. The examinations were performed in a temperature controlled environment (23°C) after a resting period of 30 min each. The test by means of Peltier element followed the CO_2 test after regaining the initial finger-temperature. The examination was documented on videotape, analysis was done off-line regarding number and duration of flow stops, change of velocity of erythrocytes in the nailfold capillaries caused by cooling exposure as correlation of clinical symptoms with these parameters.

Results:

1. The cooling-test method using a thermoelectric Peltier-element proved to be the test with higher specificity: only 1 of the healthy controls developed a clinically relevant stasis event (spec. 0.94), with the use of CO_2 gas stasis occurred in nine controls (spec. 0.44).

2. Distinction between patients with clinical symptoms, Raynaud's attacks, and healthy controls was preferably achieved by the results of the Peltiertest (Peltiertest: max time of stasis in patients: $>$ 420 s; in healthy controls: 26 s. CO_2-test: max time of stasis in patients: 93 s; in healthy controls: 156 s).
3. Flow stops triggered by the Peltierelement showed higher correlation to clinical symptoms and frequency of Raynaud attacks. Therefore, the current liability to vasospastic events is better reflected by flow stops caused by the Peltier-test.

Conclusion: This study showed, that the local cooling exposure test using a Peltier-element displayed results with higher clinical relevance, than the test by means of decompressing CO_2 gas.

Continuous brain tissue pO_2-monitoring

J. Dings, J. Meixensberger and K. Roosen

Department of Neurosurgery, University of Würzburg, Germany

Secondary ischemic insults worsen the outcome of patients with severe head injury (SHI) and subarachnoid hemorrhage (SAH). Brain tissue pO_2-monitoring ($p(ti)O_2$) offers the possibility to carry out an online monitoring of cerebral microcirculation/oxygenation. The polarographic microcatheter has a diameter of 0.5 mm and a pO_2-sensitive surface of 7.8 mm^2. It is fixed with a screw in the frontal bone and lies 2.5 cm in the frontal cerebral white matter. The procedure of inserting the catheter takes 10–15 min in the ICU. During the last four years, on all patients (55 SHI, 35 SAH) needing intracranial pressure (ICP) monitoring, brain pO_2 was additionally monitored. Mean monitoring time was 7.6 ± 2.4 days. During that time the good quality data reading was 97%. No infection was seen. Two small contusions, not needing treatment, occurred. After removal mean sensitivity was -8.9 ± 5.6% and zero-drift 1.6 ± 1.4 mm Hg. As brain $p(ti)O_2$ depends on paO_2, $paCO_2$, ICP, mean arterial blood pressure and metabolism these parameters should be taken into consideration when interpreting brain $p(ti)O_2$. After insertion 30–60 min should be waited until brain $p(ti)O_2$ reaches a stable and reliable level. By means of a 100%-oxygentest the reactivity of the catheter is controlled. As soon as possible a CT-scan verifies the catheter position that should be out of an infarction or contusion. Critical brain $p(ti)O_2$ is below 10–15 mm Hg. Patients with a bad outcome at one year after severe head injury show significantly more brain $p(ti)O_2$ values below 10–15 mm Hg during the first week after injury compared to those with a good outcome after one year. In patients with SAH that develop vasospasm with neurological deterioration brain $p(ti)O_2$-monitoring can help to find out the (sometimes daily changing) critical cerebral perfusion pressure. By doing so secondary ischemia can be diminished or even reversed.

Evaluation of the acral blood pressure in 100 non-smokers using the arterial audiophotoplethysmography

S. el Gammal[1], B. Lambotte[1], V. Blazek[2] and P. Altmeyer[1]

[1]Dermatological Clinic of the Ruhr-University Bochum,
[2]Institute for High Frequency Engineering, Technical University Aachen, Germany

The arterial audiophotoplethysmography (aPPG) is a new method to determine the arterial systolic blood pressure in fingers and toes. While infrared light is emitted using a diode (940 nm) the pulsatile

component of the received signal is evaluated. A feed-back circuit compensates for interindividual variations in skin thickness and pigmentation. Both, infrared transmitter and receiver are mounted in an applicator to operate either in transmission or reflection mode.

105 healthy non-smokers (31 men, 74 women) with a mean age of 43 years (21–81 years old) were examined in lying position. All measurements were performed in a 20°C air-conditioned room. Probands rested 10 min prior to measurement of the right and left body sites. The systolic blood pressure was measured in the A. brachialis, A. ulnaris, A. radialis, A. poplitea, A. tibialis anterior and A. tibialis posterior using arterial ultrasound-Doppler (aUSD). Using the aPPG, the systolic blood pressure was evaluated in the A. brachialis (infrared measuring device placed on the index finger), fingers 1–5, A. poplitea (device placed on the second toe) and toes 1+2. To evaluate the large arteries, blood pressure cuffs were placed in typical location, to evaluate the fingers 2.5 cm wide cuffs were used.

On the arms we found systolic blood pressures of 126 ± 15 (aUSD) and 123 ± 15 (aPPG) in the A. brachialis and 120 ± 15 (aUSD) in the A. radialis and A. ulnaris, respectively. The fingers exhibited systolic blood pressures of 120 ± 14 in transmission mode, with slightly higher pressures in the index and middle finger. The mean systolic pressure was 10 mm lower in reflection mode. In the A. brachialis the correlation between the measured systolic blood pressure using aUSD and aPPG (reflection mode, aPPG device placed on the index finger) was 0.78. Using a transmission mode, the correlation could be improved to 0.98. Similar effects were observed on the legs. In general, correlation between aUSD and aPPG was much lower on the legs. Furthermore, mean values were lower and the standard deviation was higher in reflection mode as compared to the transmission mode. We therefore suggest to use the transmission mode when evaluating acral foot blood pressure.

It can be concluded that the correlation between aUSD and aPPG is excellent for large arteries. While the correlation between neighbouring fingers remains good (as a hint for a 50% shared common blood supply), no correlation was found between not-neighbouring fingers. We believe that this missing correlation between fingers/toes and large vessels (A. brachialis, A. radialis, A. ulnaris, respectively, A. poplitea, A. tib. ant., A. tib. post) shows, that the microcirculation (evaluated using the aPPG) is to a certain extent independent from macrocirculation in healthy subjects. The effect of impaired macrocirculation on the microcirculations will be an issue in future studies.

A new method to measure the membrane stiffness of intact erythrocytes

R. Flieger, R. Grebe and H. Schmid-Schönbein

Institute of Physiology, Biomedical System Analysis Division, Rheinisch-Westfälische Technische Hochschule Aachen, Pauwelsstr. 30, D-52057 Aachen, Germany

A new method is presented by which defined forces can be applied to erythrocytes. The shape changes due to these forces are used to compute parameters describing the membrane stiffness. For this purpose cells are given into an arbitrary medium (e.g., buffer or plasma containing all sorts of desired pharmaca can be used). The suspension is filled into a specially designed centrifuge chamber. By varying the rotational speed of the chamber the applied centrifugal forces can be changed in a wide range. While rotating, the cells sedimentate to the outer chamber wall, there forming a monolayer. The increase of force by increase of rotation frequency induces a reproducible sequence of erythrocytes shapes starting with the normal biconcave shape finally reaching a flat configuration. These rotational symmetric shapes are measured indirectly by registrating their laser light diffraction patterns. In order

to evaluate the revolution dependent shape changes the intensities of the first order maximum of their diffraction pattern is analyzed.

Advantages of this method are the very small volume of blood (15 μl) needed for one experiment, the high sensitivity (one can detect the effect of 0.1 mmolar diamid on the erythrocyte membrane), the reproducibility, and the ease of use.

Thermoregulatory and nutritive capillary skin blood flow in diabetic patients with respect to polyneuropathy

T. Forst, T. Kunt, A. Pfützner, T. Pohlmann, U. Schenk, E. Küstner and J. Beyer

Department of Internal Medicine/Endocrinology, University Mainz, Germany

Diabetic sympathetic polyneuropathy is associated with functional disturbances in microvascular blood flow and seems to be implicated in trophic foot ulceration. The purpose of our study was to investigate the role of diabetic neuropathy in the regulation of thermoregulatory and nutritive capillary blood flow in the diabetic foot.

Skin microcirculation was investigated before and after nociceptive C-fibre stimulation at the toe in 20 diabetic patients without neuropathy, 20 diabetic patients with neuropathy and in 18 non-diabetic control persons using laser Doppler fluxmetry (total skin blood flow; LDF) and television microscopy (capillary blood flow; CBV). Diabetic neuropathy was assessed by examining tendon reflexes, vibration, thermal and pain sensory thresholds and heart rate variability. Patients suffering from peripheral macrovascular disease were excluded from the study. Following an intracutaneous acetylcholine injection, a significantly diminished increase in total microvascular response was observed in diabetic patients with neuropathy compared with the healthy control group ($283 \pm 35\%$ vs. $192 \pm 35\%$; mean $\pm$ SEM; $p < 0.01$). Otherwise, no significant difference was found between the healthy control group and diabetic patients without neuropathy ($262 \pm 34\%$ vs. $282 \pm 35\%$; ns.). Capillary blood flow increased in all investigated groups by about 120% without any significant difference between the investigated groups. The stimulated LDF/CBV ratio, representing the distribution of skin blood flow, was significantly increased in diabetic patients with neuropathy compared with diabetic patients without neuropathy (0.71 ± 0.09 vs. 0.43 ± 0.7; $p < 0.05$) or the healthy control group (0.71 ± 0.09 vs. 0.40 ± 0.07; $p < 0.01$). Diabetic patients with neuropathy present a diminished total skin blood flow during nociceptive C-fibre stimulation. There is no evidence to support a diminished nutritive capillary blood flow or a capillary steal phenomenon in diabetic patients.

Microcirculatory investigations: role and clinical relevance in angiology

U.K. Franzeck

Department of Medicine, Division of Vascular Medicine (Angiology), University Hospital, Zürich, Switzerland

In recent years several new methods were developed and established methods improved, which are widely used in clinical microcirculation in the field of angiology or in internal medicine in general. In the following only the use of these methods as a routine diagnostic tool will be discussed, not the employment in clinical microcirculation research.

Capillaroscopy and the refinement of the method to *video capillaroscopy* in combination with fluorescence substances like sodium fluorescein or indocyanin green are used in angiologic routine work mainly to differentiate between primary and secondary Raynaud's phenomenon. The diagnosis of a microangiopathy can be made in approximately 90% of the patients with progressive systemic sclerosis, whereas in primary Raynaud's phenomenon no alteration of the nailfold capillaries can be found.

Fluorescence microlymphography has shown its relevance in the diagnosis of primary lymphedema and phlebedema and can potentially replace the patent blue test. This almost atraumatic investigation should gain a widespread use in clinical practice.

The clinical relevance of *transcutaneous oxygen tension measurements* ($tcpO_2$) is mainly in peripheral arterial occlusive disease and in the determination of the wound healing potential after amputation. In this respect it is nowadays the most accurate method. It also can elucidate unusual cases of erythromelalgia.

Laser-Doppler-fluxmetry has only little meaning in clinical routine, which is different to its widespread use in physiological studies. Potential use of this method which permits continuous monitoring of superficial skin microcirculatory blood flow is during the cold-provocation test in Raynaud's patients. This method can also be used in patients with algodystrophy.

ESR and hematocrit determination on a single blood sample by means of analysing system LUMiFuge

D. Frömer[1], H. Hampl[2] and D. Lerche[1]

[1]L.U.M. Gesellschaft für Labor-, Umweltdiagnostik und Medizintechnik mbH, Berlin, Germany
[2]Kuratorium für Dialyse und Nierentransplantation e.V., Berlin, Germany

In Germany approximately 48 million determinations of erythrocyte sedimentation rate per year are carried out according to the conventional method of Westergren. These investigations are very time-consuming, subject to inexact measuring results in the subjective and objective sense and demand a rather high sample volume of 2 ml. In this study we report about results obtained by our innovative analysing system – the LUMiFuge. The main measuring principle is the registration of the erythrocyte sedimentation time course caused by centrifugation of the blood samples by means of an opto-electronic sensor. The conventional 1-h-ESR value of up to eight samples is automatically calculated using the settling time course data (special cuvettes sample volume $< 200\ \mu$l) within 3 min. Additionally, hematocrit is determined in the second measuring period within 5 min. Direct transfer of the data into a central information system is possible. Good correlation between LUMiFuge and reference values in a physiologically normal range (healthy donors, $n = 51$, ESR values up to 12 mm) has been obtained (ESR: $r = 0.90$, Hct: $r = 0.99$). Applying the same method to blood samples of dialysis patients (pathologically increased ESR up to 150 mm) treated with Erythropoietin supplies also a good correlation ($n = 63$, ESR: $r = 0.94$, Hct: $r = 0.95$). The determination of the hematocrit standardised ESR values has proved to be useful for the interpretation of the rheological situation of dialysis patients' blood samples.

Flowcytometrically detected changes in platelet GPIb/IX surface expression after DDAVP-administration in von Willebrand's disease

S. Gordz[1], C. Mrowietz[1], G. Pindur[1] and F. Jung[2]

[1]Abteilung für Klin. Hämostaseologie und Transfusionsmedizin/ Universität des Saarlandes, Homburg, Germany
[2]Dresdner Institut für Herz-Kreislauf-Forschung, Bautzner Str. 113a, Dresden, Germany

Background: The influence of the intravenous administration of desmopressin (DDAVP) on platelet surface expression of GPIb/IX and of platelet activation-markers (CD62, CD63, thrombospondin) in seven patients suffering from von Willebrand's disease (vWD) was examined. DDAVP is increasingly used in the treatment and diagnosis of hemostatic disorders, especially vWD. The effect of DDAVP in platelet disorders with normal or even increased plasma levels of von Willebrand factor (vWf) leads to the hypothesis, that DDAVP, apart from its well known releasing effect for FVIII/vWf from endothelial cells, may also exert direct effects on platelets.

Materials and methods: Before and 1 h after the administration of DDAVP 0.4 μg per kg body weight a blood sample was taken and flowcytometric analysis performed. The percentage of activated platelets co-expressing GPIb/IX with at least one platelet activation marker (CD62, CD63, or thrombospondin) was determined. For the quantitative description of the GPIb/IX-surface expression the Molecules of Equivalent Fluorochrome (MEF) were determined before and after DDAVP.

Results: The surface expression of the platelet activation markers CD62, CD63, and thrombospondin did not change significantly after DDAVP-administration (CD62: $p = 0.25$, CD63: $p = 0.93$, thrombospondin: $p = 0.23$), while the surface expression of GPIb/IX was significantly increased ($p = 0.0018$).

Conclusions: A flowcytometric analysis showed, in accordance with the results of other investigators (Sloand et al., 1994), an increase in platelet GPIb/IX-surface expression after the administration of DDAVP in patients suffering from vWD. This could contribute to the increased platelet adhesiveness after DDAVP (Sakariassen et al., 1984). Contrary to this, no change in the surface expression of CD62, CD63, or thrombospondin was seen after DDAVP. This contradicts the results reported by Wun et al. who showed an increased surface expression of CD62 after DDAVP.

High concentrations of fibrinogen – a possible explanation for the high rate of restenosis following coronary angioplasty in patients with renal insufficiency

F. Gradaus, F.-C. Schoebel, K. Ivens, P. Heering, T.W. Jax, M. Leschke and B.E. Strauer

Clinic of Cardiology and Nephrology, University of Düsseldorf, Germany

Cardiovascular complications are the leading cause of death in patients with end-stage renal disease (ESRD). In 30–60% of these patients coronary artery disease can be demonstrated by coronary angiography often prompting myocardial revascularisation. Little is known about long-term success of coronary angioplasty (PTCA) in this patient group.

In 20 patients with ESRD and in 20 age- and sex-matched patients without renal disease the rate of restenosis after PTCA was compared. Restenosis as assessed by computer assisted quantitative

angiography was defined as a stenosis $>$ 50% luminal diameter at a follow-up angiography after 6–12 months. Plasma concentrations of lipids and fibrinogen were measured before PTCA (mg/dl).

The rate of restenosis was 60% in patients with ESRD and 35% in controls. In patients with ESRD concentrations of fibrinogen (483 $\pm$ 101 vs. 330 $\pm$ 64, $p < 0.001$) and triglycerides (269 $\pm$ 163 vs. 207 $\pm$ 176, $p < 0.01$) were significantly elevated in comparison to controls, while concentrations of total cholesterol (262 $\pm$ 50 vs. 238 $\pm$ 39, $p < 0.1$), LDL-cholesterol (191 $\pm$ 50 vs. 172 $\pm$ 38) and HDL-cholesterol (36 $\pm$ 15 vs. 42 $\pm$ 12, $p < 0.1$) were comparable.

A high rate of restenosis could be confirmed in patients with ESRD. Given the role of reactive thrombogenesis in the early phase following PTCA procoagulant factors like elevations of fibrinogen and triglycerides as a possible marker of impaired endogenous fibrinolysis may influence the process of restenosis in patients with ESRD.

Expression of cytokeratins, adhesion molecules, growth factors and their receptors in the skin with chronic venous insufficiency

H. Grenz, M. Peschen, E. Schöpf and W. Vanscheidt

Department of Dermatology, University of Freiburg, D-79104 Freiburg, Germany

Venous hypertension underlies the pathogenesis of venous disease and ulceration, but the steps leading from venous hypertension to venous ulcer are yet unclear. Aim of this study has been to investigate the role of cytokeratins (CK), cellular adhesion molecules (CAM), growth factors (GF) and growth factor receptors (GFR) in the development of skin changes occurring with CVI. Punch biopsies of patients with various stages of CVI and punch biopsies of normal patients were taken, and the expressions were detected by indirect immunofluorescence and immunoperoxidase techniques. Endothelial CAM's ICAM-1, VCAM-1, leukocyte CAMs LFA-1, VLA-4, GFs basic FGF, TGF-β3, VEGF, GFRs PDGFR-α, PDGFR-β, and VEGF expressions are strongly increased in the stroma of venous eczema and with venous ulcer skin, and to a smaller extent in the dermis with lipodermatosclerosis. Venous eczema and lipodermatosclerosis epidermis show an elevated EGFR, FGF, CK 10 and 14 synthesis throughout all strata. Unchanged expression of these molecules compared to normal skin is presented by telangiectases or reticular veins and pigmentation dermis and epidermis. We conclude that GFs, CAMs, and CKs play an important role in mediating inflammation, capillary growth, and epithelial hyperproliferation in venous eczema, inducing connective tissue sclerosis in lipodermatosclerosis, and causing a reduced reepithelialization tendency in venous ulcer. Disturbed CK, CAM, and GF expressions patterns throughout the various stages of CVI might be responsible for the histopathological changes.

The interaction between arterial blood flow and microcirculation in patients with PAOD in stage IIb–IV

J. Gross, P. Scheffler, G. Pindur* and H. Schieffer

Department of Internal Medicine (Cardiology–Angiology),
*Department of Clinical Haemostaseology and Transfusion Medicine, University of the Saarland, D-66421 Homburg/Saar, Germany

We investigated whether the reduction in blood flow in the macrocirculation is followed by a decrease of microcirculatory parameters.

We studied healthy individuals ($n = 12$), patients with PAOD stage IIb ($n = 40$) and stage III/IV ($n = 20$).

1. Baseline measurement: Simultaneously, we measured arterial blood flow in the common femoral artery (CFA, MAVIS®-method), blood pressure, heart rate, arterial Doppler pressure of the A. doralis pedis, A. tibialis posterior, transcutaneous oxygen pressure ($tcpO_2$, lower leg, forefoot), temperature of the foot, plasma viscosity (PV) and the erythrocyte aggregation index (SEA).

2. After application of PGE1: These measurements were also registered during and after the intravenous application of 60 μg PGE1.

The blood flow in the CFA decreased from 189.7 ± 23.6 (healthy) to 120.3 ± 19.1 (PAOD IIb) and 95.2 ± 32.8 ml/min (PAOD III/IV), respectively, the $tcpO_2$ values of the forefoot ranged from 61.0 ± 11.4 (healthy), 29.6 ± 8.5 (PAOD IIb) to 19.2 ± 11.5 mm Hg (PAOD III/IV). PV and SEA correlated to the stage of PAOD. After application of PGE1 we measured an increase of the blood flow ($> 100\%$), followed by an increase of the $tcpO_2$-values (after 60 min).

We conclude: 1) The blood flow as well as the $tcpO_2$-values were significantly lower ($p < 0.001$) in patients with PAOD than in healthy individuals. 2) The effects of PGE1 are caused by an enhanced perfusion, rather than a direct influence to PGE1 on the microcirculation.

Capillary blood pressure and capillary pressure pulse amplitude in patients with Raynaud's phenomenon due to systemic sclerosis compared to healthy volunteers

M. Hahn*, T. Heubach, A. Steins and M. Jünger

Department of Dermatology, University of Tübingen, Liebermeisterstraße 25, 72076 Tübingen, Germany

Capillary blood pressure (CP) and capillary pressure pulse amplitude are important determinants of the microvascular function. In some patients with Raynaud's phenomenon (RP), especially in cases with underlying systemic sclerosis (SSc) this function has clearly failed as evidenced by necrosis of the fingertips. CP was measured in finger nailfold capillaries using glass micropipettes attached to a servo-nulling system in a controlled temperature environment ($22 \pm 0.5^\circ$C). CP was measured in 11 age, sex and skin temperature matched healthy volunteers (mean age: 49.2 y, range: 29–71 y, eight women, three men; $24.7 \pm 1.9^\circ$C) and 11 patients (mean age 46.9 y, range 24–72 y, eight women, three men; $23.7 \pm 0.9^\circ$C) who suffer from secondary RP due to SSc. In addition all patients were screened for arterial stenosis of hand and finger arteries by duplex sonography. The average CP in patients was significantly lower compared to healthy controls (patients 14.3 ± 4.4 mm Hg; controls 19.1 ± 3.7 mm Hg; $p = 0.007$). In 4 of 11 patients the CP was non-pulsatile whereas in all controls the CP was pulsatile. The capillary pressure pulse amplitude was significantly lower in patients than in healthy controls (patients 0.8 ± 1.5 mm Hg; controls 3.5 ± 1.6 mm Hg; $p = 0.002$). No stenosis of hand- and fingerarteries of the examined fingers could be detected. These observations show the inadequate microvascular function even at comfortable ambient temperature in patients with RP compared to healthy controls. This may reflect a pathological increase in precapillary resistance in patients with secondary RP even in the absence of cold provocation.

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Follow-up of microcirculation after free tissue transfer

N. Hartmann and G. Thiemann

Department of Oral, Maxillofacial and Plastic Surgery, Department of Radiotherapy and Nuclear Medicine, City Hospital, Münsterstrasse 240, 44145 Dortmund, Germany

Laser flowmetry for soft tissue transfer and scintigraphic procedures for bone flaps have been established in the last years in the follow-up of microvascular tissue transfer although many microsurgeons are still relying more on clinical impression than on technical monitoring. In the last four years a three-phase bone scintigraphy with 99m-Tc-DPD in combination with single-photon emission computed tomography (SPECT) was performed in 18 patients for follow-up after microvascular bone transfer. The time range between operation and scintigraphy was three days to twelve months. In all cases the clinical result corresponded with the scintigraphic control; in two patients we saw differences in the clinical course. As noninvasive methods three-phase bone scintigraphy and SPECT allow statements concerning perfusion and vitality of the transplant and rating of possible complications; further investigation seems to be necessary concerning the prognostic value of these methods.

Absence of severe hypertensive retinopathy in a Turkish kindred with autosomal dominant hypertension and brachydactyly

L. Hattenbach[1], H. Toka[2], H. Schuster[2], O. Toka[2], C. Thalhammer[2], H. Haller[2], F. Luft[2] and C. Ohrloff[1]

[1]Zentrum der Augenheilkunde, Klinikum der Johann Wolfgang Goethe-Universität, Frankfurt a.M., Germany
[2]Franz-Volhard-Klinik am Max-Delbrück-Zentrum für molekulare Medizin, Humboldt-Universität Berlin, Germany

Purpose: We performed a complete clinical and ophthalmological evaluation in six subjects of a Turkish kindred with a unique form of autosomal dominant hypertension starting in early childhood, which cosegregates 100% with brachydactyly and maps to chromosome 12p.

Methods: Two affected men aged 46 and 31 years, three affected women aged 40, 31, and 30 years, and one nonaffected man aged 29 years were studied, including a complete ophthalmological and physical examination, echotracking (NIUS 02) and duplex Doppler determinations.

Results: Systolic blood pressures ranged from 170 to 250 mm Hg in affected persons. In all affected individuals, only mild retinal changes with arteriolar narrowing and tortuosity were observed. These patients showed increased radial artery wall thickness.

Conclusions: We conclude that the absence of a severe hypertensive retinopathy in this novel form of inherited hypertension is due to a protective mechanism.

Alterations of neutrophil adhesion and activation under fibrinolytic therapy of acute myocardial infarction

B. Hummel, G. Berg, H. Schwerdt, A. Link and H. Schieffer

Innere Medizin III, Universitätskliniken des Saarlandes, Homburg/Saar, Germany

Polymorphonuclear neutrophils (PMN) are attributes considerable significance in myocardial reperfusion. In a pilot study, alterations of PMN function during systemic fibrinolysis in acute myocardial infarction (AMI) have been investigated in humans. Samples have been taken from 30 patients with AMI (age: 58 ± 12 years; 13 anterior, 17 posterior wall infarctions; maximum of creatine kinase 688 ± 348 U/l). The following parameters of PMN function were measured before as well as 15 and 45 min after initiation of systemic fibrinolysis with rt-PA ($n = 25$) or r-PA ($n = 5$): 1) PMN adhesion (NAD) with a new method using the plasma viscosimeter, 2) PMN activation (NBT) by ingestion of nitroblue tetrazolium. In 20 patients an acute coronary angiography was performed; the reperfusion success was assessed according to TIMI grades. During systemic fibrinolysis NAD decreased significantly from 6.1 ± 7.8 to 3.3 ± 3.1 ($p = 0.0427$). A significant reduction was also observed in phagocyting NBT from 42 ± 19 to $25 \pm 17\%$ ($p < 0.0001$) and in resting NBT from 8 ± 7 to $5 \pm 7\%$ ($p = 0.0002$). Successful reperfusion coincided with a more marked reduction of resting NBT (TIMI II–III: 5.5 ± 2.6 to $1.2 \pm 0.9\%$ vs. TIMI 0: 10.8 ± 9.7 to $8.2 \pm 8.8\%$; $p = 0.1866$) and with a significantly higher reduction of phagocyting NBT (TIMI II–III: 39 ± 12 to $19 \pm 11\%$ vs. TIMI 0: 45 ± 25 to $32 \pm 20\%$, $p = 0.0364$) during fibrinolysis. Systemic fibrinolysis in AMI is accompanied by a marked reduction in PMN adhesion and activation. The extend of decrease in activation seems to be dependent on the successful reperfusion of the infarcted vessel.

Fibrinogen and quality of life in patients with refractory angina pectoris and chronic-intermittent urokinase therapy

T. Jax, A. Peters, F.-C. Schoebel, D. Stein, J. Siegrist*, M. Broers*, B.E. Strauer and M. Leschke

Klinik für Kardiologie, Pneumologie und Angiologie,
*Institut für Medizinische Soziologie, Heinrich Heine Universität Düsseldorf, Germany

In patients with severe coronary artery disease and refractory angina pectoris chronic-intermittent urokinase therapy was established as an 'ultima-ratio' concept to improve myocardial microcirculation. So far there was no suitable way of evaluating objectively the subjective change of quality of life.

With the help of the PLC-questionnaire (profile of quality of life of chronically ill patients) 14 patients were asked before and after undergoing chronic-intermittent urokinase therapy. This questionnaire examines six different aspects of quality of life and is expressed as a score between 0 and 4. Rheological parameters were measured at the time of the questionnaire.

During therapy the levels of fibrinogen (302 ± 70 vs. 197 ± 33 mg/dl, $p < 0.001$) and plasma-viscosity (1.36 ± 0.5 vs. 1.29 ± 0.7 mPas, $p < 0.001$) decreased significantly. Quality of life increased significantly in all six aspects, especially for the 'ability of good performance' (1.59 ± 0.73 vs. 2.22 ± 0.54, $p < 0.01$), the 'ability to relax' (2.20 ± 0.54 vs. 2.84 ± 0.48, $p < 0.001$) and the 'positive mood' (1.7 ± 0.68 vs. 2.47 ± 0.54, $p < 0.01$).

With regression a linear relation between values of fibrinogen and the score of quality of life could be found ($r^2 = 0.27$, $p < 0.01$).

Chronic-intermittent urokinase therapy is an effective therapy to improve the quality of life in patients with refractory angina pectoris. A relationship between the rheological and fibrinolytical improvement of myocardial perfusion and quality of life could be established.

Hemostatic risk factors in coronary artery disease – a two year follow-up in 243 patients

T.W. Jax, F.C. Schoebel, D.Stein, F. Gradaus, M. Heins*, D. Steins, K. Pels, B.E. Strauer and M. Leschke

Department of Cardiology, Pneumology and Angiology, and
*Institute of Clinical Chemistry, Heinrich Heine Universität Düsseldorf, Germany

Patients (pt.) with coronary artery disease and stable angina pectoris need an adequate risk-stratification concerning the incidence of lethal or potentially lethal cardiovascular events (CE). In 243 pt. with angiographically proven coronary artery disease and stable angina pectoris risk factors from the patients history were obtained and conventional lipid-parameters, hemostatic, rheological and fibrinolytical parameters were measured in plasma. All pt. were followed over a period of two years for the incidence of CE: unstable angina pectoris, acute myocardial infarction, PTCA, ACB and cardiac death. Five pt. were excluded because of non-cardiac death. Pt. with CE had significantly elevated values of tissue-Pasminogen-activator versus patients without CE (9.3 ± 3.5 vs. 8.2 ± 3.0, $p < 0.05$). The analysis of anamnestic risc factors showed, that Diabetes mellitus typ II (DM) ($n = 43$) is a strong predictor for the occurrence of CE (64% vs. 34%, $p < 0.0001$). For that reason we compared pt. with DM to pt. without diabetes ($n = 194$). At a similar level of multiple vessel disease in both groups (70% vs. 71%), especially the rate of myocardial infarction and PTCA was raised (AMI: 12% vs. 1%, $p < 0.001$, PTCA: 40% vs. 19%, $p < 0.01$). The diabetic pt. had higher fibrinogen levels (351 ± 76 vs. 312 ± 64 mg/dl, $p < 0.01$), a subsequently higher plasma-viscosity (1.38 ± 0.23 vs. 1.31 ± 0.16 mPas, $p < 0.01$) and erythrocyts-aggregation (13.2 ± 2.5 vs. 12.1 ± 3.1 E, $p < 0.05$), and they showed a significantly higher level of Plasminogen-activator-inhibitor (6.11 ± 3.4 vs. 4.7 ± 2.7 U/l, $p < 0.05$). The comparism of diabetic pt. with and without CE showed only a significant difference for the level of cholesterol (260 ± 49 vs. 236 ± 47 mg/dl, $p < 0.05$). Although the level of t-PA was elevated in pt. with CE, this difference was not significant (9.3 ± 4.3 vs. 7.6 ± 2.7 ng/ml, $p = 0.3$). As a marker for an impaired endogenous fibrinolysis t-PA might be of importance for the incidence of CE. In pt. with DM multiple alterations in the fibrinolytical system and the bloodrheology might be able to produce a prothrombotic state and subsequently explain the higher incidence of CE in these pt.

Hemorheological findings in diabetes patients

H. Kiesewetter[1], F. Jung[2] and J. Koscielny[1]

[1]Institut für Transfusionsmedizin und Immunhämatologie, Universitätsklinikum Charité, Medizinische Fakultät der Humboldt Universität zu Berlin, D-10098 Berlin, Germany
[2]Dresdner Institut für Herz- und Kreislaufforschung, Bautzner Str. 113, D-01099 Dresden, Germany

For the registration of early onset changes in the microcirculation and hemorheological parameters in diabetes patients 273 children with IDDM (insulin-dependent diabetes mellitus) were examined in a sectional study during their hollidays, school hours and rehabilitation time in the Bundes diabetischer Kinder und Jugendlicher e.V. in Kaiserslautern. At the end of their stay the children were angiologically and ophthalmologically examined; the cutaneous (cutaneous video-capillary-microscopy) and retinal microcirculation (retinal video fluorescence angiography) and diverse clinical chemistry (blood fluidity, HbA1C) were determined. The change in the early detection parameters seen in patients with non-IDDM with concomitant cardiovascular risk factors does not occur in IDDM patients. Of the 273 children the blood sugars of 90 were adjusted adequately and of 67 unsatisfactorily. The rest was

average. Good blood sugar adjustment was defined as HbA1C values lower than 7% and unsatisfactory adjustment as HbA1C values higher than 8%. In comparison to healthy children the children with bad adjustment of blood sugars showed the typical changes in hemorheological parameters and cutaneous and retinal circulation. Morphological changes in the capillaries in the form of capillary torquation and dilatation in the venous branch as well as the rigid red blood cells and adhesive white blood cells are striking. Comparable changes can be observed in adult diabetes patients.

Online capillary pressure measurements performed *in vivo* in skin capillaries in patients with chronic venous insufficiency

T. Klyscz, M. Hahn, M. Jünger and G. Rassner

University of Tübingen, Department of Dermatology, Liebermeisterstraße 25, D-72076 Tübingen, Germany

Most current theories about the development of chronic venous leg ulcers claim the increase of blood pressure in the cutaneous capillaries as the main basic pathophysiological disorder. In a new developed technical setup using the servo-nulling measurement technique the real capillary pressure was measured in the nailfold capillaries of the toe in patients with chronic venous insufficiency (CVI).

The patient was examined in supine position, the thigh laying on the examination stretcher and the lower leg was positioned on the stage of the video microscope about 60 cm below heart level. The servo-nulling pressure measurement system allows to measure blood pressure in skin capillaries by direct cannulation. The measurement system described here allows first time dynamic recordings of capillary pressure in the skin capillaries at the toe. Capillary pressure in patients with CVI ($n = 12$, age: 61 y) was 12.6 mm Hg and 12.0 mm Hg in controls ($n = 9$, age: 24 y). The venous pressure (Pv) did neither distinguish between patients (Pv: 52 mm Hg) and controls (Pv: 51.8 mm Hg). Our results proof, that under resting conditions the blood pressure is not increased in nailfold capillaries in patients with CVI. Hemodynamic disturbances because of venous reflux are not present in the capillaries of the skin at the foot as long as the patient is under resting conditions and does not use his calf muscle pump.

Laser-Doppler-flowmetry used as control of skin blood flow changes in morphaea plaques under antibiotic therapy

Th. Klyscz, Th. Schwarz, D. Zuder, A. Steins and M. Jünger

Department of Dermatology, University of Tübingen, Liebermeisterstraße 25, D-72076 Tübingen, Germany

Laser-Doppler-flowmetry is an important diagnostic technique for non-invasive evaluation of cutaneous blood flow, for example, in patients with peripheral arterial occlusive disease or chronic venous insufficiency.

Blood flow measurements were performed by laser-Doppler-flowmetry (LDF) in eight patients with localized scleroderma (morphaea type) to study skin microcirculation before and under antibiotic therapy. Measurements were performed by means of Periflux PF2 laser-Doppler (Perimed, Stockholm) with a 632 nm wavelength laser in the sclerotic centre, lilac ring and perilesional area. As LDF-values have to be correlated with individual normal blood flow values, measurements were additionally

performed in normal-appearing skin in an opposite skin area of the same patient. At the lilac ring of morphaea plaque the laser-Doppler flux was enlarged up to 420% compared to unaffected skin in the same patient. – Two female patients with morphaea plaques since more than ten years prior to examination had never been treated in the past. Even in those two cases LDF-values in sclerotic parts of morphaea plaques were up to 100% higher than in normal-appearing skin. – Immediately after two weeks of antibiotic therapy LDF flux normalized in those six patients with a finally successful outcome – which was proved by series of follow-up examinations during the next few months. In two patients with unchanged or worsened LDF values after therapy there was a lack in clinical success even after a half-year time. By means of LDF measurements therapeutic response to antibiotic therapy can already be assessed at a very early stage of therapy, even when the clinical situation is still unchanged. LDF measurements should become part of therapeutic control in patients with circumscribed scleroderma of the morphaea type.

The influence of hemodilution therapy on the perifoveal microcirculation in central retinal vein occlusion*

H. Knabben[1,2], S. Wolf[1], U. Solbach[1], A. Remky[1], T. Kube[1] and M. Reim[1]

[1]Augenklinik der RWTH Aachen, Pauwelstrasse 30, 52057 Aachen, Germany
[2]Clinique Ophtalmologique Universitaire de Créteil, 40, Avenue de Verdun, 94010 Créteil, France

Purpose: The perifoveal microcirculation in patients with central retinal vein occlusion (CRVO) is significantly disturbed when compared to healthy volunteers. Previously, we showed a beneficial effect of hemodilution therapy on the arteriovenous passage time. In this pilot study the perifoveal microcirculation of patients with CRVO was investigated before and after hemodilution therapy.

Methods: Sixteen patients with acute CRVO were included in this study. We examined the perifoveal microcirculation before and after ten days of hemodilution therapy using a scanning laser ophtalmoscope. With a digital image analyzing system the perifoveal intercapillary areas, the foveal avascular zone and the mean capillary blood flow velocity were quantified.

Results: The mean capillary blood flow velocity was significantly increased after ten days of hemodilution therapy (before treatment: 1.41 ± 0.37 mm/s; after treatment: 1.66 ± 0.44 mm/s). The mean perifoveal intercapillary areas and the foveal avascular zone showed no significant changes during follow-up.

Conclusion: In patients with CRVO the capillary blood flow velocity improved significantly, but normal values were not reached. Further controlled studies will need to show, how far this is directly influenced by hemodilution therapy.

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Microcirculatory changes after red blood cell concentrate

J. Koscielny[1], R. Latza[1], K. Doerschel[2], U. Kalus[2] and H. Kiesewetter[1]

[1]Institut für Transfusionsmedizin und Immunhämatologie, Universitätsklinikum Charité, Medizinische Fakultät der Humboldt Universität zu Berlin, D-10098 Berlin, Germany
[2]Laser Medizin Zentrum, Krahmerstr. 6–10, D-12207 Berlin, Germany

Clinical efficacy of red blood cell (RBC) transfusion as regards microcirculation and blood fluidity was observed in ten patients with chronic anaemia (mainly myelodysplastic syndrome). The confirmatory parameters were: Laser Doppler flow (Laser-Doppler-2-canal system from the Laser Medizin Zentrum in Berlin) in cutaneous tissue and transcutaneous oxygen partial pressure; the explorative: hematokrit, plasma viscosity, RBC aggregation. All parameters were determined two hours after transfusion. Two RBC concentrates with the following characteristics were transfused: white blood cell depleted, SAG Mannitol, volume of one concentrate approximately 300 ml, mean hematokrit 60–65%, mean storage duration: 14 days. Laser Doppler flow adjusted to a frequency range of 4 to 36 kHz increased by 90% and the transcutaneous oxygen partial pressure by +12 mm Hg (31.5%). Systemic hematokrit increased by eight points (+33.3%), plasma viscosity decreased by 0.03 mPas (−2.5%). An increase of RBC aggregation was observed in correlation with the hematokrit. Therewith an improved oxygen supply of the tissue was observed after transfusion of RBC concentrates without complications by means of an increase in blood flow in the cutaneous microcirculation. The reduction of plasma viscosity is probably caused by intake of interstitial fluid into the vascular system after vasodilatation caused by transfusion. Diverse influences of the various consistencies of RBC concentrates or duration of storage on microcirculation and blood fluidity in patients with chronic anaemia should be tested.

Diagnostic relevance of nailfold capillary microscopy; immunologic investigations and digital artery Doppler measurements in the diagnosis of Raynaud symptomatic

K. Kröger, G. Neuhaus, A. Hinrichs, N. Rensing and G. Rudofsky

Clinic of Angiology, Klinikum Essen, Germany

Purpose: The Raynaud symptomatic is a frequent but not specific symptom of every acral alteration of blood flow. Thus a lot of different diagnoses have to be considered. If there are no specific symptoms in the physical examination or the medical history of the patients we always perform a nailfold capillary microscopy, immunological blood investigation and a pressure measurement of digital arterial blood pressure. The diagnostic relevance of these tools is shown.

Method: We analysed the data from 306 patients (240 female and 66 male) which were sent to us with a Raynaud symptomatic. The age ranged from 16 to 72 years.

Results: Pathologic capillary morphology was found in 145 patients, megacapillaries which are the most pathognomic changes in only 35 patients. Pathologic values for immunologic blood parameters as ANA, SCL70, ANCA, ANA-western blot and others were found in 134 patients. A characteristic constellation of blood values that correlate with a characteristic change in capillary morphology was not found. A pathological reduction of the digital artery Doppler measurements at all fingers of one hand occurred in 45 patients.

Conclusion: Nailfold capillary microscopy demonstrates a lot of non-specific findings. Investigation of immunologic blood parameters are more effective in the diagnosis of the Raynaud symptomatic but are very expensive.

Volume effect of plasma expanders in volunteers

W. Kröll, S. Izmail, S. Sabutsch, S.E. Gaßmayr, H.A. Adams and W.F. List

Department of Anesthesiology and Intensive Care Medicine, Karl-Franzens-University, Graz, Austria

Objectives: Various plasma expanders are available for different indications; especially under prehospital conditions a large volume effect of an expander is desirable for rapid restoration of altered hemodynamics. A point of discussion about which solutions are preferable arises, because HES solutions which differ due to their molecular weight, the degree of substitution and the concentration are offered from the pharmaceutical companies, as to be equal with regard to the volume effect and the duration of action.

Method: The investigation was performed in 70 healthy volunteers, which received either 10% HES 200/0.5, 6% HES 200/0.5, 6% HES 200/0.62, 6% HES 450/0.7, 3.5% polygelin and Ringer's solution. The amount of HES infused was 500 ml within 30 min. The volume effect of the HES solutions was calculated from the measured blood- and plasma density and hematocrit. The observation period was eight hours.

Results: With the application of 10% HES 200/0.5 there was an increase of plasma volume of about 780 ml; 2 hrs after the end of infusion the increase in plasma volume was about 500 ml and 8 hrs after the end of infusion the increase was about 250 ml. The changes in plasma volume of the other HES used were similar: initial increase: about 600 ml, 2 hrs later: about 400 ml and 8 hrs later about 250 ml; after infusion of polygeline the immediate increase in plasma volume was about 550 ml, 2 hrs later the plasma volume decreased to about 200 ml and 8 hrs after the end of infusion the plasma volume was about 120 ml.

Conclusions: 10% HES 200/0.5 shows the largest volume effect, the duration of the expanding effect of this type of HES is about 3 hrs. There was no difference in the volume effects of the other HES-solutions used. Polygelin too showed a slight expanding effect, however, this effect is only of short duration, using a crystalloid solution no volume expanding effect can be expected. If a large volume effect of a plasma expander solution is required, 10% HES 200/0.5 should be used.

Influence of glucose toxicity and advanced glycation endproducts (AGE) on endothelial mRNA-expression of adhesion molecules and of the receptor for AGE and their relevance for leucocyte-endothelial interaction

Th. Kunt, Th. Forst, A. Pfützner, M. Engelbach, A. Wilhelm, B. Früh, G. Buchert and J. Beyer

Department of Endocrinology, University of Mainz, Germany

Increased adhesion of leucocytes to cultured human endothelial cells under hyperglycemic conditions has been described. This is not mediated by increased expression of endothelial adhesion molecules.

Aim of this study was to determine the role of AGE and their receptor (RAGE) on endothelial cells and monocytes. Granulocytes, lymphocytes and monocytes (from type I-diabetics and healthy control subjects) were incubated with human umbilical vein endothelial cells (HUVEC) under normo- and hyperglycemic conditions. Competitive adhesion assays were performed with synthesized AGE-albumin. Expression of adhesion molecules and endothelial RAGE was quantified by: ELISA, quantitative RT-PCR and *in situ* hybridization. High glucose levels did not induce increased expression of endothelial adhesion molecules. However, increased binding of lymphocytes and especially of monocytes, but not of granulocytes, was observed. Binding of monocytes from diabetic patients was significantly elevated in comparison to controls. Blocking of the monocyte RAGE by AGE-albumin led to a decreased adhesion of monocytes from diabetics. This effect was not observed after blocking the RAGE on monocytes from controls. Our findings prove that increased binding of leucocytes to endothelium under hyperglycemic conditions is not mediated by enhanced expression of endothelial adhesion molecules. Furthermore, the increased binding of monocytes from diabetics could be reduced by blocking the monocyte RAGE. In conclusion, the monocyte RAGE is possibly involved in adhesion of monocytes to endothelium in diabetic angiopathy.

Correlation of rheological alterations, hypercoagulability and disturbances of microcirculation in PAOD

H. Lawall, Th. Woller and B. Angelkort

Medizinische Klinik Nord, Städt. Kliniken Dortmund, 44145 Dortmund, Germany

Rheological alterations and an increased coagulability are often reported in patients with PAOD. This study investigates whether there is a correlation between microcirculation, rheological parameters and coagulability in the affected leg. In 15 patients (age 52–78 y, grade IIb after Fontaine) arterial and venous blood samples of the mainly affected led were taken and compared. The following parameters were investigated: erythrocyte aggregation (ea), spontaneous platelet aggregation (spa), plasma viscosity (pv), fibrinogen (fib), D-Dimere, TAT, F1/F2.

Transcutaneous oxygen pressure (44°C) and video capillaroscopy were applicated on the forefoot of the affected leg. All patients show raised rheological parameters (ea, spa, pv, fib) and an increased coagulability (TAT, F1/F2), more distinct in the arterial blood. A significant negative correlation (art. and ven.) can only be found for fibrinogen and plasmaviscosity to capillary density and $tcpO_2$-values at rest and during reactive hyperemia. The clotting markers show no correlation to microcirculation. We conclude that patients with PAOD show distinctively more rheological disturbances and activated coagulation in arterial blood than in venous blood.

These results may cause thrombembolic lesions in the affected extremity. The data indicate that in PAOD increased levels of fibrinogen and plasmaviscosity are associated with reduced microcirculation.

Morphological and hemodynamic basics of diabetic microangiopathy

H. Lawall

Medizinische Klinik Nord, Städt. Kliniken Dortmund, 44145 Dortmund, Germany

In both diabetes types complex alterations of hemorheology, capillary morphology and capillary perfusion can be found. This results in a reduction of tissue perfusion and may cause organ failure.

Apart from morphological alterations disturbances of microcirculation make a contribution to the development and progression of diabetic microangiopathy. Hemodynamic disturbances are followed by structural morhological lesions. First of all, there is an increased capillary flow. Hyperperfusion leads to raised capillary pressure and increased capillary permeability. Microvascular endothelial response causes basement membrane thickening, perduction of pericytes and microvascular sclerosis. With increasing duration of diabetes and dependent on the metabolic situation, the process results in a limitation of vasodilatation with reduced reactive hyperaemia as well as in loss of autoregulation. Increased arteriovenous shunts contribute to the reduction of microcirculation. Later on capillary rarefication can be observed.

Hyperglycemic associated metabolic processes and probably genetic factors may explain the clinical features of diabetic microangiopathy in different organ systems.

Magnesium ions as potassium antagonist in critical ischemia

E. Leniger-Follert

Max-Planck-Str. 68, 58093 Hagen, Germany

As already reported (Leniger-Follert, 1995) magnesium ions in appropriate concentration dilate by hyperpolarisation of the smooth muscle cell membrane the resistance vessels constricted by potassium depolarisation in patients with microcirculation disturbance. The aim of the present investigation was to examine whether the application of magnesium ions also ameliorates perfusion in critical ischemia and prevents the imminent amputation of the leg in a patient with severe arterial occlusive disease. A 65 years aged patient with amputation of the right forefoot in 1978, with endangiitis obliterans and total occlusion of all arteries of the right leg suffered from a chronical large, nonhealing ulcer in the area of the amputation stump and from strong pain in rest despite most intensive continuous conventional therapy. The amputation of the whole leg was imminent. With daily local application of magnesium ions on the ulcer and additional intravenous injection of magnesium ions in a calculated concentration the whole leg inclusive the foot became warm. The granulation in the ground of the ulcer began within a few days. Within half a year the ulcer healed and the patient was able for the first time since 1978 to walk freely without help and without pain. We conclude that magnesium ions as potassium antagonist also ameliorate the perfusion in critical ischemia and prevent the imminent amputation of the leg. Obviously, this new therapy dilates beside the arterial and arteriolar resistance vessels also the preformed collateral vessels. Therefore, the application of magnesium ions as potassium antagonist is a useful and promising new therapy for all central and peripherical disturbances of blood flow.

Influence of neutrophil separation on the expression of adhesion molecules

A. Link, B. Hummel, H. Schwerdt, J. Schwamborn* and H. Schieffer

Innere Medizin III und *I. Universitätskliniken des Saarlandes, 66421 Homburg/Saar, Germany

In various fields investigation of the polymorphonuclear neutrophil (PMN) function is of considerable significance. Hence it is important to have reliable methods for examining the neutrophil function available. The first step in most of the PMN function assays is separation of PMN from the whole blood. In the present investigation we examined if PMN separation leads to an activation of the separated cells. Therefore, expression of surface membrane adhesion molecules was compared in a

whole blood assay and in a single step gradient separation assay. Samples were taken from 20 healthy volunteers (10 male, 10 female; 39.7±11.8 years of age). PMN activation was measured cytometrically using the following antibodies against PMN surface membrane receptors: L-selectin (CD 62 L), Beta-2-integrin Mac-1 (CD 11b) and Intercellular Adhesion Molecule 1 (CD 54). PMN activation was determined in whole blood and after separation of PMN using density gradients. After PMN separation an increase in all of the three adhesion molecules could be observed; the increase of CD 54 was significant (Wilcoxon test): CD 62 L: 62 ± 37 in whole blood, 82 ± 28 after separation, $p = 0.0674$; CD 11b: 94 ± 55 in whole blood, 111 ± 47 after separation, $p = 0.1454$; CD 54: 13 ± 12 in whole blood, 81 ± 35 after separation; $p < 0.0001$. With the present data available it can be assumed that separation of PMN from whole blood influences the expression of neutrophil adhesion molecules. This has to be taken into consideration when tests of PMN function are performed with separated cells.

Examination of nailfold capillaries by magnifying-lens with a novel immersion technique

F. Lössner[1] and R. Bauersachs[2]

[1]Krankenhaus München-Bogenhausen, Division of Angiology, 3rd Medical Department, Munich, Germany
[2]Division of Angiology, University of Frankfurt, 1st Medical Department, Frankfurt, Germany

Problem: Is it possible to identify relevant morphological changes in nailfold capillaries (NC) with the use of a dermatoscope?

Methods: We examined NC of both hands (excluding thumbs) in 20 patients referred to our unit for suspected scleroderma with a modified single-lens dermatoscope (Heine Optotechnik, Herrsching/Germany, Modell Delta, mag. 10×) in a novel immersion technique using ultrasound gel. A first observer examined NC by dermatoscope, while a second observer examined the same patients by stereomicroscope (Wild, Heerbruck, Switzerland, Mod. M3B, mag. 10–100×).

Results: For the morphological parameters “normal”, “megacapillaries”, “microbleeding”, “avascular fields” an accordance of $> 95\%$ (kappa statistics), and for the parameters “tortuosity” and “branching” an accordance of 88% could be obtained.

Conclusion: We present a diagnostic tool for quick, effective and reliable evaluation of NC in a bedside manner. In pathological findings, however, documentation by microscope and videotape or photographs has to be done in the standard procedure.

Dependence of the elastic area compressibility modulus in RBC of guinea pigs and preterm infants on different compositions of membrane polyunsaturated fatty acids

J. Meyburg, T. Böhler, M. Leichsenring and O. Linderkamp

University Children’s Hospital, INF 150, 69120 Heidelberg, Germany

Background: Levels of long chain polyunsaturated fatty acids (LCP) are higher in human milk than in commercially available milk formulae. Changes in membrane lipid compositions may influence mechanical properties of the RBC membrane.

Methods: Guinea pigs received defined amounts of LCP by dietary intake of cacao butter, sunflower seed oil or fish oil for 20 weeks. Each group consisted of eight animals. Preterm infants with birth weights < 1500 mg were fed for six weeks with human milk (11 infants) or preterm formula (11 infants). The elastic area compressibility modulus K was determined in 15 RBC of each individual using a micropipette technique. Membrane LCP contents were measured by means of gas chromatography in phosphatidylcholine (PC) and phosphatidylethanolamine (PE) lipid layers.

Results: K was higher in animals fed with fish oil (201.7 $\pm$ 12.9 dyn/cm, $p < 0.02$) when compared to cacao butter (175.1 $\pm$ 18.6 dyn/cm) and sunflower seed oil (175.9 $\pm$ 18.6 dyn/cm). A strong correlation between K and membrane LCP contents (PC: $p = 0.004$; PE: $p = 0.02$) was found. Preterm infants fed with human milk had higher LCP levels (PC: 14.4 $\pm$ 1.5% vs. 11.4 $\pm$ 2.3%, $p = 0.02$; PE: 50.8 $\pm$ 2.5% vs. 46.8 $\pm$ 2.7%, $p = 0.002$). Higher area compressibility moduli (207.3 $\pm$ 25.9 dyn/cm vs. 191.8 $\pm$ 28.4 dyn/cm) were also found, but the difference was not significant. After excluding all children with sepsis or RBC transfusions, we could demonstrate the same clear correlation between K and membrane LCP contents (PC: $p = 0.005$; PE: $p = 0.009$).

Conclusions: Increased RBC elastic area compressibility moduli may be a result of elevated levels of LCP in RBC membrane phospholipids due to increased dietary intake.

Hemorheologic disorders in patients with congenital dysfibrinogenemia

S. Mörsdorf, F. Jung, U.T. Seyfert, Ch. Mrowitz, G. Pindur and E. Wenzel

Department of Clinical Hemostaseology and Transfusion Medicine, University Clinics of the Saarland, 66421 Homburg/Saar, Germany

Congenital dysfibrinogenemia is based on different alterations of the structure of fibrinogen thus influencing the hemostaseological properties of the molecule. A variety of different mutations of the molecule have been described and most of the patients have been detected to be heterozygous. Clinical manifestations of the disorder are showing a wide range from asymptomatic states to mild bleeding diathesis as well as thrombotic complications. Fibrinogen is also known as an important factor influencing the rheological properties of the blood, plasma and the interactions between red blood cells. Therefore, we were interested to investigate beside coagulation properties also rheological properties like plasma viscosity (PV) and erythrocyte aggregation index (SEA) in dysfibrinogenemic patients. A total of 22 patients out of six families with dysfibrinogenemia (Homburg I–VI) was examined and in 13 patients dysfibrinogenemia was ascertained. Compared to the non-affected relatives ($n = 9$) and the normal controls ($n = 297$), despite comparable concentrations of fibrinogen in immunological assays, the pathologic fibrinogen in affected patients showed a significantly stronger influence on these hemorheologic parameters than the fibrinogen of the relatives and the normal group. Thus, this mechanism may promote thrombus formation in patients, however, this hypothesis remains to be cleared in further investigations.

Oral anticoagulants and capillary damages

S. Mörsdorf, N. Schaal, F. Jung, Ch. Mrowitz, G. Pindur and E. Wenzel

Department of Clinical Hemostaseology and Transfusion Medicine, University Clinics of the Saarland, 66421 Homburg/Saar, Germany

Oral anticoagulants are known to promote capillary damages like increased capillary permeability and fragility. However, this rare complication was believed to occur only in cases of massive intoxication with coumarins and was thought to be of no clinical relevance in patients within the so called 'therapeutic range'. To investigate the influence of phenprocoumon (Marcumar®) on microcirculation, in a total of 19 patients being part of a well controlled study population in a long term follow-up study on oral anticoagulant treatment ('Saarland-Model'), the capillary morphology was examined by video-based capillary microscopy since December 1995. Fourteen out of the 19 patients showed acute capillary bleedings in a frequency ranging from 0.33 to 4.29 per 100 capillaries. In matched controls without oral anticoagulant therapy ($n = 10$), no capillary bleedings were found. The number of capillary bleedings showed neither a correlation with the INR values at examination nor with the number of clinical evident bleeding events, percentage of 'stable phases' and percentage of INR values within the therapeutic range in 17 long term patients. Coumarins, therefore, seem to promote capillary damages and bleedings to a considerable extent even within therapeutic INR ranges and even without clinical bleeding signs.

Influence of ultrasound contrast media without pulmonary passage on the microcirculation of rats: prospective randomised parallel group experiment

A. Moll[2], F. Jung[1], C. Mrowitz[3], K.D. Beller[4] and E. Wenzel[3]

[1]Dresdner Institut für Herz- und Kreislaufforschung, Dresden, Germany
[2]Institut für Anaesthesiologie und Intensivmedizin Universitätskliniken Homburg, Homburg/Saar, Germany
[3]Abteilung für Klinische Hämostaseologie und Transfusionsmedizin, Universitäskliniken Homburg, Homburg/Saar, Germany

The aim of this study was to examine whether the injection of ultrasound contrast media which cannot circulate through the pulmonary circulation influence the microcirculation. In order to perform the ultrasound contrast media Echovist and sonicated NaCl were injected into $n = 20$ rats at random. Primarily 0.2 ml/kg was injected, then 2 ml/kg after ten minutes. One minute before until 3 min after each injection the red blood cell velocity (vRBC) was determined in the same capillaries of the major omentum using *in vivo* microscopy recorded by video. The mean vRBC was calculated. The result were as follows: the vRBC after injection of 0.2 ml/kg or 2 ml/kg sonicated NaCl did not influence the microcirculation ($p = 0.1352$; $p = 0.5881$). No arrest of flow was seen. Contrary to this Echovist injection caused a significant decrease of the vRBC with 0.2 ml/kg by 23.4% ($p = 0.0109$) and by 58.4% ($p = 0.0001$) with 2 ml/kg with a very delayed return to base line values. Arrest of flow was observed after low dose Echovist in two rats and after high dose in eight rats. This leads to the conclusion that the injection of Echovist drastically and significantly influences the microcirculation whereas sonicated NaCl does not.

The influence of non-ionic X-ray contrast media on the cutaneous circulation of patients with coronary heart disease

C. Mrowietz, F. Jung, R. Bach, K. Dörschel, B. Meffert and G. Müller

Abteilung für Klinische Hämostaseologie und Transfusionsmedizin, Universität des Saarlandes, Homburg, Germany

Application of X-ray contrast media (X-CM) can lead to undesirable adverse reactions. These reactions are thought to be caused by the increase of blood viscosity due to the high viscosity of X-CM and resulting microcirculatory impairment. To examine this question a clinical comparison study of two non-ionised isoosmotic X-CM varying in viscosity was performed. The cutaneous circulation was recorded before and after injection of a 20 ml X-CM bolus Visipaque®270 (Iodixanol 270) or Imagopaque®150 (Iopentol 150) (Nycomed Arzneimittel, München) into the axillary artery of $n = 10$ patients with coronary heart disease prior to angiography. The circulation measurement system was a laser-Doppler (LD) system DOP, version 2.2 (Laser-Medizin-Zentrum, Berlin). During examination continuous monitoring of the blood pressure, heart rate and surface skin temperature was given. The results show that before injection of X-CM LD signals of the two patient groups do not differ. The injection of X-CM with low viscosity (Iopentol 150) did not influence the microcirculation yet the highly viscous X-CM (Iodixanol 270) decreased LD signals significantly. These differed markedly at 10 s ($p = 0.0248$) and 20 s ($p = 0.0025$) after injection. At all other times the signals did not differ. This shows that depending on the viscosity of the solution a short term decrease in cutaneous blood flow can be determined using the laser-Doppler system DOP after the injection of X-CM.

Functional aspects of cutaneous microcirculation in patients with systemic sclerosis compared to healthy controls

M. Mück-Weymann, D. Hiller and H.P. Albrecht

Department of Psychosomatic Medicine and Department of Dermatology, University of Erlangen–Nürnberg, Schwabachanlage 6, D-91054 Erlangen, Germany

Simultaneous measurements of flux and cutaneous oxygen tension ($p_{cu}O_2$), on the back of the hand, by laser-Doppler fluxmetry (LDF) and an oxygen tension electrode were used to determine static and functional parameters of the cutaneous microcirculation in progressive systemic sclerosis (PSS). Hyperemic responses after arterial occlusion (3 min) and local heating (up to 42°C) were investigated in 19 patients with PSS and in 15 healthy controls.

The baseline values for $p_{cu}O_2$ were significantly reduced inversely to the elevated flux values in the patients. Unchanged or slightly increased poststimulatory maximum flux values (that proved an undisturbed distensibility of the cutaneous vessels), together with the elevated baseline flux lead to significantly reduced dynamic responses, i.e., reactivity, of cutaneous microcirculation to the above hyperemic stimuli in PSS-patients. The severely limited oxygen supply defiant to the mobilization of perfusion reserves from deeper dermal vessels showed a pattern of 'hyperemic hypoxia'.

An exhaustion of the functional cutaneous perfusion reserves and an altered compliance of the dermal vessels due to their disturbed reactivity and/or to the fibro-sclerotic perivascular tissue are the assumed causes for our findings.

The influence of an ovarial hyperstimulation on microcirculation

P. Ohlmann, K. Hoppe, M. Stieber, F. Jung, C. Mrowitz and W. Schmidt

Department of Obstetrics and Gynecology, University Homburg/Saar, Germany

Problem: The estrogen-dependent reduction of cardiovascular morbidity is sufficiently evidenced by literature. As there are increased indications of oestrogen receptors in the vessel lining a direct effect of estrogen on the vessel lining cannot be excluded. The objective of this study has therefore been the determination of the effects of extreme hormone variations onto microcirculation.

Method and Results: By means of nailfold-capillary microscopy the rest velocity of the erythrocytes (V) has been determined in dependence of estrogen concentrations (E2) in 12 patients. The following parameters have been settled: erythrocyte aggregation (EA), viscosity of plasma (PV), haematocrit (HK) and thrombocyte aggregation (TA). Measurements have been taken before treatment (t_0); after down regulation (t_1) with GnRh-analoga, on the 6th day of stimulation (t_2) as well as on the day of ovulation triggering (moment of maximum oestrogen level) (t_3). The results of the study are as follows:

T	E2 (pg/ml)	V (mm/s)	EA	PV	TA	HK (%)
t_0	28.4	0.57	14.37	1.27	1.08	38.7
t_1	13	0.27	15.88	1.33	1.77	40.2
t_2	443.4	0.44	17.63	1.34	0.93	39.2
t_3	2278.7	0.48	16.7	1.4	1.7	38.3

Discussion: Parts of the microcirculation seem to be estrogen-dependent. A lack of E2 leads to a simultaneous decrease of the microcirculation by a reduction of V by 52.6%. Due to an increase of the E2-values the initial values are reached approximatively. The changes of PV, TA, SEA and HK are significant but controversial. So we think that the mechanism is an influence on estrogen receptors directly in the vessel lining and not an influence on hemorheological parameters.

Long-term intermittent urokinase therapy improves clinical symptoms and hemodynamics in patients with end-stage coronary artery disease and refractory angina pectoris

A.J. Peters, F.-Ch. Schoebel, S. Steiner, M. Leschke and B.-E. Strauer

Medizinische Klinik und Poliklinik B, Klinik für Kardiologie, Pneumologie und Angiologie, Heinrich-Heine-Universität, Düsseldorf, Germany

Long-term intermittent urokinase therapy reduces clinical symptoms and improves the quality of life in patients with refractory angina pectoris and end-stage coronary artery disease. The hemodynamic effects of this rheologic and fibrinolytic therapeutic approach have not been analysed yet. In 11 patients with severe angina pectoris (Canadian Cardiovascular Society Class III) and no option for an invasive revascularization procedure long-term intermittent urokinase therapy (500,000 IU Urokinase per i.v. injection, three times a week over a total period of 12 weeks) was performed. Invasive hemodynamic measurements (Swan-Ganz-Catheter) were carried out at rest and after bicycle exercise before and after treatment. Urokinase therapy reduced clinical symptoms (from 19.8 ± 6.5 to 5.0 ± 4.3 anginal

events per week, $p < 0.001$), fibrinogen (from 410 ± 88 to 238 ± 40 mg/dl, $p < 0.01$) and plasma viscosity (from 1.45 ± 0.1 to 1.33 ± 0.33 mPas, $p < 0.01$). Furthermore, urokinase therapy reduced pulmonary capillary wedge pressure at rest (from 9.1 ± 5.1 to 5.6 ± 2.8 mm Hg, $p < 0.05$) at comparable levels of systemic vascular resistance (1510 ± 340 before and 1420 ± 510 dyne s cm^{-5} after treatment, p n.s.). Cardiac index at rest (2.9 ± 0.5 before and 2.7 ± 0.3 l/min/m^2 after treatment, p n.s.) and exercise values of cardiac index (4.1 ± 0.8 before and 4.2 ± 0.5 l/min/m^2 after treatment, p n.s.) and pulmonary capillary wedge pressure (29.3 ± 8.6 before and 27.4 ± 6.3 mm Hg after treatment, p n.s.) were not changed significantly. Long-term intermittent urokinase therapy reduces pulmonary capillary wedge pressure as a sign of improved diastolic function probably due to an enhancement of myocardial perfusion at the level of the coronary microcirculation.

Growth factors in diabetic microangiopathy

A. Pfeiffer

Medical University Clinic Bergmannsheil, Bürkle de la Camp-Platz 1, 44789 Bochum, Germany

Hyperglycemia is the primary determinant of diabetic microangiopathy. Growth factors may play different roles in this process in different organs: In the eye changes of growth factors are likely to be secondary to a loss of smal capillaries due to biochemical consequences of hyperglycemia (glycation, aldose-reductase, protein kinase C). Capillary loss results in hypoxia which increases capillary permeability and allows penetration of serum growth factors such as IGF-I and also may stimulate synthesis of the vascular endothelial growth factor and others. Angioneogenesis normally may be inhibited by transforming growth factor β (TGF-β). The activation of this factor in ocular vitreous probably is inhibited by serum derived protease inhibitors such that both a stimulation of angioneogenesis and a loss of inhibitory factors cooperate to cause proliferative retinopathy. Neuropathy is associated with a loss of trophic factors such as NGF which are transported in a retrograde manner and required for neuronal survival. TGF-β seems to be overproduced in nephropathy and may contribute to the synthesis of extracellular matrix proteins causing diabetic glomerulosclerosis. TGF-β production may be induced by hyperglycemia through activation of protein kinase C which is known to stimulate the TGF-β1 promoter. In conclusion multiple growth factors are likely to contribute decisively to the pathogenesis of diabetic complications.

Exercise-dependent influence of naftidrofuryl on tissue oxygenization

G. Pindur, H. Kessler, C. Mrowietz, S. Moersdorf, J. Groß and F. Jung[1]

Abteilung für Klinische Hämostaseologie und Transfusionsmedizin, Universitätskliniken des Saarlandes, D-66421 Homburg/Saar, Germany
[1]Dresdener Institut für Herz- und Kreislaufforschung, D-01099 Dresden, Germany

Naftidrofuryl is known to improve cutaneous and muscular tissue oxygen partial pressure (pO_2) at rest conditions. Twelve healthy volunteers have been investigated on the basis of an open prospective study to find out whether naftidrofuryl also influences muscular oxygenization during exercise conditions. The intramuscular pO_2 was measured using a flexible probe for the M. tibialis anterior prior to, during and after a standardized walking exercise before and after taking 300 mg naftidrofuryl orally per day for one week. Naftidrofuryl showed a significant influence on the muscular pO_2. At rest

the mean pO_2 after naftidrofuryl treatment was 38.6 ± 22.9 mm Hg which was significantly higher (approximately 40%, $p < 0.05$) than prior to naftidrofuryl (22.3 ± 12.1 mm Hg). The increased pO_2 level remained elevated even at exercise conditions. The pO_2 differences are increasing along with augmented exercise. At a low degree of walking exercise (3 km/h, 5% gradient) the pO_2 showed a trend to be elevated. In the cases of enforced exercise (5 km/h, 10% gradient) these differences were significant ($p < 0.05$). At this exercise level pO_2 had an average minimum of 33.9 ± 12.0 mm Hg which was significantly higher relative to the initial pO_2 values prior to naftidrofuryl. We conclude from these data that naftidrofuryl improves muscular oxygenization not only at rest conditions but also during exercise.

Streptolysin O (1 HU/ml) deteriorates erythrocyte deformation in adults and in neonates

J.M.B. Pöschl, P. Ruef, M. Schnauffer and O. Linderkamp

University-Children's Hospital, Department Neonatology, INF 150, 69120 Heidelberg, Germany

Group A streptococci (GAS) often cause infections in adults, but rarely in neonates. GAS may produce hemolysins as Streptolysin O (SLO). We studied the effect of 1 HU/ml SLO on neonatal and adult RBC deformation (cone-plate rheoscope), hemolysis (546 nm) and the RBC indices MCV and MCHC during 60 min of incubation.

SLO incubation of adult RBC resulted in almost linearly increasing time-dependent hemolysis reaching 82%, whereas hemolysis of neonatal RBC was below 60% after 1 h. After 60 min of SLO incubation, RBC deformation was significantly ($p < 0.05$) more reduced in adults than in neonates. An inverse overall relationship ($r = 0.68$) between SLO-induced hemolysis and RBC deformation was found after 1 h incubation. In adult RBC the MCV increased and the MCHC decreased during 60 min SLO incubation, whereas in neonatal RBC the MCV remained unchanged and the MCHC decreased.

We conclude that SLO causes less hemolysis and less impairment of RBC deformation in neonates than in adults. The decreased RBC deformation of unhemolysed RBC indicates that, before lysis, mechanical RBC membrane properties and the mean cellular volume are altered by SLO. Perhaps membrane–bacteria or membrane–toxin interactions play a major role in the different susceptibility to GAS infections in adults and neonates.

Prevalence of micro- and macrovascular disease in patients with diabetic foot ulcers

H. Reike, E. Rischbieter, V. Wienhausen, G. Wimbert and B. Angelkort

Medizinische Klinik Nord, Städt. Kliniken Dortmund, Germany

The aim of the study was to determine the prevalence of complications associated with diabetes in patients with the syndrome of the diabetic foot treated in our clinic between 1987 and 1992. Data from 107 patients (59 male, 48 female, mean age 65.4 years, mean duration of diabetes 15.95 years) were collected. We found arterial hypertension in 69.1%. Causes of foot ulceration were: vascular disease in 21.5%, neuropathy in 34.5%, neuropathy and vascular disease in 40.1%, chronic venous insufficiency in 4.8%. Prevalence of macrovascular complications of diabetes was 48.6% for coronary heart disease (CHD) (history of myocardial infarction in 19.6%), 21.5% for ischemic cerebrovascular disease (CVD) (history of transient ischemic attack in 13.1%, history of ischemic

stroke in 8.4%), and 69.2% for peripheral vascular disease (PVD). Combinations of CHD, PVD and CVD were found in 14%, combinations of CHD and CVD were found in 18%. Prevalence of microvascular complications was 50% for diabetic nephropathy, 80.4% for neuropathy and 57% for retinopathy, 26.2% of patients with diabetic foot syndrome suffered from all these microvascular complications, 27.1% from nephropathy and neuropathy, 35.5% from neuropathy and nephropathy and 41,1% from retinopathy and neuropathy. Conclusion: macro- and microvascular complications are often found in patients with diabetic foot syndrome. This might be the reason for the increased mortality associated with diabetic foot ulcer.

Classification and pathogenesis of vasculitides

E. Reinhold-Keller

Poliklinik für Rheumatologie der Med. Universität zu Lübeck und Med. Krankenhausabteilung Rheumaklinik Bad Bramstedt, Germany

The systemic vasculitides comprise a heterogeneous group of clinicopathologic entities characterized by inflammatory alteration of the blood vessel wall. Most of them are mediated by immunopathogenic mechanisms (“immune vasculitides”). The vasculitidis can occur as a primary event, e.g., ANCA-associated vasculitides (primary vasculitides), which is the case in most immune vasculitides, or secondary to established diseases, e.g., Rheumatoid arthritis, Lupus erythematodes (secondary vasculitidis). To date there is only scarce information on the etiology of primary systemic vasculitides (PSV): hepatitis B and C virus have been considered causative agents in the polyarthritis nodosa and mixed “essential” cryoglobulinemia, there are also hints that infections may play a role in ANCA-associated vasculitides. The role of adverse drug reactions and genetic predisposition in the etiology of PSV has not been finally defined yet. The classification of vasculitides relies on valid definitions of vasculitidis entities and so follows the underlying disease in secondary vasculitides. Opposedly, in PSV reproducible application of the ACR classification criteria has only recently been enabled by the establishment of definitions of PSV by the Chapel Hill Consensus Conference, which consider the size of the predominantly involved vessels, serological markers (e.g., ANCA) as well as immunohistological features. ANCA-associated vasculitides (AAV) include PSV that affect predominantly small vessels such as Wegeners granulomatosis, microscopic polyangiitis (mPA) and Churg-Strauss-Syndrome (CSS). The former is closely associated with cANCA, induced by proteinase 3, mPA is characterized by pANCA with myeloperoxidase specificity and the latter, CSS, can – to a far lesser extent – be associated with, either c- or pANCA. All AAV have in common that they occur without complement consumption and show histologically no deposition of immune complexes (“pauci-immune”).

Correlation of rheological screening parameters to amputation level in the Diabetic Foot Syndrome

E. Rischbieter, H. Reike and B. Angelkort

Medizinische Klinik Nord, Municipal Hospital, D-44145 Dortmund, Germany

In case of a differential therapy according to the differential diagnosis in the Diabetic Foot Syndrome it is possible to lower the number of major amputations (below, through and above knee) by at least 50%. Hemorrheological parameters in laboratory screening tests may be indicators for the prediction of a major amputation risk.

We examined the role of fibrinogen and hematocrit in predicting major amputations in patients with the Diabetic Foot Syndrome.

Methods: We correlated the level of fibrinogen and hematocrit value on admission to the hospital with each other and with the final amputation level (conservative therapy (no amputation), minor amputation (amputation of toe, ray or forefoot), major amputation) in 107 patients with the Diabetic Foot Syndrome (34.6% neuropathic, 20.6% angiopathic, 40.2% neuroischemic, 4.7% venous origin).

Results: There is a significant correlation between fibrinogen and level of amputation (no/minor amp.: 452 mg/dl, major amp.: 563.5 mg/dl; $p = 0.0055$). The same applies to hematocrit and amputation level (no/minor amp.: 40.33%, major amp.: 36.86%; $p = 0.0361$). There was no correlation between fibrinogen and hematocrit ($p = 0.6649$).

Conclusions: Because of a high correlation between fibrinogen and hematocrit as laboratory screening parameters in clinical routine and amputation level in patients with the Diabetic Foot Syndrome these parameters may be predictors of major amputation. Whether they are just parameters of alterated microcirculation or tissue nutrition/oxygenation or pure epiphenomena of infection (protein of acute phase, infection associated anemia) or both have to be determined because of possible therapeutic consequences.

Does low-dose intermittent urokinase therapy influence diastolic left ventricular function in patients with refractory angina pectoris after?

C.M. Schannwell, F.C. Schoebel, B. Pölitz, S. Heggen, M. Schmitz, M. Leschke and B.E. Strauer

Clinic of Cardiology, Pneumology and Angiology, Heinrich Heine University Düsseldorf, Germany

Low-dose intermittent urokinase therapy has been established as a combined rheologic and thrombolytic approach for antiischemic treatment in patients with endstage coronary artery disease and refractory angina pectoris. The impact of this therapeutic approach on the left ventricular diastolic function as a parameter for myocardial ischemia has not been investigated so far.

In 25 patients with refractory angina pectoris 500,000 IU of urokinase were administered intravenously three times a week a treatment period of 12 weeks (36 injections). Pulsed-wave Doppler echocardiography as a useful tool for the noninvasive assessment of left ventricular diastolic function was performed and the following Doppler indices were obtained in all patients and 21 normal age-matched control subjects: peak early (E) and late diastolic flow velocity (A); deceleration time (DT) of flow velocity in early diastole and isovolumetric relaxation time (IVRT). Patients with refractory angina pectoris had a higher peak A velocity (0.68 ± 0.04 vs. 0.48 ± 0.03 m/s; $p < 0.01$), a prolonged deceleration time (262 ± 13 vs. 193 ± 11 ms; $p < 0.01$) and isovolumetric relaxation time (117 ± 4.1 vs. 82 ± 2.7 ms; $p < 0.01$), a lower E/A ratio (1.2 ± 0.05 vs. 1.5 ± 0.04; $p < 0.01$) and E area/A area ratio (1.87 ± 0.5 vs. 2.51 ± 0.6; $p < 0.01$). After low-dose intermittent urokinase therapy diastolic parameters nearly normalized: peak A velocity (0.52 ± 0.03 vs. 0.48 ± 0.03 m/s; n.s.), isovolumetric relaxation time (97 ± 5.3 vs. 82 ± 2.7 ms; n.s.), deceleration time (212 ± 13 vs. 193 ± 11 ms; n.s.), and E/A ratio (1.5 ± 0.07 vs. 1.5 ± 0.04; n.s.).

Conclusion: Diastolic left ventricular function is severly impaired in patients with refractory angina pectoris. Antiischemic effectiveness of low-dose intermittent urokinase therapy can be verified by improved diastolic function.

Maternal and fetal Red-Blood-Cell-flexibility after delivery

B. Schauf, S. Schneider and W. Künzel

Department of Obstetrics and Gynecology, University of Giessen, Germany

Objective: Red-Blood-Cell (RBC)-flexibility is one of the factors determining microcirculation. Women with pregnancy induced hypertension (PIH) exhibit reduced maternal RBC-flexibility. It was tested, whether there is a difference between fetal and maternal RBC-flexibility in uncomplicated pregnancy at term and in PIH.

Method: RBC-flexibility was determined using the Laserdiffractoscope. Maternal and fetal RBC-flexibility was measured simultaneously after delivery at term ($N = 37$) and in PIH ($N = 15$) at shear stress from 0–300 dyn/cm^2.

Results: In both uncomplicated and PIH-complicated pregnancy fetal RBC-flexibility compared to maternal RBC-flexibility shows a steeper increase in RBC-deformation with increasing shear stress leading to significantly higher flexibility of fetal RBC at lower shear stress compared to maternal RBC-flexibility (e.g., elongation value at 18.5 dyn/cm^2: 0.265 ± 0.027 versus 0.228 ± 0.03). At higher shear stress above 69 dyn/cm^2 the curve flattens resulting in lower maximum deformability of fetal RBC compared to maternal RBC (e.g., at 300 dyn/cm^2: 0.465 ± 0.022 versus 0.477 ± 0.026). In PIH, fetal RBC-flexibility is not affected (e.g., at 18.5 dyn/cm^2: 0.265 ± 0.027), whereas maternal RBC-flexibility is significantly reduced (0.179 ± 0.03).

Conclusion: As a consequence of lower blood pressure (BP) in newborns compared to adults, it seems to be logical, that fetal and newborn RBC-flexibility has to be higher at low shear forces to maintain adequate microcirculatory flow. The unaffected RBC-flexibility of the newborn in PIH complicated pregnancy contrasts with the reduced flexibility of maternal RBC in PIH.

Capillary microscopy findings in systemic sclerosis and dermatomyositis

J.A. Schmidt

Medische Universitäts-Klinic, Magdeburg, Germany

Capillary microscopy is of high diagnostic value for systemic sclerosis, dermatomyositis and mixed connective tissue disease (MCTD). Microscopically, these diseases are mainly characterized by giant capillaries and avascular fields (scleroderma-pattern). In addition one sees atypical or bushy capillaries (more frequently in dermatomyositis than in systemic sclerosis of MCTD), and micro bleedings. The so-called scleroderma pattern is seen in systemic sclerosis in 80–100%, in dermatomyositis in 60–80% and in MCTD in 50–60%. The prognostic and clinical meaning of the so-called “active pattern” and “slow pattern” (according to Maricq) in systemic sclerosis and MCTD is unclear. In dermatomyositis, an increased incidence of giant capillaries and avascular fields seems to accompany a more severe organ involvement. However, it is not possible to reliably differentiate between the three mentioned disease entities by means of capillary microscopy.

Abnormal antithrombins after irradiation of fresh frozen plasma; platelet rich plasma and platelet concentrates

U.T. Seyfert, S. Mörsdorf, J. Riggert, K. Bachmann and F. Jung

Department of Clinical Hemostaseology and Transfusion Medicine, University Clinics of the Saarland, 66421 Homburg/Saar, Germany

Irradiation of blood components before transfusion seems to be the best means of reducing the incidence of transfusion associated graft vs. host disease. We looked for adverse effects on plasma, platelet rich plasma and platelet concentrates before and after irradiation (15 Gy and 30 Gy) using a haemocompatibility lab panel.

Results: After irradiation activation of the coagulation system (increased F VIII : C/F VIII: Ag ratio, $p = 0.001$), increased factor XIII activity in platelet concentrates ($p = 0.02$). No changes in proteolysis. No significant changes in AT III activity. Crossed AT III immunoelectrophoresis results in dominance of high molecular weight AT III fractions. No changes in CD 62, CD 63 and platelet glycoproteins and platelet release.

Conclusions: There were no adverse effects of irradiation on platelet function testing, release reaction and glycoproteins. Activation of clotting factors and pathologic features in crossed immune electrophoresis appear also in FFP. Questions have also been raised as to whether irradiation could potentiate the leakage of plasticizers.

Transcutaneous partial pressure ($tcpO_2$) on pedal-ergonometric exercise in patients with occlusive arterial disease stage II (Fontaine) in comparison with healthy controls

A. Steins, D. Zuder, M. Hahn, T. Klyscz and M. Jünger

Department of Dermatology, University of Tübingen, Liebermeisterstraße 25, D-72076 Tübingen, Germany

Measurement of the $tcpO_2$ nowadays is firmly established in routine diagnostics of occlusive arterial disease. Especially in stage III and IV (Fontaine) a good correlation is found with clinical symptoms. In stage II the transcutaneous oxygen tension, measured under resting conditions have proven as little reliant because of a significant overlapping between patients and healthy controls. Hypoxia, which is reflected by the $tcpO_2$, might be expected distally to the occlusion because of a cuto-muscular shunt on exercise with strained muscles. Of the patients 52 (17 female, 35 male) with occlusive arterial disease stage II were examined in our study. The average age was 65.3 $\pm$ 8.2 years. The mean painless walking distance was 312.5 $\pm$ 202.6 meters, the maximum walking distance was 568.4 $\pm$ 291.4 meters. The ankle–arm pressure gradient in the area of dorsalis pedis artery amounted to 0.68 $\pm$ 0.2, in the area of posterior tibial artery 0.65 $\pm$ 0.2. By four of these patients we measured an ankle–arm pressure gradient higher than 0.9. We examined a group of 20 controls (13 female, 7 male) with an average age of 56.9 $\pm$ 11.3 years. The ankle–arm pressure gradient at all measured arteries were higher than 1.0. The mean $tcpO_2$ on rest amounted to 36.5 $\pm$ 13.3 mm Hg in patients and 50.7 $\pm$ 10.1 mm Hg in the controls. On exercise the $tcpO_2$ decreased by 21.6 $\pm$ 14.6 mm Hg in patients and by 6.9 $\pm$ 4.6 mm Hg in controls. As sign of a reactive hyperaemia after the end of exercise under resting conditions we measured an increase of $tcpO_2$ of 5.1 $\pm$ 8.5 mm Hg in patients

and of 8.03 ± 5.02 mm Hg in controls. Controls showed as a sign of increased perfusion – already higher values on exercise, whereas patients took an average time of 5.9 ± 5.6 min to reach the initial value after exercise. The measurement of $tcpO_2$ as a non-invasive test has proven to be a method to register the underlying cause of claudicatio pain qualitatively and to quantify an appearing ischemia on exercise. It is therefore still an appropriate method like it has been applied in former studies for the differential-diagnosis of intermittent exercise-induced leg-pain.

Laser-Doppler anemometry for measuring capillary blood cell velocity in human skin capillaries located perpendicularly to the skin surface

M. Stücker, V. Baier, T. Reuther, L. Schulze, K. Hoffmann and P. Altmeyer

Department of Dermatology, Ruhr-University Bochum, Germany

Capillary blood cell velocity (CBV) in human nailfold capillaries has been a parameter to measure blood flow for a long time. Measurement of CBV is now possible in capillary loops located at a 90° angle to the skin surface, by means of a new laser-Doppler anemometer.

The aim of this study was to evaluate this new device in a clinical situation, to control reproducibility and to compare our results with results obtained from previous studies using other microscopic techniques.

During rest mean CBV of 0.47 mm/s (SD ± 0.37 mm/s) could be measured. After cooling in a cold water bath at a temperature of 6°C and subsequent warming in a warm water bath CBV changed significantly. However, reproducibility was weak in these procedures. After suprasystolic occlusion a post occlusive reactive hyperemia could be seen. Peak values were 0.90 mm/s (SD ± 0.46 mm/s). The time to reach peak capillary blood cell flow (pCBV) was 24.9 s (SD ± 9.2 s). Reproducibility of both values was very high. Also, after application of an ointment consisting of a rubefacient a significant hyperemic response could be seen.

With laser Doppler anemometry it is possible to measure CBV in many other areas of the human skin than nailfolds. All measurements can be carried out online. Therefore, it is a useful tool to assess the microcirculation of the skin in the clinical situation.

Non-invasive measurement of endothelial function of the radial artery – the echo-tracking-system Nius 02

Ch. Thalhammer, B. Verges, K. Wagner, F.C. Luft and H. Haller

Franz-Volhard-Klinik, Humboldt-Universität, Wiltbergstr. 50, 13122 Berlin, Germany

Introduction: Endothelial dysfunction is an early defect in the development of atherosclerosis. Endothelium-dependent, NO-mediated vasodilation after ischemia is a method to evaluate the endothelial function of peripheral arteries. Endothelium-independent vasodilation can be measured after application of nitroglycerine. These functional tests are usually done with plethysmography or high-resolution ultrasound in the brachial artery. In contrast, the high-precision echo-tracking-system Nius 02 enables us to non-invasively test the endothelial function of the radial artery.

Methods: Investigation of the radial artery is performed in supine position after a resting period of 15 min in our vascular laboratory (constant temperature of 24°C). Continuous registration of the diameter curves of the radial artery is performed during an ischemic period of 3 min and application of 0.4 mg nitroglycerine.

Results: This new method helps us to measure the endothelium-dependent vasodilation after ischemia and the endothelium-independent vasodilation after sublingual application of nitroglycerine.

Conclusions: We present a useful non-invasive method to evaluate the endothelial function of the radial artery.

Nailfold capillaroscopy (NC) in lupus erythematodes (LE), rheumatoid arthritis (RA) and reactive arthritis (REA)

A. von Bierbrauer

Medizinische Poliklinik – Angiologie, Philipps-Universität Marburg, Baldinger Straße, 35033 Marburg, Germany

NC is a simple, non-invasive method for *in vivo* examination of the microvascular system in patients with collagen vascular diseases. It is widely accepted, that NC is of outstanding value for the diagnosis of scleroderma and Raynaud's phenomenon. However, in patients with LE, RA and REA no specific or even pathognomonic microvascular abnormalities can be detected. In 20–50% of the patients with these diseases the overall incidence of capillaroscopically detectable microvascular abnormalities is increased, compared to healthy controls. The most important morphological abnormalities are dysmorph capillaries (bushy, coiled and tortuous capillaries) and signs of disturbance of the endothelial barriere (microbleedings, perivascular edema). Macrocapillaries and avascular fields, which characteristically can be seen in scleroderma, are not found.

In LE there are morphological abnormalities of the capillaries in about 40% of the patients. There seems to be a positive association between capillary abnormalities and pulmonal involvement as well as between capillary abnormalities and anti-cardiolipin antibodies, both as a sign of systemic microvascular damage.

In uncomplicated RA, when comparing the whole collective with healthy normals a slightly increased incidence of morphological abnormalities can be observed. However, for the diagnosis in the individual patient NC in general does not seem to be very helpful. Only in complicated cases with accompanying rheumatoid vasculitis an increased number of dysmorph capillaries and microbleedings can be found. Concerning the value of NC in REAR there are existing only very few studies. These studies suggest that, e.g., in lyme-borreliosis, an increased number of bushy capillaries and microbleedings can be found, whenever the inflammatory process has become a systemic disease with the microvascular system as a mediator or target organ system.

In LE, RA and REA the diagnostic value of NC can be improved by intravital application of fluorescent dyes for examination of the trans-endothelial diffusion.

The influence of intermittent inhalative oxygen therapy on the transcutaneous oxygen pressure ($tcpO_2$ at 44°C) and laser-Doppler-flux in patients with peripheral arterial occlusive disease and neuropathy in the diabetic foot

A. Wagner, H. Reike, E. Rischbieter, H. Lawall, V. Wienhausen, M. Rottmann, H. Brill, A. Risse and B. Angelkort

Medizinische Klinik Nord, Städt. Kliniken Dortmund, Münsterstr. 240, 44145 Dortmund, Germany

In all lesions of the diabetic foot, those with peripheral arterial occlusive disease and neuropathy have the poorest prospects. The importance of revascularization, stage-guided wound care, normoglycemic metabolism, systemical antibiotics and pressure relief are proofed therapy options. A further improvement of the prognosis to reduce the amputation rate by new therapeutic options would be desirable. One of these options is the hyperbaric oxygen pressure therapy.

Method: Sixteen patients with diabetic foot including neuropathy and peripheral arterial occlusive disease (ten with upper-leg and lower-leg stenosis or occlusion and six with exclusively lower-leg stenosis) inhaled 100% oxygen with a respiration-mask for 15 min. Before, while, 30 and 60 min after inhalation the transcutaneous oxygen pressure ($tcpO_2$) and the laser-Doppler-flux was measured in the affected tissue. The lesions were classified according to the Wagner grades in the diabetic foot. Three patients had grade IV, four had grade III, five had grade II, one had grade I and three patients had grade 0. The mean Doppler-values were 70 mm Hg over the A. dorsalis pedis and 35 mm Hg over the A. tibialis posterior. Two patients suffered from mediasclerosis, so the mean Doppler-values for the remaining 14 patients were 50 and 42 mm Hg over the foot-arteries. That resulted in a mean ankle-brachial-index of 0.52 for all patients, excluding those with mediasclerosis where we found an index of 0.36.

Results: The transcutaneous oxygen pressure ($tcpO_2$ at 44°C) increased in the tissue of all patients, in which the increase was significant at all times of measurement. The mean value before inhalation was 57.5 mm Hg, it increased to 103.6 mm Hg during the inhalation and stayed high regarding the basal $tcpO_2$ with 65.2 mm Hg after 30 min and 60.8 mm Hg after 60 min. The flux-measurement started at 69.9 before inhalation, raised up to 82.4 during the inhalation and fell again to 73.3 and 72.2 after 30 and 60 min. We did not see any change in the flux-curves.

Conclusion: This pilot-study showed, that the inhalation of 100% oxygen over 15 min leads to a lasting increase of the $tcpO_2$ in the affected tissue in patients with diabetic foot. Therefore, the intermittent inhalation of oxygen could be an additional therapeutic option in these patients and be a low-priced alternative to the hyperbaric oxygen pressure therapy. Whether the increase of $tcpO_2$ leads to a better wound healing has to be examined in a further long-term study.

Comparison of parameters of rheology and coagulation in venous and arterial blood of patients with occlusive arterial disease

T. Woller[1], H. Lawall[2], B. Angelkort[2] and K. Mathias[3]

[1]Department of Children's Surgery;
[2]Department of Internal Medicine;
[3]Department of Radiology, Städtische Kliniken Dortmund, Germany

Introduction: Changes in rheology and an increased coagulability have been described in the blood of patients with intermittent claudication. All previous investigations have analyzed these in venous blood. The present study aims to compare the findings in venous blood with those in arterial blood in the affected limb.

Method: Venous and arterial blood samples from the most severely affected limb were taken from 22 patients with occlusive arterial disease. The following parameters were analyzed: α_2-macroglobuline, plasma viscosity, fibrinogen, circulating platelet aggregates, red cell aggregation, prothrombin fragment (F $1 + 2$), thrombin/antithrombin III-complex (TAT) and D-dimer.

Results: Increases above normal values were found for red cell aggregation, circulating platelet aggregates, F $1 + 2$ and TAT in both venous and arterial samples. Arterial samples showed significant elevations above the venous levels for TAT and F $1 + 2$, a similar trend was found for circulating platelet aggregates. A significant correlation between venous and arterial values was found only for α_2-macroglobuline, fibrinogen, D-dimer and red cell aggregation.

Conclusion: Blood from patients with occlusive arterial disease shows disturbances in rheology and increased coagulability. However, parameters determined from venous blood do not always correspond to those from the arterial side. A highly significant correlation was observed for fibrinogen, α_2-macroglobuline and D-dimer only. Activation of coagulation – clinically related to an increased risk of thromboembolic events – was particularly evident in the arterial blood of the group of patients studied here.

Neovascularisation and vascular functions in venous leg ulcers and in wounds

D. Zuder, A. Steins, T. Klyscz, M. Hahn and M. Jünger

Department of Dermatology, University of Tübingen, Liebermeisterstraße 25, D-72076 Tübingen, Germany

Introduction: Venous leg ulcers, in contrast to physiological wounds, are characterised by extremely prolonged healing and by a high recurrence rate. The disturbed cutaneous blood flow in CVI could be a reasonable cause. Therefore, we examined two patient-groups, one of which had patients suffering from venous leg ulcers. The other had patients with wounds after excision of cutaneous tumours. The study aimed to reveal various types of neovascularisation in the two types of wounds.

Patients: Ten patients (four female, six male) with CVI stage III after Widmer, average age 57.3 $\pm$ 9.7 years, mean ulcer size 7.9 $\pm$ 11.2 cm^2 and a mean healing time of 7.9 $\pm$ 4.6 weeks. By comparison we examined a group of eight patients (three female, five male) with wounds caused by skin surgery. Average age was 56.2 $\pm$ 20.8 years, mean wound area 25.8 $\pm$ 23.3 cm^2 and a mean healing time of 6.6 $\pm$ 2.1 weeks.

Microangiopathic changes were examined regularly by means of videomicroscopy, transcutaneous oxymetry and laser-Doppler-fluxmetry till the complete epithelialisation. The healing process in venous ulcers and wounds caused by surgery was accompanied by an increase of the nutritive cutaneous perfusion. This can be experienced by the clear increase of nutritive cutaneous capillaries and $tcpO_2$ increased in those wounds which healed fast. The cutaneous vascular reserve remained impaired in venous leg ulcers even after healing. On the contrary, in wounds after excision a cutaneous vascular reserve could be measured and it mounted to normal values after epithelialisation.

Conclusion: Delayed wound healing in venous ulcers seemed to be caused by a profound microangiopathy. Neovascularisation in venous leg ulcers remains reduced. A physiological density (30 cap./mm^2) could never be found. Physiological wound healing was accompanied by a quick increase of capillary density and $tcpO_2$. Cutaneous vascular reserve here was only restricted but never abolished. In venous leg ulcers a further increase of perfusion could not be provoked. Affected skin areas showed a persistent microangiopathy after healing. This might explain the high recurrence rate in venous leg ulcers.