Heat–washout: A New Method for Measuring Blood Flow Rate in Areas with and without Arteriovenous Anastomoses

Physiological and pathophysiological examinations

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Dekan

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III Midttun M & Sejrsen P. Cutaneous blood flow rate in areas with and without arteriovenous anastomoses during exercise. Scand J Med Sci Sports 1998; 8: 84-90.

IV Midttun M. Blood flow rate in arteriovenous anastomoses - from the cradle to the grave. Clin Phys 2000; 20; 5: 360-365.

V Midttun M, Sejrsen P & Paaske WP. Blood flow rate during orthostatic pressure changes in the pulp skin of the first toe. Eur J Vasc Endovasc Surg 1997; 13: 278-284.

VI Midttun M, Sejrsen P & Paaske WP. Peripheral blood flow rates and microvascular responses to orthostatic pressure changes in claudicants before and after revascularisation. Eur J Vasc Endovasc Surg 1999; 17: 225-229.

VII Midttun M, Sejrsen P & Paaske WP. Is non specific aneurysmal disease of the infrarenal aorta also a peripheral microvascular disease? Eur J Vasc Endovasc Surg 2000; 19: 625-629.

Preface

The work in this thesis was done from 1991 to 1998 in the Department of Medical Physiology, The Panum Institute, and in the outpatient department T, Skejby Hospital.

I am deeply indebted to Per Sejrsen, MD, MDSc, associate professor emer., for allowing me into his laboratorium, and for his continuos critical supervision of my work, for his never failing enthusiasm, for his friendship, and for always being there with answers for all my questions - his contribution can not be measured. I am deeply grateful to William Paaske, MD, professor, MD, MDSc, FRCS, FACS, for his never ending enthusiasm, inspiration, and critical comments to my work, his continuos support, and for giving me the opportunity to measure blood flow rate in "real patients" which was one of my ambitions. To Morten Colding-Jørgensen, MD, MSc, principal scientist, for through his critical comments to help me in the development of the heat-washout method. Many thanks to Annette Orth, medical technologist, for all her practical help and her friendship throughout my studies. To my good old friend, Lisbeth Nielsen, technical writer, for putting the finishing touches to all the figures and tables. To all my family and friends who patiently let me examine their blood flow rates. Thanks to the clinical staff in the outpatient department T, Skejby Hospital, for always being so kind and helpful during my examinations there. And to the patients who came from far way to let me measure their blood flow rates. Many thanks to my husband, Jens Kristian Weidlich, B.SC.Eng. (hon), B. Com. for his continuous support, computer help, and for just being there.

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To Jens Kristian, Viktoria, and Kristin.

Physiological Examinations

Introduction

Throughout the years various methods using heat as an indicator for measuring blood flow rate have been described.

Gibbs (1933), Stow and Shieve (1959), and Perl and Cucinell (1965) measured temperature differences between tissue and blood in three different ways. Gibbs (1933) introduced a thermoelectric blood flow recorder consisting of a needle, supplied with a constant amount of heat, that was thrust into a vessel or into a tissue through which blood was flowing. The temperature varied with blood flow rate. By measuring the temperature of the needle it was possible to obtain an index of the blood flow rate. Stow and Schieve (1959) introduced the thermometer-heater unit. The method applied the Fick's principle to the heat flow in a local tissue site. During the measurements a needle thermometer was inserted into the skin of the calf. "Blood flow" rates were calculated before and after blood flow cessation of the calf. Perl and Cucinell (1965) introduced a somehow similar method consisting of two thermistor-containing needles, one of which was heated by constant electrical power input. The needles were inserted into the gastrocnemius muscle. The temperature of both thermitors was recorded continuously. After occlusion of the blood flow to the leg, each temperature vs. time plot exhibited a change of slope. The change of slope of the temperature difference, divided by the temperature difference (°C (min · °C)$^{-1}$) was identified with the local perfusion (ml(min ·ml)$^{-1}$) existing just before occlusion. These methods were all based upon two measurements, one with blood flow, and one during blood flow cessation. The difference between these two measurements were assumed to be the heat elimination rate.

Hensel and Brandt (1977), and Corcoran et al. (1987) measured temperature differences between heated and unheated discs. Hensel and Brandt (1977) introduced a 6-plate element that measured the average temperature difference between the heated and the reference plates, and Corcoran et al. (1987) introduced a method for measuring thermal clearance. The trans ducer measured the temperature difference between a copper disc at its centre, in thermal contact with a heating coil, and an unheated concentric copper annulus at its periphery, both of which were in direct contact with the skin.

Other methods and variations of methods have been described as well (Mendlowitz 1954, Coffmann, 1972, Adams et al., 1980, Hirata et al., 1988, etc.). In 1949 Kety related the rate of washout of the radioactive isotope ^{24}Na from muscle tissue to the blood flow through the tissue. However ^{24}Na is not freely diffusible and can therefore not be used for quantitative measurements (Sejrsen, 1971). Subsequently Sejrsen introduced the ^{133}Xe-washout method in 1968, and until now this has been the only atraumatic method capable of measuring absolute skin blood flow rate in ml(100 g · min)$^{-1}$. Due to a relatively slow diffusion coefficient of ^{133}Xe, the ^{133}Xe-washout method is not capable of measuring blood flow rate in cutaneous tissues containing arteriovenous anastomoses (AVA's) though. In comparison heat diffuses about 100 times faster than ^{133}Xe, and was therefore found useful as an indicator of blood flow rate in AVA's.

Aims of the present review.

1) The aims of the study was to descreibe the heat-washout method.

2) To validate the heat-washout method by comparing the method to the ^{133}Xe-washout on the forearm at increasing local temperatures.

3) To describe the usefulness of the heat-washout method during a series of physiological and pathophysiological studies, and describe the advantages and the disadvantages of the method.

4) To study blood flow rate in the AVA's in the thumb pulp, the pulp of the first toe, ear lobe, nose, and other locations of the face in healthy subjects.

5) To study blood flow rate in the AVA's of the thumb pulp and the capillaries of the skin fold between the thumb and the index finger during exercise in healthy subjects.

6) To study blood flow rate in the AVA's of the pulp of the first toe of 15 children, and 16 adults aiming at possible differences in blood flow rate related to age or gender.

7) To study blood flow rate in AVA's and capillaries of the cutaneous tissue of the first toe in patients with intermittent claudicatio and critical ischaemia compared to healthy subjects at orthostatic changes.

8) To study blood flow rate in AVA's of the first toe in patients with intermittent claudicatio before and after surgical reconstruction.

9) To study blood flow rate the pulp of the first toe and in the subcutaneous capillaries of the interstice between the first and the second toe during orthostatic changes in patients previously operated for a ruptured abdominal aneurysm in order to examine whether they had a peripheral microvascular component or not. The structural differences between the wall of the AVA's and the arterioles were used. The results were compared to healthy subjects.

The ^{133}Xe-washout method - used for validation of the heat-washout method.

Basically the heat-washout method is analogous to the ^{133}Xe-washout method, therefore the ^{133}Xe-washout method will be described first. The most striking difference between the two methods is that the former method uses heat as and indicator, and the latter uses ^{133}Xe.

The ^{133}Xe-washout method was introduced by Sejrsen in 1968 as an atraumatic method for determination of absolute blood flow rate in cutaneous and subcutaneous tissues in human skin.

In the present investigations blood flow rate was measured by atraumatic labelling of the skin with ^{133}Xe dissolved in isotone saline. A round diffusion chamber, with of diameter of 1.2 cm made by a 20 μm thick gas-tight Mylar membrane was mounted on the skin by double-sided adhesive tape, and 0.1 - 0.2 ml of ^{133}Xe (initial activity of about 555 MBq · ml^{-1}) was introduced through a needle sewn through the tape. After 3 min the solution was aspirated through the needle, the chamber removed, the area wiped off, and the surplus of ^{133}Xe blown away (Sejrsen, 1968).

Subsequently ^{133}Xe-washout was registered in periods of 10 or 20 s for usually 60 min by external recording of the γ-emission by use of a scintillation detector (Meditronic, Denmark) with a NaI (Tl) crystal coupled to a ratemeter adjusted around the 81 kev γ-peak of 133Xe. The detector was placed in a fixed distance of about 5 - 10 cm from the labelled area, ensuring a constant geometry during washout. Wide collimation was used, and thereby combined local convection and diffusion was minimized (Bojsen, 1985). After subtraction of the background activity, the count values were plotted in a diagram with a logarithmic y-axis against time on a linear x-axis. The biexponential curves were analysed as described previously by Sejrsen (1969, and 1971). Using curve resolution (Sejrsen, 1969, Henriksen et al., 1986) blood flow rate f_{Xe}, in the cutaneous tissue was calculated using the slope of the fast component, k_{Xe} (min^{-1}), and the Kety local washout principle, $f_{Xe} = k_{Xe} \cdot \lambda_{Xe} \cdot 100$ ml (100 g · min)$^{-1}$ (Kety, 1949). λ_{Xe} is the tissue to blood partition coefficient for ^{133}Xe. A λ_{Xe} -value of 0.7 (ml · g^{-1}) for ^{133}Xe was used for cutaneous tissue (Sejrsen, 1971).

There was practically no recirculation of ^{133}Xe since ^{133}Xe removed from the field by the blood stream will pass from the blood to the alveolar air in the lungs and be exhaled at first lung transit, and the amount of recirculation will be insignificant.

The ^{133}Xe-washout method itself does not change local skin temperature, and veins in the area do not have any influence on the results. It takes about 45 - 60 min to make a sufficient cutaneous and subcutaneous curve, and subsequently curve resolution is demanded. Making a washout curve from the cutaneous tissue between the thumb and the forefinger takes only 20 min. It is very important that the distance between the skin measured on and the defector is kept constant throughout the entire examination. Changing the distance will increase or decrease the counts registered, and consequently change the result. Therefore the subject measured on has to be completely immobile during the entire measuring period.

By heating the area of study with the heat-washout probe (described in detail below) to a predestined temperature between 37 and 45°C for 10 min, it was possible to measure skin blood flow rate with ^{133}Xe at different local temperatures. After ^{133}Xe-labelling the probe was replaced on to the area within 10 s, and heating was continued during the entire washout period.

The heat-washout method

A Clark type electrode E 5250 developed by Radiometer a/s, Copenhagen, Denmark, was used. Originally the probe was constructed for measuring transcutaneous oxygen tension (tc-PO_2-electrode) (fig.1a), and was used experimentally by Jaszczak & Baumback in 1985. The probe produces heat from an internal heating element, and measures local skin temperature to a depth of 3 mm. (Jaszczak & Poulsen, 1981). To minimize heat loss to the surroundings the probe is constructed with a thermostatically controlled cap covering all surfaces of the probe, except for the one in contact with the skin, resulting in heat delivery in one direction only (to the skin). The cap ensures isothermal conditions in the cap and in the probe. The outer diameter of the probe was 2.3 cm, and the central measuring plate 1.0 cm. During heat-washout measurements the tc-PO_2-part was inactivated. The probe was mounted upon the skin with a double-sided, adhesive, ring shaped membrane and silktape. Contact fluid was interposed between the probe and the skin. To ensure a constant and low fixation pressure of 2.5 $g \cdot cm^{-2}$ ($\approx$ 2 mmHg) a spring in a plastic cylinder was mounted on top of the probe. As it did not matter whether the spring was mounted or not, it was only used during the first study.

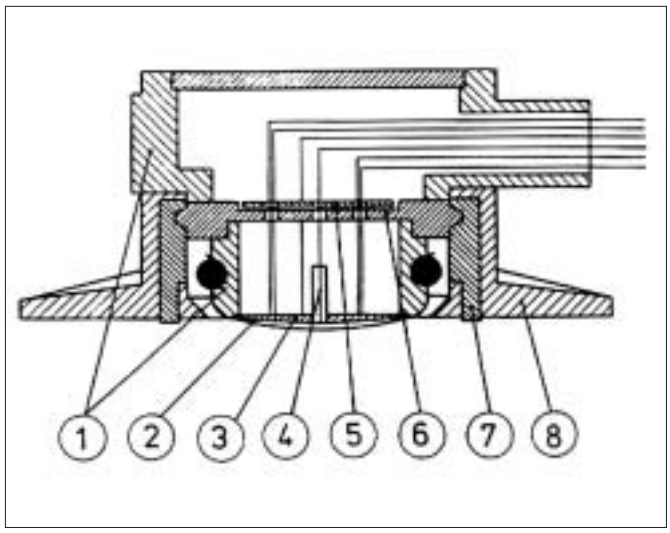

Fig. 1a. The Radiometer E5250 tc-PO2-electrode used for heat-washout measurements. The probe consists of (1) plastic housing, (2) polypropylene membrane, (3) ceramic sensor substrate, (4) platinum cathode, (5) heater substrate, (6) heat shield, electrode part, (7) heat shield annular part, (8) skin fixation ring. The thermosensor is no (4), and the thermostatically controlled cap is no. (5), (6), and (7). The illustration is copied from Jaszczak & Poulsen, 1981. (Midttun et al. 1996).

When the measurements were made on small fingers and toes, three cotton strings were placed along the circumference of the cap of the probe for insulation. During measurements performed on the forearm, a lead shield formed as a half cylinder was placed around 2 cm distally and to the sides of the probe to avoid the influence of blood passing the area in the venous rete. The shield was 7 cm in diameter, 12.5. cm in height, 3 mm in thickness, had a sharpened edge of 1 mm, and was exerting a pressure of about 300 mmHg.

During all measurements room temperature was kept constant at about 21 - 24°C. When nothing else is indicated, the subjects were wrapped in a thermic blanket and ordinary blankets to keep him or her in thermic steady state with warm hands and feet throughout the measurements in order to obtain the highest possible blood flow rate in the AVA's.

The heat-washout measurements were performed as follows: The probe was mounted on the skin, and after a few minutes, a baseline skin temperature, T_b, was recorded. Next the probe was heated for 3 - 5 min until the probe and the underlying skin had reached a predetermined steady state temperature (usually 41 or 43°C) as evidenced by constant heat dissipated from the probe. The heat was then turned off, and the temperature, T, was recorded every 10 s until a stable baseline temperature, T_b, was obtained. The baseline temperature was usually equal to the temperature before heating, but as the probe reduces heat loss from the skin under the probe, and local temperature and metabolism increase slightly (please see below), the local temperature may change ± 0.1 - 0.2°C. This does not influence the final result. T_b gives a straight line when plotted in a semilogarithmic diagram with time on the x-axis, indicating exponential heat-washout. If T_b differs from the T_b registered before start, the difference must be corrected by subtracting or adding 0.1 - 0.2°C. The first one or two points of the washout curve were usually just above the line. They were presumably caused by heat equilibration between the probe and the tissue, and were not included in determination of the slope. The experiments described below have shown that when measuring in areas with high blood flow rates (thumb pulp), blood flow rate can be calculated using only the first 3 - 4 points registered after the calibration period. This indicates that a difference between the two T_b's registered does not influence the final result. In areas with lower blood flow rates (the arm) more points have to be included due to a longer washout period (fig.1b).

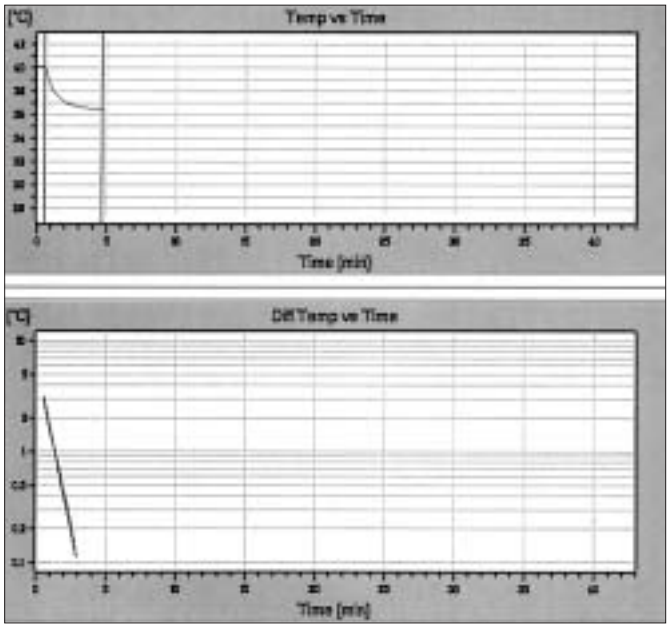

Fig. 1b. Heat-washout from the pulp of the thumb - (upper curve) the heat-washout curve and (lower curve) the curve plotted in a semilogarithmic diagram.

Just like the ^{133}Xe-washout calculations, blood flow rate was calculated using the formula of Kety (1949), $f = k_{heat} \cdot \lambda_{heat} \cdot$ 100 ml (100 g · min)$^{-1}$ for local washout . The tissue to blood partition coefficient for heat, λ_{heat}, is 0.954 (ml·g^{-1}) (Perl & Cucinell, 1965). To simplify, a value of 1 (ml·g^{-1}) was used.

When studying blood flow rate using indicators, certain assumptions about the system and the indicator have to be made (Kety, 1949, Henriksen et al., 1986). To avoid blood flow rate changes throughout the experiment, the subject must be in a thermic **steady state** (positive heat balance) throughout the duration of the entire measurement to ensure the highest possible and most stable blood flow rate in the AVA's. This is ensured by a constant room temperature, and that the measurements are not started until the subject wrapped in blankets has warm hands and feet. The subject must not drink or eat during the examination. Throughout the washout period **equilibrium** for the indicator (heat) must be maintained between tissue and blood. This is possible due to the high diffusion coefficient of heat being about 100 times faster compared to gases, which favours a rapid equilibration of heat between tissue and blood during the washout period. The indicator (heat) must **not disappear** by any other way than by the blood stream. The only way heat can be removed from the area under the probe is by the blood stream, and by heat conduction. A small heat-loss from the probe to the surrounding air, and a small conductive heat loss to the surrounding air, via the probe and the tissue was registered (see experiments described below), but for practical purposes heat loss due to conduction and convection is insignificant. The heat produced by tissue metabolism is minimal and does not influence the result. About 1500 kcal are used per 24 hours by a person of 70 kg. This corresponds to 0.015 cal(g · min) $^{-1}$. It takes 0.89 cal to increase 1 g of tissue 1 °C. An increase in tissue temperature of 10°C results in an increase of the metabolic rate of about a factor of 2 (Kruhøffer P, 1970, Jaszczak P, 1987). In the present investigation the tissue temperature was increased about 5°C, corresponding to an increase in the metabolic rate of about 50% corresponding to about 0.0075 cal(g· min)$^{-1}$. The result of heating in a 10 minutes period will be an increase in the tissue temperature of about 0.1°C. Corrections performed for changes in the baseline temperature will eliminate this effect. This has also been the size of the corrections made due to changes in the baseline temperature in the performed study. **Homogeneity** of the system is required, i.e. when tissue (skin) elements of various types are present (epidermis, corium, sebaceous glands, hair follicles, sweat glands, etc.), they have to be registered by equal effectiveness. The **partition coefficient**, λ_{heat}, for the indicator between tissue and blood has to be known. This value was taken from the data of other investigators (Pearl & Cucinell, 1965). Registration of the washout curve is crucial. The linear slope over more than two decades of the heat-washout **curve** in a semilogarithmic plot indicates a high degree of monoexponentiality, equal to a first order washout process.

Experiments

The following studies were made to evaluate the heat-washout method per se, and to compare the method to the ^{133}Xe-washout method.

All experiments in this thesis were approved by the local Ethical Committee, and the use of ^{133}Xe by the Danish Isotope Committee as well. All subjects gave their informed, written consent. When children were examined a parent gave his or her informed, written consent. The experiments were made in two subjects and in a sitting position when nothing else is indicated.

In vitro experiment with the heat-washout method.

To study the magnitude of heat loss from the heat-washout probe itself to the surroundings during heat-washout, the following experiment was per-

formed once. In a room with a temperature of 24°C the probe was mounted on a cube of polystyrene and heated to 43°C for a couple of minutes. The heating was turned off, and the slope of the "heat-washout-curve" was calculated with the room temperature as baseline temperature, Tb, resulting in a heat loss corresponding to a blood flow rate of 0.2 ml(100 g · min)$^{-1}$. This result was taken as an expression of the heat loss from the probe itself during washout, and is estimated to be about that size during washout from human skin as well.

Experiments made on the volar side of the forearm.

To determine the *conductive heat* loss from the tissue of the heated area on the forearm to the surroundings the following experiment was performed: "Blood flow rate" was measured by the heat-washout method on the forearm during 10 min of blood flow cessation induced by a blood pressure cuff mounted on the upper arm and inflated to 230 mmHg. The probe was heated to 37, 39, 41, 43, and 45°C before "washout" was started. The room temperature 24°C was used as baseline temperature, T_b, as this was expected to be the baseline temperature, if it were possible to continue the "washout curve" till the end, but due to discomfort in the arm of the subject, the measurement was continued only for 10 minutes. The measurements were made once at each temperature level, and resulted in a heat loss corresponding to a blood flow rate of about 1 ml(100 g · min)$^{-1}$, (mean 0.7, median 0.7 ml(100 g · min)$^{-1}$ in subject 1, and mean 1.4, median 1.3 ml(100 g · min)$^{-1}$ in subject 2).

Before measurements were made with the two methods simultaneously, *capillary* blood flow rate was measured separately by ^{133}Xe in the forearm after preheating the area to 39, 41, and 43°C, respectively, for 10 min. ^{133}Xe-washout registrations were made for 60 min. The measurements were taken once in each subject. Blood flow rate turned out to be 15.0, 26.7, 41.5 ml(100 g · min)$^{-1}$ at the three temperatures, respectively, in subject 1, and 19.4, 22.3, and 44.9 ml(100 g · min)$^{-1}$ in subject 2.

Measurements made simultaneously with the heat-washout and the ^{133}Xe-washout method

on the volar side of the forearm. The area was preheated for 10 min at a predetermined temperature (37, 39, 41, 43, and 45°C) and during ^{133}Xe-labelling. To avoid uptake of ^{133}Xe in the plastic material of the probe, the adhesive fixation ring and the hole of the ring was covered with a 20 μm thick gas-tight Mylar membrane. Subsequently ^{133}Xe-washout was started, and after mounting the heat-washout probe on top of the area labelled with ^{133}Xe, heat-washout was initiated 3 min later. ^{133}Xe-washout registrations were made for 60 min, and heat-washout until at stable baseline temperature, T_b, was obtained. The measurements were made twice at each temperature, and the results are shown in fig. 2. When the preheating temperature was low (37°C), the ^{133}Xe-washout curve from cutaneous tissue lasted about 20 min, and when the local preheating temperature was high (45°C), ^{133}Xe-washout lasted only 9 min. At unheated skin ^{133}Xe-washout from cutaneous tissue lasted about 30 min.

A linear regression analyses, using the least squares, resulted in a correlation coefficient between the results obtained with the two methods of 0.986. The correlation line had a slope of 0.968, SD± 0.037, and an intercept with the y-axis of 2.50, SD± 1.28, n = 21, t = 24.8 (p<0.001). The line does not go through 0.0 due to a small heat loss to the surrounding air via the probe and the tissue as described above (fig. 2). Using a Bland Altman plot as shown in fig. 3 it is demonstrated

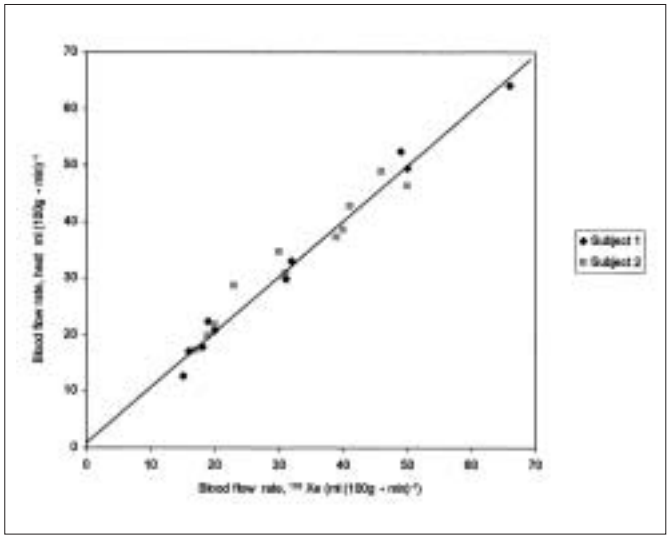

Fig. 2. Heat-washout and ^{133}Xe-washout measurements performed simultaneously on the forearm during occlusion of blood in the venous rete by a lead shield. A linear regression analysis using the method of least squares, resulted in a correlation coefficient of 0.986, t = 24.8 (p<0.001). The slope of the line is 0.968, SD±0.037, and the intercept on the y-axis is 2.50, SD±1.28, n = 21. ♦ = subject 1, from the left to the right, is obtained at the following temperature levels: 37, 37, 39, 41, 41, 39, 43, 43, 45 and 45°C. Subject 2, n, *from the left to the right was obtained at the following temperatures 37, 37, 39, 41, 39, 41, 43, 43, 43, 45, and 45°C.*
(Midttun et al. 1996)

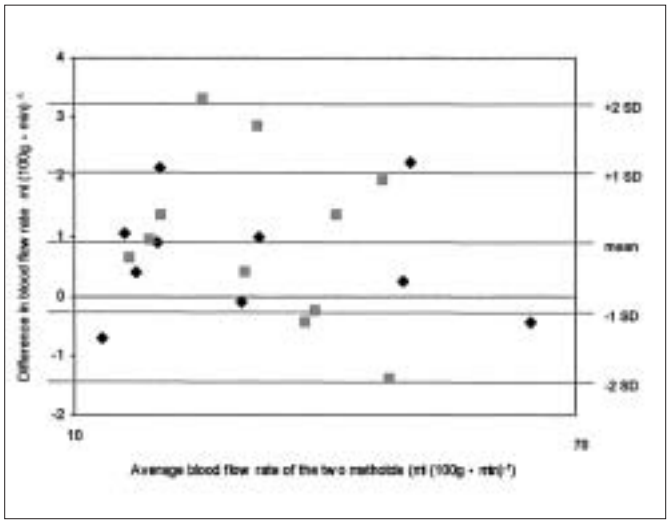

Fig. 3. Bland-Altman plot.
Subject 1, t . Subject 2, n.

that all but one of the results were within the limit of 2 SD.

Experiments made on the skin fold between the thumb and the forefinger

To examine capillary blood flow rate in an area consisting of a cutaneous layer only, measurements were made on the skin fold between the thumb and the forefinger. The proximal part of the hand was covered by a 3 mm thick lead shield, leaving 2 - 3 mm of the skin fold uncovered (Sejrsen, 1969). The measurements were made three times in each subject. The area under study was preheated to 43°C for 10 min before labelling and ^{133}Xe- washout was initiated. This resulted in a mean blood flow rate of 32.3 ml(100 g · min)$^{-1}$, (median 30.6 ml(100 g · min)$^{-1}$) in subject 1, and 34.3 ml(100 g · min)$^{-1}$ (median 38.2 ml(100 g · min)$^{-1}$) in subject 2. Due to the hyperaemia created during heating, these blood flow levels were observed to be constant for around 10 min before they started decreasing.

Summary

In the present study heat was applied to the skin using an atraumatic technique. The analysis of the experimental results were based on well known and experimentally validated general indicator kinetic principles for radioactive indicators. In principle, the experiments were analysed in kinetic terms as local saturation, external (residue) detection experiments in analogy to the well known and widely used Kety (1949) principle for measuring local blood flow rate.

The results seem to confirm that the heat-washout method is useful for measuring local, cutaneous, capillary, blood flow rate at local temperatures between 37 and 45°C. There is only a small insignificant conductive heat loss to the surroundings via the probe and the tissue (about 1 and 1,4 ml(100 g · min)$^{-1}$, respectively)). It may be stated that blood flow rate decreases during temperature decrease when the heating is turned off during washout registration. However, ^{133}Xe-washout measurements made after atraumatic labelling of the skin fold between the thumb and the forefinger (an area consisting of a cutaneous layer only), and 10 min preheating to 43°C before ^{133}Xe-washout was initiated, have shown a constant and elevated blood flow rate during about 10 min (the hyperaemic period) even though heating is discontinued. Similar measurements were made on the forearm, where a similar steady-state washout period following 10 min of preheating at various temperatures was observed during the hyperaemic period. When the preheating temperature was low (37°C), the ^{133}Xe-washout curve from cutaneous tissue lasted for 20 min. If the local preheating temperature was high (45°C), this period lasted only 9 min. From unheated skin ^{133}Xe-washout from cutaneous tissue lasted about 30 min. Previous studies have shown a period of constant and elevated blood flow rate during 20 min following hyperaemia due to a trauma caused by intracutaneous injection of ^{133}Xe dissolved in isotonic saline into the skin fold between the thumb and the forefinger (Sejrsen, 1969, and 1971). The results in the present study indicate that the heat-washout measurements on the forearm, lasting from 5 - 10 min take place during the hyperaemic period, a period with an apparently constant and elevated blood flow rate, even though the local temperature is decreasing. The explanation of the constant and elevated blood flow rate is most probably due to metabolites produced during the heating period, causing a local trauma. When measuring outside AVA's visible veins have to be excluded. The subject must be in a thermic steady state, but does not have to be immobilised during the examinations that takes from 5 to 20 min dependent on the region examined.

As the heat-washout method itself increases local capillary blood flow rate in the area under the probe, it is preferable to measure blood flow rate in areas dominated by AVA's (finger and toe pulps) that are under central control (see below).

Arteriovenous anastomoses

After validation of the heat-washout method in skin areas without AVA's, measurements were made on the pulp of the thumb, an area with multiple AVA's, in order to measure absolute blood flow rate in these vessels.

The presence of AVA's in the hands and nose were described for the first time in 1862 by Sucquet. Hoyer published his classical description of AVA's using intravascular injection techniques and three-dimensional microscopic studies of sectional material in 1877. Grand observed living AVA's in the rabbit ear in 1930, and Popoff described the AVA's throughly in "The digital vascular system" in 1934, (fig. 4), (Hale and Burch, 1960). In modern literature, J.R.S. Hales is one of the predominant characters concerning studies of AVA's (Hales, 1985).

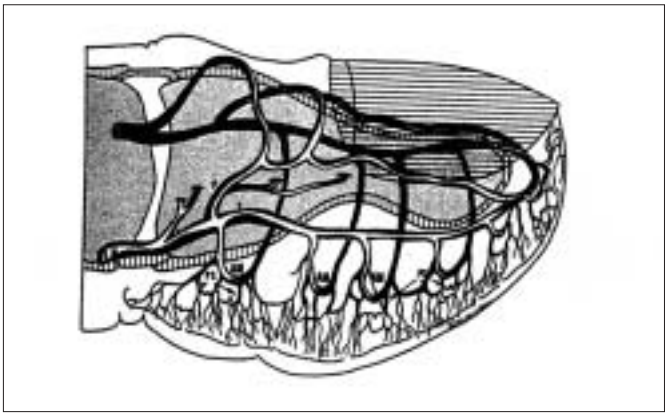

Fig. 4. Thumb pulp with AVA's (AM). Illustration from Hale 1960.

AVA's are vessels with a thick muscular wall and a luminal diameter of about 20 - 70 μm, average 35 μm. They are located in the cutis, especially in the pulp of the fingers and toes, in the nose, and in the ear lobes (Grant & Bland, 1931). As previously mentioned it is not possible to measure blood flow rate in areas with AVA's with the ^{133}Xe-washout method because of their large diameter. The diffusion coefficient for ^{133}Xe in tissue is about $0.6 \cdot 10^{-9}$ $m^2 \cdot s^{-1}$ (Sejrsen & Tønnesen, 1968), and therefore it is not possible for the AVA's to obtain equilibration of ^{133}Xe-gas between tissue and the flowing blood. Only a very short period in the initial ^{133}Xe-washout phase can be influenced partly by blood flow in AVA's. Heat has a diffusion coefficient of 10^{-7} $m^2 \cdot s^{-1}$, which makes a heat equilibration between tissue and the flowing blood possible. Blood flow rate in AVA's is dependent on core temperature and sympathetic activity, but independent of local temperature (Hales, 1985, Hales & Molyneux, 1988).

Various methods for measuring blood flow rate in regions with AVA's have been suggested. In 1954 Mendlowitz used venous occlusion plethysmography on the distal half of the terminal phalanx of the second finger. The results were given with the dimension $cm^3 \cdot cm^{-2} \cdot min^{-1}$. Using a thickness of the cutaneous tissue of 2.5 mm in that region resulted in a value of about 100 $ml(100\ g \cdot min)^{-1}$. Measurements made with calorimetry in the same region by the same author gave similar results (Mendlowitz, 1954). In 1972 Coffman used venous occlusion air plethysmography and local injection of $Na^{131}I$ for measuring total and nutritional finger tip blood flow rate. It was concluded that the methods used were only approximations, and they were unable to quantify blood flow rate in AVA's and in the nutritive capillaries. $Na^{131}I$ is not freely diffusible in the tissue and an equilibrium between tissue and blood during washout was consequently not obtained. In 1987 Midtgård et al. used microperes for measuring absolute blood flow rate in AVA's of sheep, but as the animal had to be killed afterwards the method was not useful in human studies. Laser-Doppler used by Hirata et al. (1988) is not suitable for quantitative measurements, because the method measures blood flow in an uncertain depth (Hales et al., 1993).

Finger venous occlusion plethysmography.
For further validation of the heat-washout method it was compared to finger venous occlusion plethysmography, that quantifies total blood flow rate of the distal part of the phalanx of the thumb. The measurements were performed as follows: A thermocouple for temperature measurement was placed on the pulp of the distal phalanx of the first finger after introduction into a cylindrical plastic chamber. The chamber used by subject 1 was 25 mm in length and 20 mm in diameter, and for subject 2, 36 mm in length and 26 mm in diameter. The proximal opening of the chamber was tightened to the skin surface by Secomastic padding. A polyethylene catheter was used to connect a Statham P23BB pressure transducer to the distal end of the chamber. The chamber and catheter were filled with water. The pressure registrations were made by a Servogor pen-writer (Goerz Electro, Austria). Calibrations were made by introducing 0.1 - 0.3 ml of additional water, from a syringe, into the system. A finger cuff of 20 · 100 mm was fixed around the proximal phalanx of the thumb. The inflowing blood volume per unit of time in the distal phalanx of the thumb was

registered after a fast inflation of the finger cuff to a pressure of 50 mmHg. The procedure was repeated ten times with an interval of 10 - 15 s.

To calculate the inflow of blood per unit of time, a straight line was drawn between the beginning of the upstroke of the two first fully registered pulse waves. This procedures gave an average of inflow of blood per unit of time to the finger segment within the first pulse wave after cuff inflation. A mean value of 10 measurements was calculated. To calculate blood flow rate in the distal phalanx of the thumb in ml(100 g · min)$^{-1}$, it was introduced into a water filled, graded cylinder glass. The volume of the finger segment was calculated from the water volume displaced by the finger segment.

Experiments made on the thumb by venous occlusion plethysmography

All measurements were made with the arm placed at heart level. The finger was placed in a water bath with the temperature increasing from 36 - 43°C in subject I, and from 36 - 41°C in subject 2. The measurements were taken at 1°C intervals, 10 times at each temperature. Furthermore finger venous occlusion plethysmography measurements were made during arterial occlusion using a cuff on the upper arm inflated to 230 mmHg, followed by inflation of the finger cuff to 50 mmHg. The results are shown in fig. 5. Blood flow rate varied with temperature from 32.7 to 49.7 ml(100 g · min)$^{-1}$ in subject 1, and from 36.9 to 63.5 ml(100 g · min)$^{-1}$ in subject 2. During arterial occlusion it was observed that a subsequent inflation of the finger cuff to 50 mmHg yielded an increase in the registered pressure curve of the plethysmograph. The result of the squeezing varied with the temperature. The squeezing effect differed between the two subjects, with the smallest contribution from the finger with the smallest dimension. The effect resulted in an increase of blood flow rate of around 5 ml(100 g · min)$^{-1}$ for subject 1, and 10 ml(100 g · min)$^{-1}$ for subject 2. The squeezing effect has been corrected in the fig. 5. The results were lower than those obtained by others (Mendlowitz, 1954), presumably because of the correction for the squeezing effect, and because more of the proximal part of the phalanx was included in the plethysmograph in Mendlowitzs study (1954).

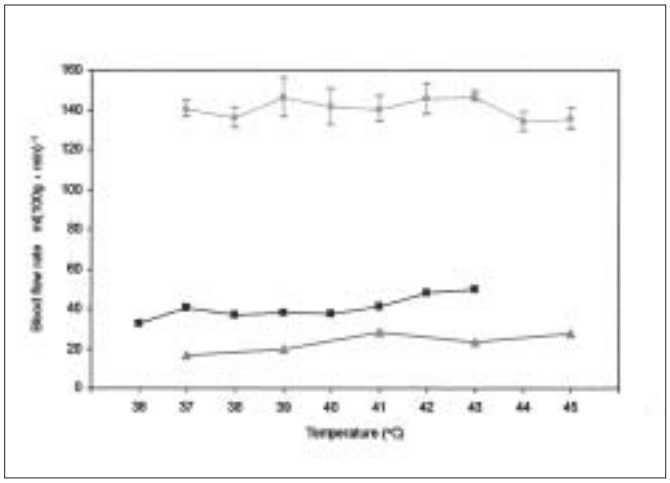

Fig. 5. Blood flow rate in ml(100 g · min)$^{-1}$ in the thumb pulp measured by the ^{133}Xe-washout method, ▲, at 37 - 45°C, by the venous occlusion plethysmography, ■, at 36 - 43°C, and by the heat-washout method, •, at 37 - 45°C, ± SEM given as bars.
(Midttun & Sejrsen 1996).

Experiments made on the thumb pulp by the ^{133}Xe- and the heat-washout method

To validate the contribution of capillary blood flow rate to the total blood flow rate measured by the heat-washout method at different local temperatures the present experiments were performed. The measurements were made as previously described for the forearm with local heating of the thumb pulp to 37, 39, 41, 43, and 45°C before and during ^{133}Xe-washout from the cutaneous capillaries. The measurements were performed twice at each temperature. Blood flow rate was from 16.7 to 27.8 ml (100 g · min)$^{-1}$ in subject 1, and from 13.9 to 21.4 ml (100 g · min)$^{-1}$ in subject 2. The results from subject 1 are presented in fig. 5.

Experiments made on the thumb pulp by the heat-washout method

In 10 subjects (5 men, mean age 45, and 5 women, mean age 40) heat-washout measurements were made starting at 37, 39, 41, 43, and 45°C. In subjects with a high baseline temperature, the lowest temperature used was 38°C. The measurements were performed once at each temperature level. The results are given in fig. 6, confirming that blood flow rate in the AVA's are independent of local temperature.

In two subjects similar measurements were performed five times at each temperature level. The results of the latter are presented as $\Delta T = T - T_b$ on a logarithmic scale against time, see fig. 7. Blood flow rate varied from 148.5 to 160.0 ml(100 g · min)$^{-1}$ with a mean value of 152.6 ± 2.2 (SEM) ml(100 g · min)$^{-1}$ for subject 1, and from 94.5 to 106.6 ml(100 g · min)$^{-1}$ with a mean value of 102.6 ml ± 2.2 (SEM)(100 g · min)$^{-1}$ for subject 2.
The results are in accordance with those in the ten

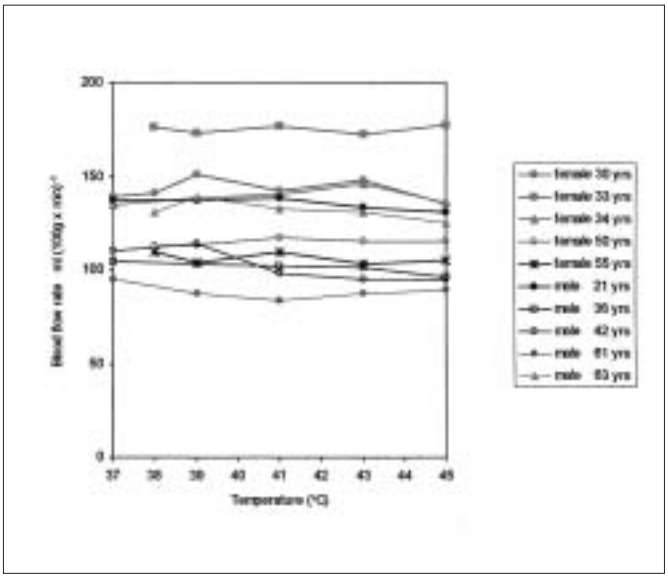

Fig. 6. Blood flow rate in the pulp of the thumb in 10 subjects, 5 women, and 5 men, measured by the heat-washout method at temperature levels from 37 to 45°C at heart level. In subjects with a high baseline temperature, 38°C was used as the lowest temperature level. Given from the top, on the right side of the page: women no 1, 2, 3, 6, 7 (age 33, 34, 30, 50, 55). Men no. 4, 5, 8, 9, 10 (age: 21, 63, 36, 42, 61). (Midttun et al. 1996).

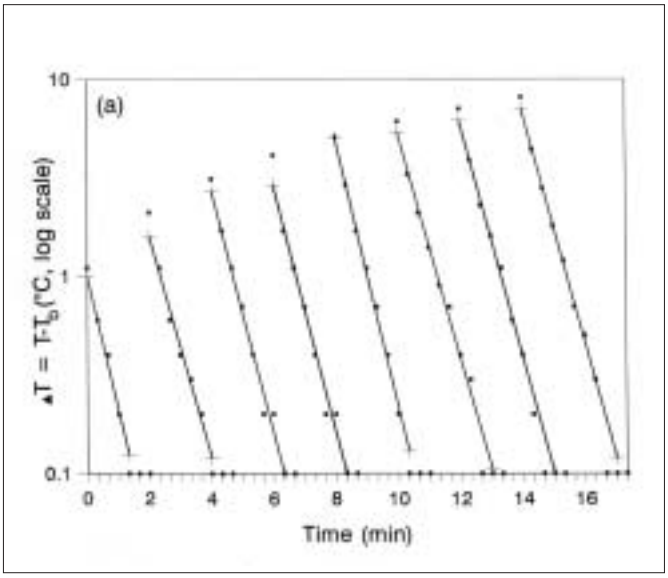

Fig. 7. Heat-washout curve from the pulp of the thumb after heating the probe to 38, 39, 40, 41, 42, 43, 44, 45°C, respectively, before washout. The measurements are carried out successively within a 2 h period. To present the results from the subject in a single figure, the curves are plotted with a time interval of about two min between the start points of the curves. The ordinate is the difference, ΔT, between the measured temperature, T, and the baseline temperature, T_b, ($\Delta T = T - T_b$) given in a logarithmic scale. The abscissa is time in minutes in a linear scale. The crosses indicate the start and the end of the calculated regression line.
(Midttun et al. 1996).

subjects above. The variation in blood flow rate was due to a slight increase in capillary blood flow rate in the region caused by increased local temperature.

Blood flow rate in AVA's was obtained by subtracting the blood flow rate values obtained by the ^{133}Xe-washout measurements on the thumb pulp (around 20 ml(100 g · min)$^{-1}$), from the results obtained by the heat-washout method. The capillary contribution was relatively small compared to the total blood flow rate measured and may therefore usually be ignored.

Local heating does not change blood flow rate in the thumb pulp in contrast to in the forearm, because blood flow rate in AVA's is independent of local temperature changes (Hales 1985, Hales & Molyneux, 1988) contrary to the capillaries where blood flow rate increase with increasing local temperature. Therefore the heat-washout method seems suitable for measuring local blood flow rate in areas with AVA's.

In areas with AVA's a stabel heat gradient is created during heating. When the heating is turned off, the surplus of heat will be washed away by the flowing blood having a lower temperature than the heated tissue area. This is the basis of the heat washout curve. When the registration was performed in areas with capillaries, an elevated blood flow rate is created in the tissue under the probe. This is presumably due to the increased temperature and metabolism resulting in an increased contents of metabolites in the tissue resulting in arteriolar dilatation. The hyperaemic period lasted from 5 to 10 minutes. During this period blood flow rate was elevated and stable. Blood flow rate in the capillaries of the pulp is low compared to the total blood flow rate measured by the heat-washout method, therefore the hyperaemia in the capillaries is considered insignificant in areas with AVA's because these have a much higher blood flow rate as triggered by a central command.

Blood flow rate in arteriovenous anastomoses and capillaries in thumb, first toe, ear lobe, and nose

Grant and Bland (1931) found about 293 AVA's per cm^2 tissue in the pad of the second toe compared to 236 in the finger tip, and 501 in the finger nail bed, compared to 593 in the toe nail bed. As a consequence, blood flow could be expected to be higher in the AVA's in the toes than in the fingers. Apparently there is no knowledge of the amount of AVA's in the ear lobe, however they are previously described as "numerous", and apart from having a thinner wall than AVA's in other regions, their structure is similar (Prichard & Daniel, 1956). Presumably detailed information about AVA's in the nose, cheek and forehead does not exist, but according to Hoyer (1877) they were observed by Sucquet as far back as in 1862, and more resent examinations made on the nose confirmed the existence of AVA's in that region (Bergersen, 1993).

In the present study blood flow rate was measured in the AVA's and capillaries in the following regions: The pulp of the thumb and the first toe, the proximal phalanx of the first toe and finger, the skin fold between the thumb and the forefinger, the side of the nose, the ear lobe, and other parts of the face in healthy subjects. Blood flow rate was measured with the heat-washout method and the ^{133}Xe-washout method above, below, and at the level of the jugular notch, during and after cooling, and after ischaemia. A mean value and SEM was calculated. The examinations were performed to examine whether autoregulation of blood flow, the local sympathetic veno-arteriolar reflex, and hyperaemia were present.

Autoregulation of blood flow

Autoregulation of blood flow is the ability of tissues or organs to keep their blood flow rate essentially constant during changes in arterial pressure, when venous pressure is constant (Henriksen et al., 1973). Blood flow rate was measured by the heat-washout method in the **thumb pulp**. The arm was wrapped in a woollen blanket, and was leaning against a wooden plate with the thumb fixed at the level of the jugular notch, and 20, 40, and 60 cm above that level. The measurements were all made with the probe heated to 43°C before heat-washout that was performed 5 times at each level. The subject was in a sitting position.

Next, blood flow rate was measured in the **pulp of the first toe** at the level of the jugular notch, 20 and 80 cm above, 5 times at each level. Furthermore the examinations were made in six more subjects with the toe placed at the level of the jugular notch and 50 cm above, once at each level. The examinations were all made with the subject in recumbent position. The leg was wrapped in a woollen blanket to avoid cooling.

With the *^{133}Xe-washout method* blood flow rate was measured in the **thumb pulp** at normal skin temperature, with the hand placed at the level of the jugular notch, and 20 and 60 cm above this level. One measurement was made at 43°C, at the level of the jugular notch, and 60 cm above this level. On the dorsal side of the **proximal phalanx of the thumb** blood flow rate was measured at the level of the jugular notch, and 20, and 60 cm above that level. In the **skin fold** between the thumb and the forefinger measurements were made at the level of the jugular notch, and 20, 40, and 60 cm above this level, three times at each level. In six subjects blood flow rate was measured in the **pulp of the first toe** at the level of the jugular notch, and 50 cm above. In two subjects the measurements were made 20 and 80 cm above this level as well. One measurement was made at 41°C, at the level of the

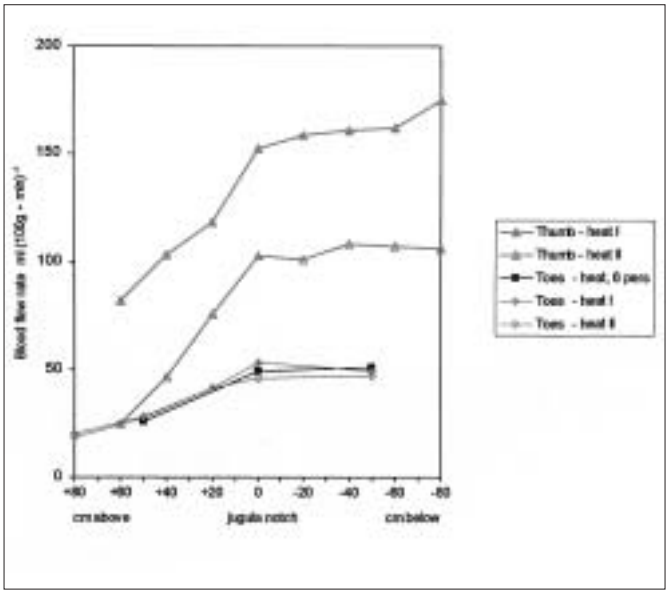

Fig. 8. Blood flow rate in the pulp of the thumb and the first toe measured by the heat-washout method. The two upper lines show blood flow rate at, above, and below the level of the jugular notch in the thumb pulp (subject 1, ▲, and subject 2, Δ). The three lower lines show blood flow rate in the pulp of the first toe at, above, and below heart level in six subjects, ■, n = 12, in subject 1, ♦, and in subject 2, ◊, n = 5. The figure indicated that the AVA's react as passive vessels at orthostatic changes.
(Midttun & Sejrsen 1996).

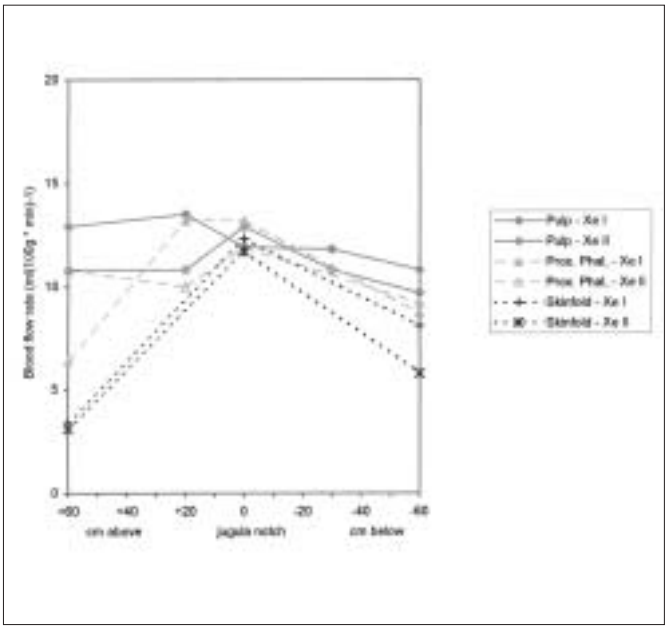

Fig. 9. Shows blood flow rate measured by ^{133}Xe-washout in the pulp of the thumb (subject 1, ♦, and subject 2, ◊). On the dorsal side of the proximal phalanx of the thumb (subject 1, s , and subject 2, Δ), and in the skinfold between the thumb and the forefinger (subject 1, +, and subject 2, ×). (Midttun & Sejrsen, 1996).

jugular notch. Finally measurements were made in the **proximal phalanx of the first toe** at normal skin temperature, and 20, 50, and 80 cm above the level of the jugular notch.

Results - autoregulation of blood flow

The results of the above mentioned examinations are presented in fig. 8 and 9. Autoregulation of blood flow was not present in the **AVA's**. Blood flow rate in these vessels decreased corresponding to the falling pressure head above the level of the jugular notch. Autoregulation of blood flow was not present in the arterioles supplying the capillaries in the **skinfold** between the thumb and the forefinger either. It was present in arterioles supplying the capillaries in the **pulp of the thumb** and the **first toe** to at least 50 cm above the level of the jugular notch, as well as in the **proximal phalanx** of the **thumb** and the first toe 60 and 80 cm above the level of the jugular notch.

Previous studies have shown autoregulation of blood flow in subcutaneous tissue in the interstice between the first and the second toe of the forefoot to 30 cm above heart level (Henriksen, 1974). The reason why autoregulation of blood flow is present to a higher level in the pulp and in the dorsum of the proximal phalanx than in regions located more proximally on the hand or foot, might be that in regions with both AVA's and capillaries, or in the immediate vicinity of regions with AVA's, the capillary blood flow rate is favoured due to the reduced AVA-flow during elevation of the extremity. The small arteries supporting both arteries and AVA's have a dimension permitting support to both arterioles and AVA's, and when blood flow rate in the AVA's decrease during elevation, the pressure head to the capillaries is presumably favoured.

In fig. 8 the curves express the total cutaneous blood flow rate in AVA's and capillaries, and autoregulation of blood flow in the capillaries is maintained even at an elevation of 80 cm. Blood flow rate in the toes, measured by the heat-washout method, 80 cm above heart level was very low, and when capillary blood flow rate, measured at the same temperature, was subtracted to obtain blood flow rate in the AVA's only, almost no blood flow remained in the AVA's.

Local sympathetic veno-arteriolar reflex

Blood flow rate in human cutaneous and subcutaneous tissues decreases about 40% when vascular transmural pressure is increased about 25 mmHg (Henriksen & Sejrsen, 1976, Henriksen, 1977) due to the local sympathetic *veno-arteriolar reflex*.

By the ***heat-washout method*** blood flow rate was measured 5 times in the **pulp of the thumb** 20, 40, 60 and 80 cm below the jugular notch. The arm was leaning against a wooden plate and wrapped in a woollen blanket, with the area of interest fixed at the selected level. In six subjects in recumbent position measurements were made once in the **pulp of the first toe**, with the foot placed 50 cm below the level of the jugular notch.

With the ***^{133}Xe-washout method*** blood flow rate was measured in the thumb pulp 20, 60, and 80 cm below the jugular notch. In the **proximal phalanx of the thumb and the first toe** blood flow rate was measured 50 cm below the jugular notch. In the ***skin fold*** between the first and the second finger blood flow rate was measured 50 cm below the level of the jugular notch, as well in positive as in negative heat balance. Furthermore a blood pressure cuff on the upper arm was inflated to 40 mmHg after a few min of ^{133}Xe-washout, still with the hand placed at the level of the jugular notch. Washout registrations were continued for another few min before the pressure was released. Each measurement was made three times, and a mean value was calculated.

Results - local sympathetic veno-arteriolar reflex

The results are presented in fig. 8 and 9. *No* veno-arteriolar reflex was present in the **AVA's** of the pulp of the thumb or the first toe. Below heart level arterial and venous pressure increase in parallel corresponding to the height of the column of blood. Blood flow in these positions most probably remains unchanged because the AVA's, due to their thick muscular wall have a low compliance and lack the ability to modulate wall tonus to vary vessel radius. Consequently blood flow resistance does not change. Blood flow rate in the **capillaries** of the region (see fig. 8 and 9) also remained unchanged below heart level. Previous examinations have shown that the veno-arteriolar reflex was present in the capillaries of the subcutaneous tissue of the first interstice of the dorsum of the forefoot, and 50 cm below heart level (Henriksen, 1974). Others have measured blood flow rate by Doppler-flowmeter and found a decrease in blood flow rate in the pulp of the first toe when placed 50 cm below heart level (Hassan et al, 1986). However, a Doppler flowmeter is highly problematic. The signal gives a qualitative result depending on both the amount of erythrocytes and their flow velocity. Blood volume will change in the tissue at positions above and below heart level, and therefore the results will not only depend on blood flow rate (Hirata et al., 1988). The veno-arteriolar reflex was present in the **proximal phalanx of the thumb** and the **first toe**. However the reflex was less pronounced than on the dorsum of the forefoot. In the cutaneous **skinfold** between the thumb and the forefinger a veno-arteriolar reflex was observed in subject 1. In subject 2 it was not possible to registrate a local veno-arteriolar reflex until the subject was in a negative heat balance.

It was previously stated that the veno-arteriolar reflex has an edema protecting effect, because it counteracts an increase in mean capillary pressure, and thereby an increase in capillary filtration rate by changing the ratio of pre- to post-capillary resistance (Henriksen & Sejrsen, 1976). However, it remains unclear why a veno-arteriolar reflex is not present in the pulp. It seems that a positive heat balance may eliminate the reflex mechanism, because in this situation the arterioles dilate in order to increase blood flow rate to eliminate the surplus of heat. The thermic threshold for elimination of the veno-arteriolar reflex is presumably individually different. Corresponding results were previously found by others (Henriksen & Sejrsen, 1976).

Post ischaemic hyperaemia

Hyperaemia is an increase in blood flow rate in a region when its circulation is reestablished after a period of blood flow cessation.

Measurements were made on the **thumb pulp** with the ***heat-washout method*** at the level of the jugular notch. The probe was heated to 39, 41, 43, and 45°C before washout was started immediately after 10 min of **ischemia**, made by a pressure cuff on the upper arm, inflated to 230 mmHg.

With the hand placed at the level of the jugular notch blood flow rate was measured in the **thumb pulp** by the ***^{133}Xe-washout method*** at normal skin temperature, and at 43°C, immediately after 10 min of ischemia as above described. The measurements at normal skin temperature were made with the subject in negative as well as positive heat balance to clarify the importance of having warm versus cold hands during the examination. Following the same procedure, 3 measurements were made in the **skinfold** between the thumb and the forefinger with the hand placed at the level of the jugular notch.

Results - post ischaemic hyperaemia

Blood flow rate in the **thumb pulp** measured by ***heat-washout*** was 189.0, 130.0, 173.3, 148.7 ml(100 g · min)$^{-1}$ in subject 1, and 138.6, 138.6, 133.3, and 161.2 ml(100 g · min)$^{-1}$ in subject 2. Measured by ***^{133}Xe-washout*** blood flow rate was 25.8, and 21.6 ml(100 g · min)$^{-1}$ for 2 - 3 min in the two subjects, it then decreased to the usual values of 11.2, and 13.5 ml(100 g · min)$^{-1}$. Similar post ischaemic blood flow rates were obtained when the measurements were performed with the subjects in a negative heat balance. In the **skinfold** between the thumb and the forefinger, blood flow rate increased 4 - 5 fold in both subjects.

The mechanism of reactive hyperaemia is most probably due to accumulation of arteriolar dilating metabolites that are normally removed, or restored, by the circulating blood. The AVA's are not under metabolic control, and they are therefore not expected to show post-ischaemic hyperaemia (Hales et al., 1978 and 1982, Berne & Levy, 1993). The post-ischaemic increase in blood flow rate measured with the heat-washout method in the thumb pulp was insignificant. As the heat-washout method measures the sum of blood flow rate in the capillaries and in the AVA's, the slight post-ischaemic elevation is presumably due to a hyperaemic contribution from the arterioles supplying the capillaries. When measurements were made at 41,

and 43°C following 10 min of ischaemia, blood flow rate almost doubled for 2 - 3 min, when performed with the subject in a positive heat balance. When the subject was in a negative heat-balance, the post-ischaemic blood flow rate was unchanged, and the pre-ischaemic blood flow rate was a little lower, consequently the pre- to post-ischaemic increase in blood flow rate was higher in a cold than in a warm person.

Previous studies have shown an 8 fold increase of capillary blood flow rate in the finger pulp following 6 min of ischaemia, and an about 5 fold increase in skin fold blood flow rate (Engelhart & Kristensen, 1983). The results from the skin fold correspond well with the present results, but the finger pulp blood flow rates were much lower in the present study. The discrepancy is most probably due to the fact that a resolution of the ^{133}Xe-washout curves into cutaneous and subcutaneous washout rates was not performed in Engelhart & Kristensen's study.

Indirect cooling of the thumb

Measurements were made with the ***heat-washout method*** on the **thumb pulp** during indirect cooling, with the 2nd - 5th finger placed in a water bath of 8 - 9°C, and the feet placed in a water bath of 12 - 13°C for 1 hour, before and during the measurement. The probe was mounted on the thumb pulp of the cooled hand. The measurement was taken once in each subject. One measurement was made on the thumb pulp of subject 1 immediately after the contra lateral hand was placed in ice water.

Results - indirect cooling of the thumb

Blood flow rate decreased to 9 ml(100 g · min)$^{-1}$ in subject 1, and to 10.6 ml(100 g · min)$^{-1}$ in subject 2 during cooling. Fluctuations in blood flow rate were observed in subject 2, with two periods of 2 min each with no blood flow rate at all. When the contralateral hand was put into ice water, blood flow rate decreased to 56 ml(100 g · min)$^{-1}$ during the first 2.5 min, to 43 ml(100 g · min)$^{-1}$ for the following 2 min, and finally to 28 ml(100g · min)$^{-1}$.

The examinations confirmed the statement that the AVA's are under central command (Hales, 1985, Molyneux, 1977), because blood flow rate decreased in the pulp of the finger that was not in contact with the cold water. The fluctuations with periods of 2 min each observed during the unstable phase are in accordance with observations made by Dahl et al. (1992).

Face

With the ***heat-washout method***, and the probe heated to 43°C before washout, 5 measurements were made on the **ear lobe** in sitting and recumbent position. Similar measurements were made on the side of the **nose**, as close to the nose tip as possible. In order to investigate whether islands of AVAs were scattered in other locations of the face, two measurements were made in the centre of the **forehead** in recumbent position. A lead shield exceeding a pressure of 300 mmHg on the skin was placed about 1 cm cranially to the probe to exclude blood flow in the venous rete. And finally two measurements were made **in front of the tragus** in sitting position.

With the ***^{133}Xe-washout method*** blood flow rates were measured in the **ear lobe** and the side of the nose in sitting and recumbent position, at normal skin temperature, 41, and 45°C. In the centre of the **forehead** one measurement was made at normal skin temperature in recumbent position. One measurement was made **in front of the tragus** in sitting position at normal skin temperature in subject 1.

Results - face

The results of ***heat-washout*** and ***^{133}Xe-washout*** measurements at 41°C in the **ear lobe** and **nose** are presented in fig. 10. The results of ^{133}Xe-washout at normal skin temperature and 45°C was 14.6, and 19.4 ml(100 g · min)$^{-1}$ in subject 1, and 11.3, and 16.2 ml(100 g · min)$^{-1}$ in subject 2. In

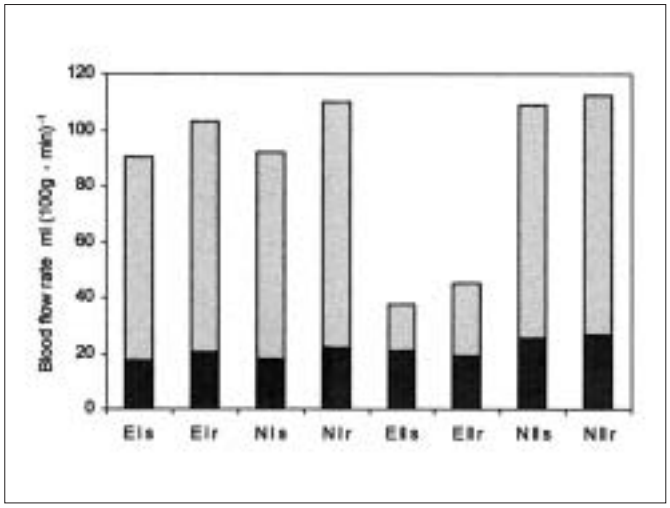

Fig. 10. Blood flow rate in the ear lobe (E), and in the side of the nose (N) in sitting (s) and recumbent (r) position in subject 1 and 2, n = 5. The gray columns denote blood flow rate in the AVA's. The black columns show blood flow rate in the capillaries measured by the ^{133}Xe-washout method at 41°C. The total height of the columns shows the blood flow rate measured by the heat-washout method. (Midttun & Sejrsen, 1996).

the nose blood flow rate was 17.1, and 19.4 ml(100 g · min)$^{-1}$ in subject 1, and 14.9, and 23.1 ml(100 g · min)$^{-1}$ in subject 2.

Blood flow rate measured by the ***heat-washout method*** in the forehead was 24.1, and 36.4 ml(100 g · min)$^{-1}$. **In front of the tragus** blood flow rate was 44.1, and 37.7 ml(100 g · min)$^{-1}$. When measured by ***^{133}Xe-washout*** blood flow rate in the **forehead** was 23.9 ml(100 g · min)$^{-1}$ in subject 1, and 30.4 ml(100 g · min)$^{-1}$ in subject 2. **In front of the tragus** blood flow rate was 17.1 ml(100 g · min)$^{-1}$ in subject 1.

Discussion

There are various problems related to measurement of blood flow rate in the nose and the ear lobe. Most AVA's are located in the tip of the nose, but because of the relatively large size of the probe it had to be mounted on the side of the nose as close to the tip as possible. Furthermore it is difficult to keep the subject in a thermic steady-state with constantly open AVA's. However, performing the examinations on a hot day made it easier to keep these regions warm with the highest possible blood flow rates.

The results of the measurements of cutaneous blood flow rates in the ear lobe and on the side of the nose obviously indicate that AVA's are present as suggested by Bergersen (1993), and it was observed that they react with a pattern similar to the AVA's in the pulp. The mean blood flow rate in the AVA's in both regions decreased by about 15% when the position was changed from recumbent to sitting. This was expected from the height of the elevation above the jugular notch. The arterioles supplying the capillaries in these regions show autoregulation of blood flow, just like other organs, see fig. 10 (Henriksen et al., 1973). Blood flow rate in the capillaries increased only a little when the local temperature was increased. A modest increase with increasing temperature was also observed in the capillaries in other regions with AVA's (Midttun et al., 1996). This is in contrast to the forearm, a region without AVA's, where a pronounced increase in blood flow rate was observed with increasing local temperature (Midttun et al., 1996). The total blood flow rate on the side of the nose equals that in the ear lobe in subject 1, and it was more than twice as high in the nose compared to that in the ear lobe for subject 2. This may be due to individual variations. Blood flow rate in the nose was not found to be influenced by a shift from nasal to oral respiration. Blood flow rate in the cutaneous tissue of the ear lobe, nose, and finger was about 100 ml(100 g · min)$^{-1}$, and in the finger pulp even higher (125 ml(100 g · min)$^{-1}$), however in the pulp of the toe it was about 1/2 - 1/3 of that value in spite of a great amount of AVA's. This is presumably caused by difference in the importance in temperature regulation of the different parts of the body. However the importance of nose and ears in temperature regulation is most probably limited due to their small size.

When measuring in front of the tragus it was not possible to exclude blood flow in greater veins of the region. Therefore it cannot be said whether there are AVA's in the region or not.

After excluding blood flow rate in the veins passing the region, blood flow rate measurements were made in the forehead. In subject 2 corresponding results were found with the two methods. In subject 1 blood flow rate measured by the heat-washout method was higher than the capillary blood flow rate measured by the ***^{133}Xe-washout method***. This was most probably due to AVA's in the region. Other investigators did not localize AVA's in the forehead, most probably because they are few or not present (Bergersen, 1993).

In conclusion AVA's presumably exist in the face, especially in the nose and ear, but the evidence of islands of AVA's in other locations of the face as well is strong.

Cutaneous blood flow rate in areas with and without arterio-venous anastomoses during exercise

Previous investigations made by Christensen et al. (1942) showed an instantaneous reduction of blood flow rate in the finger at the onset of bicycling, when the subject pedals against a load. It was speculated that the AVA's were involved in the blood flow reduction, and various studies have supported these findings (Bishop et al., 1957, Bevegård & Shepherd, 1966, Richardson et al., 1986). Zelis et al. (1969) showed that the exercise-related vasoconstriction was graded according to exercise intensity. Bevegård et al. (1966) found a transient constriction of resistance vessels in the hand, and 30 - 60 s of increase of forearm blood flow during the onset of exercise, presumably due to squeezing of AVA blood. Richardson et al. (1986) measured blood flow in the digital artery and nailfold capillaries by Doppler ultrasound and video densitometry, respectively, during the onset of exercise. They found a reduction in blood flow rate in the digital artery, whereas nailfold capillary flow velocity did not change significantly. Closure of the AVA's was considered a possible explanation.

The present study was undertaken to more directly measure blood flow rate in the **AVA's** of the **thumb pulp**, and the cutaneous **capillaries** of the **skinfold** between the thumb and the forefinger, simultaneously, at the onset of moderate exercise.

Material and Methods

Ten healthy subjects volunteered for the experiments, 5 women, and 5 men, mean age 45, median 44 (33 - 63 years). The subjects were dressed in sports clothes (T-shirt, long sports pants, socks, and shoes). The environmental temperature was kept constant at 21 - 24°C.

Blood flow rate was measured in the **AVA's** of the **thumb pulp** by the ***heat-washout method,*** and in the cutaneous **capillaries** of the **skinfold** between the thumb and the forefinger by the ***^{133}Xe-washout method***. Some curves showed an abrupt deflection during heat-washout (see below). Blood flow rate in both phases of these curves was calculated using the same baseline temperature, because T_b before wash-out equals the one after wash-out. The curves were monoexponential, and when they presented a deflection, the change was always abrupt, resulting in a new monoexponential line.

Exercise was performed on a mechanically braked bicycle ergometer (Monark). A moderate load (80 - 120 W for women, and 120 - 180 W for men, pedalling frequency being 60 rpm) was chosen for each subject. Before and after exercising the following variables were registered:

1 Tympanic temperature in the right ear was measured by a DM852 digital thermometer (Ellab a/s, Denmark). The tympanic membrane was identified by otoscopy, subsequently the tip of the lead from the digital thermometer was carefully introduced into the ear, until contact with the tympanic membrane was obtained. The lead was fixed to the cheek by sleek to avoid sliding.
2 Skin temperature on the dorsum of the forearm was measured by a thermocouple thermo-meter (Ellab a/s, Denmark) fixed by tape.
3 Heart rate was measured by a Polar Pulse Monitor (Finland). The monitor fixed around the thorax transmitted the heart rate to a digital "wrist display".
4 Systemic arm blood pressure was measured auscultatorily by an ordinary sphygmomanometer.

Heart rate increase in per cent of maximum heart rate increase was calculated = ((Heart rate at exercise - heart rate before start): (Maximum heart rate according to age - heart rate before start)) · 100, (Åstrand et Rodahl, 1970).

Heat-washout measurements on the thumb pulp

Blood flow rate was measured at rest ($\mathbf{R}_1$). Exercise was initiated, and after bicycling for 1 min blood flow rate measurement was started ($\mathbf{A}_1$). The subject continued bicycling until the measurement was finished, 11 min as a maximum, se Table 1a and 1b. Blood flow rate was measured again ($\mathbf{R}_2$), while the subject rested until heart rate was normalized, after about 15 min. Subsequently the experiment was repeated twice ($\mathbf{A}_2$ and $\mathbf{A}_3$) while the subject bicycled for 2 and 5 min, respectively, before the heat-washout measurement was started. Blood flow rate was measured at rest ($\mathbf{R}_3$) between $\mathbf{A}_2$ and $\mathbf{A}_3$.

Supplementary studies were made to study the influence on blood flow rate, if the subject exercised at a load that was too heavy or too light. Therefore blood flow rate was measured after one min of exercise, in subject I working at 60 W, in subject II at 120 W, in subject IV at 110 W, in subject V at 100 W, and in subject X at 150 W.

WOMEN									
	Blood flow rate ml(100g/min)$^{-1}$	$Temp_t$ (C°)	$Temp_s$ (C°)	BP (mmHg)	Heart rate (min-1)	Tot.exc (min)	Flow change (min)	Load (W)	ΔHeart rate/ ΔHeart $rate_{max}$ (In %)
I age 36	R_1: 139.7 A_1: 57.7/125.3 R_2: 160.1 A_2: 109.0/148.8 R_3: 147.3 A_3: 177.3	37.0 37.2 37.4 37.5	31.5 31.9 33.4 34.5	115/70 180/85 175/80 180/75	72 143 138 139	0 6.5 6.0 9.0	No change After 3.8 After 3.0 No change	0 120 120 120	 58 58 58
II age 33	R_1: 90.3 A_1: 41.5/104.3 R_2: 96.5 A_2: 64.7/176.0 R_3: 94.7 A_3: 93.0/147.8	36.9 37.2 37.3 37.4	32.8 33.0 34.6 35.8	105/75 130/70 120/70 125/70	71 132 130 132	0 8.5 8.3 9.3	No change After 4.5 After 4.7 After 7.3	0 100 100 100	 50 50 50
III age 39	R_1: 20.7 A_1: 44.0/144.6 R_2: 25.2 A_2: 89.7/163.7 R_3: 17.5 A_3: 153.7	37.4 37.6 37.7 37.8	33.6 31.1 31.0 31.5	95/75 145/85 150/75 145/75	59 142 147 149	0 7.0 6.5 5.0	No change After 4.2 After 4.3 No change	0 120 120 120	 49 49 49
IV age 56	R_1: 131.9 A_1: 98.8 R_2: 167.9/75.5 A_2: 190.4 R_3: 179.7 A_3: 185.6	36.7 36.7 36.6 36.7	32.5 32.1 33.0 33.0	135/95 150/80 145/80 150/80	71 134 142 148	0 5.0 5.5 9.0	No change No change No change No change	0 90 90 90	 99 99 99
V age 52	R_1: 71.0 A_1: 52.4/102.2 R_2: 108.0 A_2: 75.4/114.6 R_3: 98.4 A_3: 95.9	37.0 37.2 37.1 37.1	32.4 31.6 31.0 31.2	120/70 140/70 145/70 155/75	72 133 133 138	0 6.0 6.5 10.0	No change After 3.8 After 4.8 No change	0 80 80 80	 79 79 79

Tablel 1a *Midttun & Sejrsen, 1998*

Table 1a and 1b. Present blood flow rate in 5 women and 5 men measured by heat-washout in the pulp of the thumb. R1, R2, R3 are blood flow rate in the resting periods before exercise periods. A_1, A_2, A_3 are the results of blood flow rate measurements started after 1, 2, and 5 min of exercise. The / indicate that blood flow rate changes during the measurement. The remaining parameters measured are: Tympanic temperature (T_t), skin temperature (T_s), blood pressure (BP), heart rate, minutes of exercise (Tot.exc.), min before abrupt change in blood flow rate (flow change), work load in W (Load), and Δheart rate/Δheart $rate_{max}$ in %. The maximal heart rate used is being the average for the age group as given in standard text books.
(Midttun et al., 2000).

^{133}Xe-washout measurements

Blood flow rate was measured in the cutaneous capillaries of the skinfold between the thumb and the forefinger for 15 min in 5 subjects (subject I, II, VI, VII, and X). The period included 1 min before exercise start, 10 min of exercise with the loads indicated in table 1 and 2, and finally 4 min at rest after exercise cessation. ***Heat-washout measurements*** made simultaneously on the thumb pulp were started after 1 min of exercise.

Statistics

The Wilcoxon rank sum test for paired samples was used for evaluation of differences between means. A p value <0.05 was considered significant.

Results

The results are given in Table 1a and 1b, (see page 22+23).

MEN									
	Blood flow rate ml(100g/min)$^{-1}$	$Temp_t$ (C°)	$Temp_s$ (C°)	BP (mmHg)	Heart rate (min-1)	Tot.exc (min)	Flow change (min)	Load (W)	ΔHeart rate/ ΔHeart $rate_{max}$ (In %)
VI age 36	R_1: 109.9 A_1: 37.9/70.4 R_2: 89.0 A_2: 77.4/117.5 R_3: 112.2 A_3: 128.7	37.1 37.2 37.2 37.5	33.2 34.6 34.7 35.9	100/75 110/60 130/65 125/75	62 139 139 150	0 7.5 7.5 9.5	No change After 3.8 After 3.8 No change	0 180 180 180	 70 70 70
VII age 36	R_1: 44,6 $A_1$3: 31.6/111.1 R_2: 134.7 A_2: 87.7/122.6 R_3: 158.2 A_3: 151.6	36.6 36.9 37.3 37.2	34.0 34.2 34.0 33.6	130/95 150/70 160/80 150/85	68 122 174 174	0 10.0 6.3 8.5	No change After 4.6 After 4.0 No change	0 150 180 180	 45 88 88
VIII age63	R_1: 153.2 A_1: 117.8 R_2: 153.2 A_2: 115.9 R_3: 150.1 A_3: 130.7	37.1 37.2 37.4 37.8	33.1 33.3 33.2 31.3	160/95 200/85 200/85 220/85	60 92 104 128	0 5.5 5.5 9.0	No change No change No change No change	0 120 120 120	 80 80 80
IX age 35	R_1: 164.7 A_1: 95.0 R_2: 167.7 A_2: 162.9 R_3: 177.0 A_3: 177.5	36.9 37.1 37.4 37.7	32.0 32.5 33.7 33.6	115/55 140/85 165/85 165/90	61 134 136 144	0 5.5 5.3 8.5	No change No change No change No change	0 180 180 180	 64 64 64
X age 63	R_1: 84.2 A_1: 51.9/91.5 R_2: 85.6 A_2: 47.9/96.4 R_3: 87.2 A_3 : 62.1/89	36.9 37.0 37.4 37.7	32.0 32.1 31.5 30.0	120/85 160/85 165/90 155/100	75 139 154 152	0 7.0 8.0 11.0	No change After 5,0 After 7,0 After 8,4	0 120 120 120	 110 110 110

Table 1b *Midttun & Sejrsen, 1998*

$\mathbf{A}_1$: After 1 min of exercise, 9 of 10 subjects showed an initial decrease in blood flow rate. In subject III the initial blood flow rate was very low at rest and increased to the level of the remaining subjects during exercise. In 7 subjects the curve deflected abruptly towards a significantly higher blood flow rate ($p< 0.05$) after an average of 4.6 min of exercise (range 3.8 - 6.5). Tympanic temperature then showed an insignificant increase of about 0.1°C. $\mathbf{R}_1$ did not differ significantly from blood flow rate after the curve deflection, i.e. increase in blood flow rate following the reduction, or from $\mathbf{R}_2$. Forearm skin temperature decreased insignificantly. Systolic blood pressure and heart rate increased in all subjects during all the examinations.

$\mathbf{A}_2$: When the subject bicycled for 2 min before measurements were started, blood flow rate decreased in 5 of 10 subjects. Blood flow rate at the end of the exercise period did not differ significantly from $\mathbf{R}_1$. A significant, abrupt deflection in blood flow rate was observed in 7 subjects after about 4.5 min (range 3.0 - 7.0), ($p<0.05$). Blood flow rate after the deflection did not differ significantly from $\mathbf{R}_2$ and $\mathbf{R}_3$. Tympanic temperature had increased 0.3°C, ($p<0.02$). Skin temperature showed an insignificant increase of 0.3°C.

$\mathbf{A}_3$: When the subject bicycled for 5 min before blood flow rate measurements were started, 8 of 10 subjects showed a constant blood flow rate. Subjects II and X showed a small decrease followed by an increase after 7.3 and 8.4 min of exercise, respectively. At the end of the exercise period blood flow rate did not differ significantly from $\mathbf{R}_3$. Tympanic temperature increased significantly ($p = 0.01$) on average 0.4°C from 37.0 to

37.4°C. Skin temperatures showed an insignificant increase of in average 0.3°C.

$\mathbf{A}_1$ before the deflection compared to $\mathbf{A}_2$ increased significantly, $p<0.05$, and so did $\mathbf{A}_1$ compared to $\mathbf{A}_3$, $p<0.01$, but no significant difference was found between $\mathbf{A}_2$ and $\mathbf{A}_3$. $\mathbf{R}_1$, and $\mathbf{R}_3$ did not differ significantly.

When blood flow rates *after* the abrupt increase were compared, significant differences were found between $\mathbf{A}_1$ and $\mathbf{A}_2$, ($p<0.05$) ($\mathbf{A}_2 > \mathbf{A}_1$) , and between $\mathbf{A}_1$ and $\mathbf{A}_3$, $p=0.01$ ($\mathbf{A}_3 > \mathbf{A}_1$), but $\mathbf{A}_2$ did not differ significantly from $\mathbf{A}_3$. $\mathbf{R}_2$ and $\mathbf{R}_3$ did not differ significantly.

$\mathbf{A}_4$: The *supplementary* studies made with work loads different from those indicated in table 1a and 1b, showed lower blood flow rates in all subjects. In subject II tympanic temperature increased from 37.6 to 38.2°C. In subject I, who was bicycling at only 60 W, no blood flow changes were observed.

B: The results are illustrated in figure 11 using subject 1 as an example. On average blood flow rate was 10.6 ml(100 g · min)$^{-1}$, n = 5, (range 8.1 - 12.9 ml(100 g · min)$^{-1}$) during the first 11 min of the ^{133}Xe-washout registration (range 9.5 - 13 min.), blood flow rate then decreased in 4 subjects and increased in one. The results of the heat-washout measurements made simultaneously are given in table 1a and 1b.

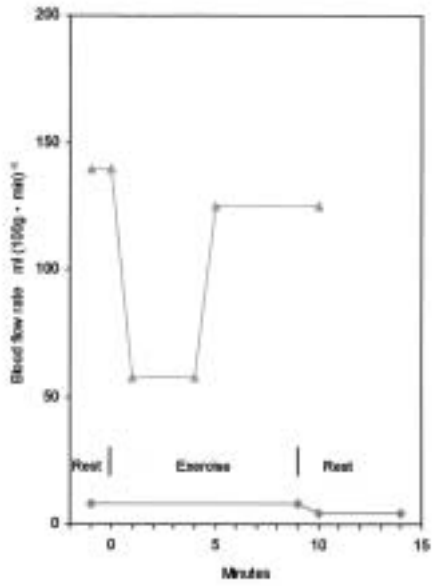

Fig. 11. Blood flow rates at rest and during 10 min of exercise in subject 1. Heat-washout was measured before start, and initiated again after 1 min of exercise (the upper line). The cutaneous capillary blood flow rate (the lower line) was measured continuously by the ^{133}Xe-washout from one minute before start, during the entire exercise period, and for four min after exercise had ended.
(Midttun & Sejrsen, 1998)

Discussion

In the first experiment, $\mathbf{A}_1$, blood flow rate in the thumb pulp, an area with AVA's, decreased in 9 of 10 subjects during the onset of moderate exercise. After about 5 min of bicycling (on average 4.6 min, range 3.8 - 6.5 min) AVA-blood flow rate increased abruptly in 7 subjects to the same level as at rest, ($p<0.05$). Tympanic temperature had risen 0.1°C. In the remaining subjects, who had a very low initial blood flow rate, blood flow rate increased in response to exercise.

In the second experiment, $\mathbf{A}_2$, where blood flow measurements were started after two min of exercise, only 5 of 10 subjects showed a decrease of blood flow rate compared to the value at rest, $\mathbf{R}_1$. Presumably the subjects had a slight surplus of heat at the beginning of the exercise period, therefore the decrease in blood flow rate was less pronounced than in $\mathbf{A}_1$. After about 5 min of exercise, blood flow rate in the thumb pulp increased abruptly.

In the capillaries of the skinfold between the thumb and the forefinger (a region with cutaneous tissue only, and without AVA's) a constant capillary blood flow rate was found before start, during about 10 min of exercise, and in the following first minute at rest, (see figure 11).

Our findings are in agreement with previous proposals, based on less direct evidence using measurement of finger temperature. These measurements showed that at the onset of moderate exercise hand blood flow rate is reduced due to a constriction of the AVA's, whereas blood flow rate in the capillaries remain unchanged (Christensen et al., 1942, Bishop et al., 1957, Bevegård & Shepherd, 1966, Richardson et al., 1986). After about 5 min of exercise the AVA's are dilated presumably to eliminate the surplus of heat.

The results are in consistence with the subjects exercising at a moderate-to-high work load (between 50 and 100% of maximum performance, see table 1a and 1b). A decrease in blood flow rate, and an increase in tympanic temperature, were only observed if the subject was exercising with a certain load (Christensen et al., 1942). This was confirmed in $\mathbf{A}_4$, where subject I was exercising at only 28% of maximum performance, and no blood

flow rate decrease was observed in the thumb pulp. When exercising at a heavy load, heat dissipation from the AVA's was delayed until after the end of exercise as observed in A4. In subject IV tympanic temperature remained unchanged during the exercise periods in spite of an exercise performance estimated to be about 99% of maximum. Leaving out that result would not change the final result. This was most probably caused by a lack of contact between the thermometer and the tympanic membrane. If a person is exercising without being able to dissipate the surplus of heat produced, core temperature will rise to a life-threatening level within 10 - 15 min (Kenney & Johnson, 1992). Older individuals have been observed to respond to exercise with less cutaneous arteriolar dilation than their younger counterparts, probably due to structural changes in the vascular bed of aged skin. Usually $\dot{V}O_{2max}$ decreases with increasing age, but subjects who do not have a reduced $\dot{V}O_{2max}$, do not experience a reduction in their ability to vasodilate (Kenney & Johnson, 1992). Absence of cutaneous arteriolar dilation was only observed in one of our four senior subjects aged 63, subject VIII, where cutaneous blood flow rate in the thumb pulp remained slightly reduced during all working periods in accordance with a relatively high work load of 80% of maximum. At this work load the sympathetic activity is high and the blood flow rate in the AVA's will consequently be reduced.

Forearm skin temperature did no show any consistent pattern during the exercise periods, most probably because skin temperature is influenced by local, and individually different, sweat secretion cooling the area by evaporation.

In a situation with a brief, moderate load of exercise and a cardiac output of about 10 - 15 $l \cdot min^{-1}$, about 2% of the total cardiac output is distributed to the cutaneous tissue (Sejrsen, 1971). Assuming the weight of the cutaneous tissue is 3.6 kg (area $1.8 m^2 \cdot 2$ mm thickness), and the capillary blood flow rate to be 6 ml $(100 g \cdot min)^{-1}$, the total cutaneous blood flow becomes 216 $ml \cdot min^{-1}$ (Sejrsen, 1971). Blood flow rate in areas with AVA's can be estimated to be about 40 $ml \cdot min^{-1}$ ($200 cm^2 \cdot$ mm thickness with a mean blood flow rate of about 100 $ml(100 g \cdot min)^{-1}$ (Midttun & Sejrsen, 1996). Other investigators have reported a total skin blood flow of 2 - 3 $l \cdot min^{-1}$ due to a less direct method of measuring, and furthermore because total forearm blood flow rate through calculations are used to express total skin blood flow (Kenney & Johnson, 1992). Consequently, the total cutaneous blood flow only constitutes a minor part of cardiac output during moderate exercise. During local heat stress cutaneous capillary blood flow rate can increase to a maximum of 40 - 50 $ml(100 g \cdot min)^{-1}$ (Midttun & Sejrsen, 1996). Blood flow rate in AVA's is an on-off phenomenon, and in this situation the AVA's will be open (Midttun & Sejrsen, 1996). This gives a maximum of about 1.5 l of blood per minute for the total cutaneous tissue under these conditions.

In conclusion the results indicate that the initial reduction in blood flow rate and later increase observed in the finger at the onset of moderate exercise take place in the AVA's and not in the capillaries.

Blood flow rate in arteriovenous anastomoses - from the cradle to the grave

Leg vessels and tissue metabolism, blood flow, etc. have recently been studied in healthy subjects by various investigators (Midttun et al., 1996, Sonesson et al., 1997, Matsukawa et al., 1998, Lind et al., 1999, Sarabi et al., 1999, Dinenno et al., 1999). Stiffness of arteries have been found to increase with increasing age as a result of an increase in the collagen-elastin-ratio of the walls, with men having stiffer arteries than women (Sonesson et al., 1997). Other investigators have stated that the ability to endothelium-dependent vasodilation is age dependent (Lind et al., 1999), and furthermore that it interacts with metabolic factors (Sarabi et al., 1999). Whole basal leg arterial blood flow and vascular conductance has been found to reduce with age in healthy adult men, and these changes are associated with elevation in sympathetic vasoconstrictor nerve activity, that seems to vary with gender and age (Dinenno et al., 1999, Matsukawa et al., 1998). The existence of AVA's in adults has been known for more than 150 years, and they were described in children by Popoff in 1934. Functional AVA's have been found in preterm infants as well, but in these babies the vasomotor control seemed immature (Jahnukainen et al., 1993, Lossius et al., 1994).

Blood flow rate in AVA's is expected to decrease with increasing age, but at what age does the decrease start, or does it decrease gradually? Is there a difference between AVA blood flow rate in children and adults, men and women, and between blood flow rates in the AVA's of fingers and toes?

These and other questions led to the present study where blood flow rates were measured in AVA's in 15 children and 16 adults at different ages and sexes. The aim was to determine the normal, and possible age dependent, values of AVA blood flow rate in healthy subjects under standard conditions.

Material and Method

The examinations were performed in a prospective, open study. Blood flow rate was measured by the **heat-washout method** in the pulp of the first toe in ***15 children*** (8 girls, and 7 boys) with a mean age of 8 years (from 3 to 15 years old), and in the pulp of the first *toe* and in the ***thumb*** pulp of ***16 adults*** (8 men) with a mean age of 60 (range 27 to 93 years old), one man and one woman from each decade. All subjects were without symptoms or signs of cardiovascular disease and not smokers. Three measurements were made in each location, and a mean value was calculated.

Results

Linear regressions analysis, and Wald test for comparing slopes were used. The results are summarized in table 2a and 2b, and in figures 12 - 15.

Using the Wald-test the statistical difference between the slope of toe pulp blood flow rate in children and adults was highly significant, ($p = 0.0001$). The slope of the curves of blood flow rate in the thumb pulp and the toe pulp did no differ between men and women ($p = 0.14$, and $p = 0.98$, respectively). Blood flow rate between thumb pulp and toe pulp was significantly different ($p<0.0125$), but the slopes between the two curves did not differ significantly ($p = 0.24$).

Discussion

It has been stated that AVA's do not exist in fetus or new born babies (Popoff, 1934), but examinations made on preterm babies and neonates have found strong indications for the existence of

	Subject	n	a	b	SE(b)	r	p
Fig. 12	Children, toe Adults, toe	14 16	118.72 93.88	-3.89 -0.39	-2.0 to 5.8 0.009 to 0.78	0.786 0.49	<0.0001
Fig. 13	Women, thumb Men, thumb	8 8	180.0 142.13	-1.14 -0.39	-0.21 to -2.1 0.45 to -1.23	0.77 0.42	=0.14
Fig. 14	Women, toe Men, toe	8 8	94.43 92.75	-0.36 -0.40	0.21 to 0.93 0.37 to 1.18	0.53 0.46	=0.98
Fig. 15	Adults, thumb and toe	16					p<0.0125

Table 2a. Present the areas examined, number of subjects, and results of the statistical calculations on which Fig. 12 - 15 are based. n = number of subjects, a = intercept on the y-axis, b = slope, SE(b) = upper and lower 95% level, r = correlation coefficients. (Midttun, 2000).

Blood flow rate in the pulp of the first **toe** measured by the heat-washout method **(children)**															
Age	3 3/12	3 11/12	4 5/12	4 11/12	5 0/12	6 3/12	7 8/12	7 9/12	8 2/12	8 4/12	10 5/12	11 0/12	11 8/12	11 10/12	15 1/12
Sex	Girl	Boy	Girl	Boy	Boy	Girl	Girl	Boy	Boy	Boy	Boy	Girl	Girl	Girl	Girl
Blood	120.8	157.5	104.2	96.3	96.4	80.0	93.4	94.6	73.7	73.1	67.5	70.6	82.5	88.2	61.7
Flow	126.3	147.9	103.5	90.1	97.0	82.9	89.3	100.6	72.6	70.1	73.9	72.7	59.3	82.4	69.0
Rate	117.2	144.0	103.5	98.5	114.0	95.8	100.0	106.8	56.2	68.2	75.9	72.7	77.1	83.5	73.4
x̄	121.4	149.8	103.7	95.0	102.5	86.2	94.2	100.7	67.5	70.5	72.4	72.0	73.0	83.7	68.0

Blood flow rate in the pulp of the **thumb** measured by the heat-washout method **(adults)**																
Age	27	29	34	38	46	48	53	58	67	65	71	77	84	84	91	93
Sex	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
Blood	121.4	112.8	127.1	156.8	179.1	127.3	128	98.9	122.6	137	135.2	117	61.9	120.9	61.9	84.3
Flow	117.8	90	144.1	154.5	158.2	129.4	136.9	102.3	110	134.7	134.2	114.9	61.9	116.2	58.8	98.7
Rate	121.4	110.8	143.4	148.4	99.2	137.6	131.2	96.9	125.9	127.7	109.9	117	51.1	120	60.9	82.4
x̄	120.2	104.5	138.2	153.2	145.5	131.4	132	99.4	119.5	133.1	126.4	116.3	58.3	119	60.5	88.5

Blood flow rate in the pulp of the first **toe** measured by the heat-washout method **(adults)**																
Age	27	29	34	38	46	48	53	58	67	65	71	77	84	84	91	93
Sex	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
Blood	92.4	50.5	61.4	79.5	70.2	95.8	101.7	82.8	69.1	54.2	68,4	85.8	38.6	54.6	79.8	40.4
Flow	98.6	51.8	59.5	80.7	66.0	96.9	99.4	74.8	63.6	69.3	78.0	79.6	60.2	58.7	88.0	42.3
Rate	98.9	54.8	98.4	82.5	60.3	112.7	67.4	82.0	68.2	62.8	61.9	53.8	40.2	46.7	69.3	30.1
x̄	96.6	52.4	73.1	80.9	65.5	101.8	89.5	79.9	67	62.1	69.4	73.1	46.3	53.3	79	40.6

Table 2b. Represent blood flow rates measured by heat-washout in the toe pulp of 15 children, in the thumb pulp of 16 adults, and in the toe pulp of 16 adults.

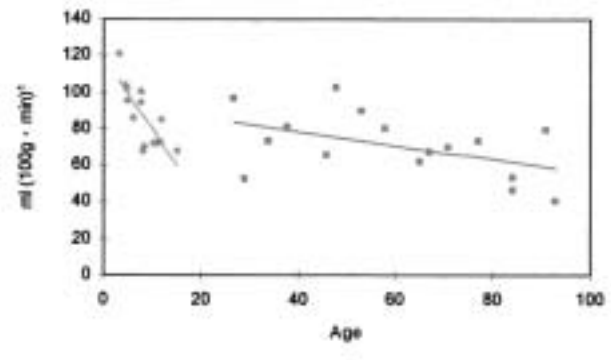

Fig. 12. Blood flow rate in the pulp of the first toe of 14 children between the ages of 3 and 15, and 16 adults between 27 and 93 years old. ♦ = children, n *= adults. (Midttun, 2000).*

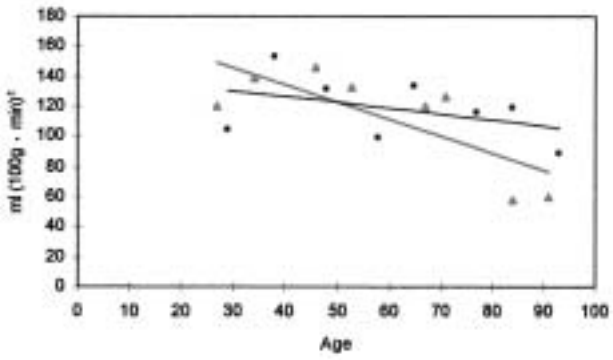

*Fig. 13. Blood flow rate in the **thumb** pulp of 16 adults (8 women, 8 men) between 27 and 93 years old.* s *and black line = women, ● and dotted line = men. (Midttun, 2000).*

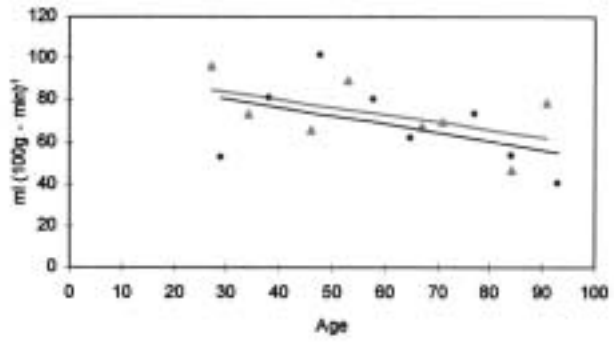

*Fig. 14. Blood flow rate in the pulp of the first **toe** of 8 women and 8 men between 27 and 93 years old. ▲ and black line = women, • and dotted line = men. (Midttun, 2000).*

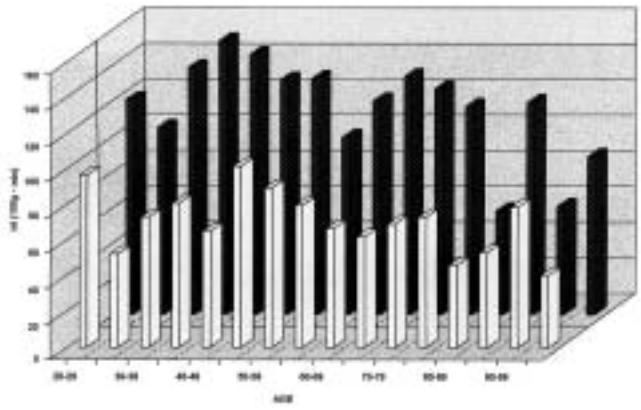

*Fig. 15. Blood flow rate in the **thumb** and the **pulp** of the first toe of 16 adults between 27 and 93 years old. Black bars = thumb pulp, white bars = toe pulp. (Midttun, 2000).*

AVA's in new born babies (Lossius et al., 1994), and in the preterm babies the vasomotor control seemed immature (Lossius et al., 1994, Jahnukainen et al., 1993). In the present study blood flow rate was measured in children between 3 3/12 and 15 1/12 years old, and only in the pulp of the first toe because of the relatively large diameter of the probe and small size of the fingers. Blood flow rate was disproportionally high in the two youngest children. That may be due to a slight heat loss from the probe to the surroundings during heat-washout because of very small toe pulps. The results of the latter was therefore excluded in the calculations, and that did not influence the final result. The statistical differences between blood flow rate in the children and adults were highly significant ($p = 0.0001$), so there is no doubt though that blood flow rate is highest in the youngest children, and lowest in the oldest subjects. In conclusion the indication of the presence of AVA's in the pulp of the first toe of children between 3 and 15 years old is strong.

Metabolism is high in children. It rises rapidly in the first weeks after birth, reaches a peak in early youth, and then declines slowly and more or less continuously throughout the remainder of the life. For instance, in boys from 7 to 20 years old metabolic rates decrease from 49 to 40 calories per m^2 per hour. Previous examinations have shown that basal metabolic rate decreases even as much during the first 20 years of life as during the following 60 years (Brown et al., 1966). The reason why the AVA-blood flow rate decrease during lifetime is most probably due to changes in metabolic rate rather than to endothelial and sympathetic changes. In the present study blood flow rate in the toe pulp at the age of 15 is at the same level as in young adults.

No significant difference in blood flow rate in thumb or toes was observed between men and women, even though the interplay between age and metabolic factors as determinant of endothelial function is different in healthy men and women (Sarabi et al., 1999), and women have about 10% lower metabolic rate under standard conditions than males of the same age and size (Brown et al., 1966). Previous examination on thumb pulp blood flow rate gave the impression that blood flow rate was higher in women than in men, but the different was not reproducible (Midttun et al., 1996).

Blood flow rate in the pulp of the fingers was significantly higher than in the toe pulps of all adult subjects ($p < 0.125$), but the relative decrease with increasing age was about the same in the two regions. The difference has previously been described (Midttun el al., 1996), however no obvious explanation for the difference was found. According to Grant and Bland (1931) the amount of AVA's is greater in the finger pulps than in the toe pulps, and furthermore the hydrostatic pressure in the AVA's of the toes is higher than in the fingers in upright position. Therefore the smooth muscle cells of the vessel wall are presumably relatively hypertrophic resulting in a smaller mean luminal diameter of the AVA's of the toes than of the fingers that may be the explanation of the difference in blood flow rate.

The function of all human organs decreases with increasing age, and from the age of 30 the mean decrease in per cent per year is the same even though the absolute decrease varies from organ to

organ. Metabolic rate seems to decrease slower than other organ functions (Viidik, 1998). Previous studies have shown that basal whole-leg arterial blood flow rate and vascular conductance are reduced with age in healthy adult men, and that these changes are associated with elevation in sympathetic vasoconstrictor nerve activity. Furthermore the lower whole limb blood flow is related to a lower oxygen demand that is independent of tissue mass (Dinenno et al., 1999). In the present study all subjects were in a recumbent and relaxed position and a positive heat balance with warm hands and feet, resulting in wide open AVA's and a great heat loss, and no sympathetic activity was supposed to influence the results. Therefore the decrease observed may be due to a combination of increasing stiffness of the AVA's, reduced metabolic rate, and presumably endothelial changes.

The examinations showed that AVA blood flow rate in the finger pulps was higher than in the toe pulps, probably due to differences in diameter and number of AVA's in the two regions. There was no significant difference in AVA blood flow rate between men and women. AVA blood flow rate decreases with increasing age. The decrease starts in the childhood in accordance with the decrease in metabolic rate, and is rapid during the first about 15 years. The curve then levels off, and the decrease continues slowly throughout the rest of the life, never the less blood flow rate in the AVA's is still higher in healthy subjects at the age of 70 (and 90) than in people suffering from symptomatic atherosclerosis (Midttun et al., 1996)

Pathophysiological Examinations

Blood flow rate during arthostatic pressure changes in the pulp skin of the first toe

The local regulation of blood flow through capillaries in the periphery of extremities has been studied in detail in skin, subcutaneous adipose tissue, and skeletal muscles (Henriksen & Paaske, 1980, Eickhoff & Henriksen, 1985). The regulation of the blood flow through the AVA's of the toe pulp in healthy subjects has been shown (Midttun & Sejrsen, 1996). However it is not known how the AVA's react to orthostatically induced pressure changes in patients with occlusive arteriosclerotic disease.

Intermittent claudication (functional ischemia) is a symptom of relative blood flow insufficiency and inadequate substrate delivery in relation to local metabolic needs during exercise, and critical ischaemia is characterized by inadequate resting blood flow. As the capillaries and the AVA's are supplied from the same arteries, local disturbances in the regulation of AVA-perfusion might play a role for the development of the symptoms and signs of arterial insufficiency. During critical ischaemia it would seem to be harmful if even a small part of the total blood flow supply should bypass capillaries and go through AVA's.

For these reasons the present study was undertaken in normals, claudicants, and patients with chronic critical ischaemia to examine the absolute and fractional blood flow rates through capillaries and AVA's in the cutaneous tissue of the pulp of the first toe, and to assess the microvascular responses in terms of blood flow rate regulation to orthostatically induced blood pressure changes.

Patients

The examinations were performed in a prospective open study on three groups of volunteers:

A) Six normal subjects (two males; median age 43 years, range 33 - 62) without symptoms or clinical signs of arterial disease. All had four pedal pulses and normal systolic ankle blood pressure. These patients were taken from the a previously published study (Midttun & Sejrsen, 1996).

B) Seven patients (three men; median age 69 years, range 53 - 84) with unilateral intermittent claudicatio of the calf muscle (Fontaine group II a) (Fontaine et al., 1954), and an ankle blood pressure index (i.e., segmental systolic ankle blood pressure/systolic arm blood pressure) above 0.30 on the symptomatic side.

C) Six patients (three men; median age 69 years, range 58 - 80) with unilateral chronic critical ischaemia were examined. The patients were characterized by persistently recurrent ischaemic rest pain that had required analgesia for more than 2 weeks and with a segmental ankle systolic blood pressure below 50 mmHg on the symptomatic side (none had ulceration or gangrene), (Second European consensus document on critical leg ischemia, 1992).

Methods

Patients with venous diseases or with diabetes mellitus were excluded from the study. Systemic (arm) blood pressure was recorded by conventional sphygmomanometry, and the segmental systolic ankle blood pressures was measured by the strain gauge method.

The subjects were resting on an examination couch in supine position in a room with a temperature between 21 - 24°C. Blood flow rate was measured with as well the ***heat-washout method*** as the ^{133}***Xe-washout*** method in the pulp of the first toe with the leg passively elevated and immobilised 50 cm **above heart level** (a), with the toe **at heart level** (b), and with the toe 50 cm **below heart level** (c). Elevation was not performed on patients with critical ischaemia because of increased pain.

^{133}***Xe-washout*** registrations were made for 40 min, and the after curves resolution were analysed as described above.

Results

The results are given in tables 3 - 5. Figure 16 presents the absolute blood flow rates obtained by the ***heat-washout method*** at the various levels in the three investigated groups. In figure 17 blood flow rates as measured with ***heat-washout*** are plotted as the blood flow rates at the given test level above or below the heart divided by the value measured at the reference (heart) level in order to show the fractional change in perfusion rate in the two test positions in relation to the reference level.

Normal subjects									
Pt.	50 cm above heart level			At heart level			50 cm below heart level		
No.	Heat		^{133}Xe	Heat		^{133}Xe	Heat		^{133}Xe
	ml·(100g·min)$^{-1}$			ml·(100g·min)$^{-1}$			ml·(100g·min)$^{-1}$		
	Right	Left	Right	Right	Left	Right	Right	Left	Right
1	20.8	23.3	5.8	53.2	60.6	6.5	53.9	59.2	13.2
2	29.2	26.7	9.7	50.7	47.3	9.0	44.2	59.4	9.2
3	32.3	27.8	9.0	40.8	49.9	11.7	46.5	52.8	6.4
4	23.3	20.9	8.1	42.9	42.6	10.8	46.9	44.1	10.4
5	25.6	28.4	13.5	57.2	50.6	10.2	63.7	47.9	6.3
6	24.0	25.0	9.3	46.0	49.6	12.1	46.0	46.1	5.8
$\bar{x}$	25.3		9.2	49.8		10.5	47.4		7.8
S.E.	0.99		1.0	1,70		0.8	1.95		1.2

Table 3. The results of the measurements of the blood flow rate in the pulp of the first toe in normal subjects with (1) the heat-washout method, and (2) the ^{133}Xe-washout method. Blood flow rate was measured at three positions of the toe pulp in relation to the reference level of the heart in supine patients: heart level, 50 cm above the heart, and 50 cm below heart level. $\bar{x}$ = median value, and S.E. = standard error of the mean. (Midttun et al., 1997)

Patients with intermittent claudication									
Pt.	50 cm above heart level			At heart level			50 cm below heart level		
No.	Heat		^{133}Xe	Heat		^{133}Xe	Heat		^{133}Xe
	ml·(100g·min)$^{-1}$			ml·(100g·min)$^{-1}$			ml·(100g·min)$^{-1}$		
	Sympt	Asympt	Sympt	Sympt	Asympt	Sympt	Sympt	Asympt	Sympt
1	26.6	47.3	-	31.7	33.6	10.4	57.0	40.4	21.1
2	42.6	29.6	7.6	32.0	31.6	13.9	83.2	59.4	7.1
3	22.8	23.8	9.7	28.5	79.4	10.8	47.3	74.4	12.1
4	-	27.4	-	27.2	91.6	-	41.1	123.8	-
5	-	39.7	-	30.9	58.1	-	49.8	34.0	11.5
6	18.5	18.0	-	45.4	58.3	8.4	57.4	54.3	7.1
7	3.0	40.9	14.7	47.6	61.1	12.2	49.9	55.5	11.3
$\bar{x}$	22.8	29.6	9.7	31.7	58.3	10.8	49.9	55.5	11.4
S.E.	6.39	3.97	2.1	3.11	8.28	0.9	5.14	11.3	2.1

Table 4. The results of the measurements in patients with intermittent claudication. Symp signifies symptomatic leg, asymp the asymptomatic. - indicates that blood flow could not be determined for technical reasons. Blood flow rate was measured at three positions of the toe pulp in relation to the reference level of the heart in supine patients: heart level, 50 cm above the heart, and 50 cm below heart level. $\bar{x}$ = median value, and S.E. = standard error of the mean. (Midttun et al., 1997).

Heat-washout results

In group **A,** normal subjects, blood flow rate halved when the toe was elevated to 50 cm above heart level, but it remained unchanged as compared with heart level value, when the toe was placed 50 cm below the heart. In group **B**, patients with intermittent claudication, blood flow rate was halved at elevation on the asymptomatic side, but on the symptomatic side it fell to 72% of value at heart level. Below heart level, blood flow rate on the asymptomatic side remained constant as compared to heart level, but on the symptomatic side blood flow rate increased by a factor 1.6. In group **C**, patients with critical ischaemia, blood flow rate was halved on the asymptomatic side by elevation, but it increased by 18% as compared to heart level, when the toe was placed 50 cm below the heart. During lowering, changes in blood flow rate was not observed on the side with critical ischaemia.

Patients with critical ischaemia									
Pt.	50 cm above heart level			At heart level			50 cm below heart level		
No.	Heat		^{133}Xe	Heat		^{133}Xe	Heat		^{133}Xe
	ml·(100g·min)$^{-1}$			ml·(100g·min)$^{-1}$			ml·(100g·min)$^{-1}$		
	Right	Left	Right	Right	Left	Right	Right	Left	Right
1	-	19.8	-	26.0	48.4	21.6	13.2	46.2	15.2
2	-	37.6	-	23.5	44.6	13.9	19.8	35.2	13.9
3	-	22.1	-	18.5	38.1	13.1	24.5	48.5	15.7
4	-	16.1	-	28.5	42.2	8.8	39.3	51.9	-
5	-	16.0	-	15.7	34.5	11.9	22.8	62.4	15.3
6	-	50.4	-	23.6	32.6	12.1	30.4	44.2	6.8
$\bar{x}$	-	21.0	-	23.6	40.2	12.6	23.7	47.4	15.2
S.E.	-	5.7	-	1.94	2.48	1.8	3.67	3.67	1.7

Table 5. The observations in patients with critical ischemia. All patients had aggravation of their ischaemic rest pain during elevation to 50 cm above heart level, so it was considered unethical to proceed with measurements of that level. Blood flow rate was measured at three positions of the toe pulp in relation to the reference level of the heart in supine patients: heart level, 50 cm above the heart and 50 cm below heart level. $\bar{x}$ = median value, and S.E. = standard error of the mean. (Midttun et al., 1997).

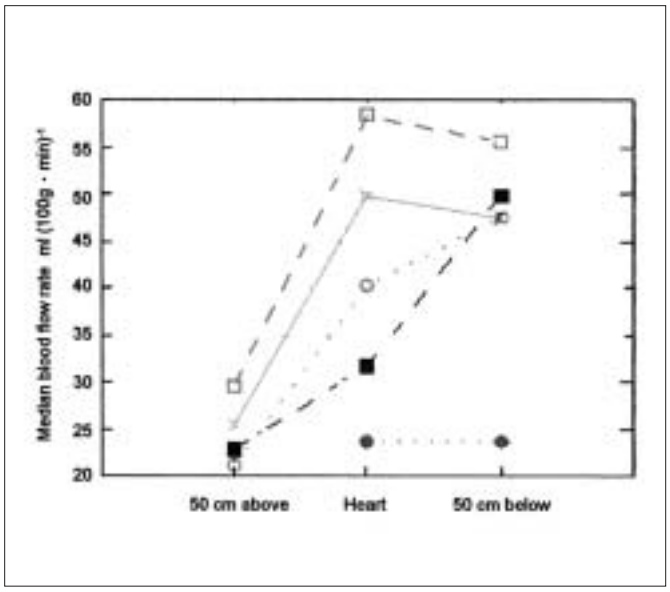

Fig. 16. The median blood flow rate in ml(100 g · min)$^{-1}$ as function of the position of the pulp of the first toe in relation to the heart as measured with the heat-washout method. (x) normal subjects; (q) claudicants: Asymptomatic side; (n) claudicants: Symptomatic side; (∘) critical ischaemia: Asymptomatic side; (•) critical ischaemia: Symptomatic side. (Midttun et. al., 1997).

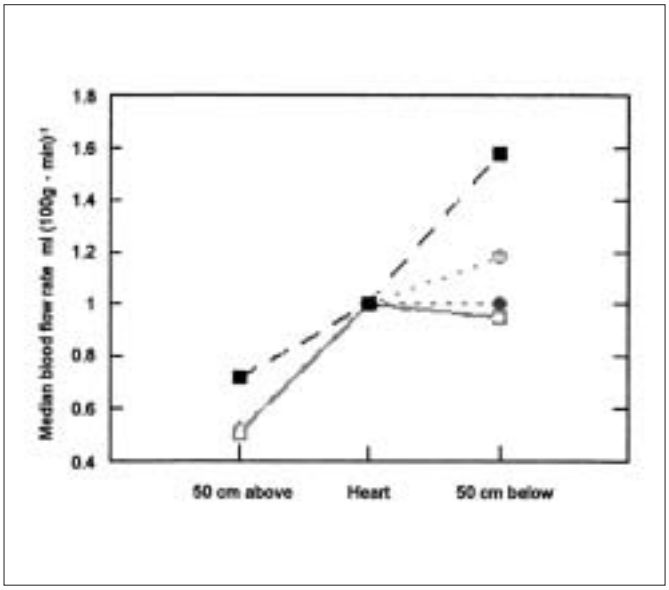

Fig. 17. Median blood flow rates as measured with the heat-washout method are plotted as the blood flow rate at the given test level above or below the heart divided by the value measured at the reference heart level in order to illustrate the fractional change in perfusion rate at the two test positions. (x) normal subjects; (q) claudicants: Asymptomatic side; (n) claudicants: Symptomatic side; (∘) critical ischaemia: Asymptomatic side; (•) critical ischaemia: Symptomatic side. (Midttun et al., 1997)

^{133}Xe-washout results

Blood flow rate remained practically the same (around 10 ml(100 g · min)$^{-1}$) regardless of the position of the toe pulp.

Discussion

Measurement of absolute capillary blood flow rate in the skin of the distal extremities in areas without AVA's at heart level, has shown that it is not possible to distinguish on this basis between normals, claudicants, or patients with critical ischaemia (Henriksen, 1977). This was also the case in the present study.

The reason why patients with ischaemic rest pain get relief from their pain when they hang the leg down is due to the fact that autoregulation and also

the veno-arteriolar reflex in the forefoot are defective in the arterioles supplying the capillaries of the forefoot due to ischaemic paralysis of the smooth muscle cells in the arteriolar media layer (Henriksen, 1974). Furthermore arteriolar constriction in normal regions positioned more proximally will increase the pressure head to distal regions due to eliciting of the veno-arteriolar reflex in the regions. Using nail fold capillary video microscopy it has been shown that patients with relief of rest pain while sitting did not always have a higher linear velocity of the read corpuscles, but did have a higher density of perfused capillaries in the sitting position (Ubbink et al., 1995). These experiments are not directly comparable to the present series, where the limb was moved passively down to the test level in the supine subject to minimize central vasoregulatory modulations of blood flow. These previous studies were performed in areas without AVA's.

Normal subjects: Previous studies have shown that in normal subjects the capillary blood flow rates of cutaneous and subcutaneous adipose tissue as well as skeletal muscle tissue are autoregulated (Henriksen et al., 1973). The result of the present study with the ^{133}Xe-washout method showed that the **capillary blood flow rate** of the skin in the toe pulp in normals remained constant within the entire examined pressure range. It follows that autoregulation of blood flow was present in the arterioles of the toe pulp, even at 50 cm above heart level, whereas the veno-arteriolar axon reflex was absent in this region, as the vascular resistance at 50 cm below the heart was identical to that at heart level.

The **AVA-blood flow rate** at 50 cm above heart level decreased to half the level of the value measured at heart level, whereas AVA blood flow rate at 50 cm below the heart was identical to that at heart level as shown by the heat-washout method.

Claudicants: In patients with intermittent claudication the capillary blood flow rate in the distal part of the symptomatic leg during rest has been shown to be similar to that of normal persons (Henriksen, 1974). This was also the case in the present study. In addition, the results of the examinations of both the symptomatic and the asymptomatic leg showed a behaviour with respect to regulation of local blood flow rate in the examined area that was identical to that of normal persons, i.e., presence of autoregulation of blood flow, but absence of veno-arteriolar reflex.

At elevation of the toe to 50 cm above heart level, blood flow rate through the AVA's on the symptomatic side fell to 72% of the value at heart level. The absolute value of AVA-blood flow rate was about half the value of that found in normal subjects and in the asymptomatic leg of these claudicants. This is probably because there is a larger resistance in the major arteries of these symptomatic, atherosclerotic legs which will tend to give smaller AVA blood flow rates at a given blood pressure at all levels.

During lowering to 50 cm below heart level AVA blood flow rate increased by a factor 1.6 on the symptomatic side which is in contrast to the unchanged blood flow rate in normal subjects and on the asymptomatic side of these patients. Blood flow rate as measured by heat-washout in the asymptomatic leg in patients with intermittent claudication showed higher values at all levels as compared to normals. This is probably due to the reduced wall thickness (atrophy) induced by relatively lower arterial blood pressure that results in increased compliance.

Patients with **critical ischaemia**: As previously stated, it was considered unethical to pursue measurements above heart level in these patients where blood flow rate must be zero or very close to that value.

During lowering to 50 cm below heart level, AVA-blood flow rate in the toe pulp of the asymptomatic leg increased by 18% as compared to the value at heart level, an intermediary response between the normal findings and the behaviour of the claudicants. It is difficult to interpret this finding in clinical terms since possible symptoms of claudication may be masked by critical ischaemia on the contra lateral side. It must be speculated that some degree of impaired local blood flow regulatory response is present even on the asymptomatic side of patients with critical ischaemia.

On the symptomatic side in these patients, no increase in AVA blood flow rate was observed during lowering of the leg. Besides, the absolute values of the AVA blood flow rates were only around half the value of that in normals. The absolute value of the AVA-perfusion coefficient was low (about 10 ml(100 g · min)$^{-1}$ as obtained by subtracting the capillary blood flow rate measured by ^{133}Xe-washout from the total blood flow rate measured by the heat-washout method. Thus, only half of the total blood flow rate passed AVA's in these patients. An increase in AVA blood flow rate was not observed during lowering. This shows that the increase in transmural pressure did not result in an increase in blood flow rate. This is presumably due to an extremely low or absent increase in

compliance in AVA's and arterioles, as expected, caused by atherosclerotic changes.

During ^{133}Xe-washout (40 min) the subject has to be completely immobilised, otherwise it is not possible to obtain a washout curve suitable for curve resolution. Curve resolution is essential when a cutaneous ^{133}Xe-washout curve is wanted. As it is almost impossible for the subjects to rest immobile for 40 min, some of the curves were not useful and were therefore excluded. Consequently, only subcutaneous ^{133}Xe-washout was chosen for the following studies.

The results show that by measuring AVA blood flow rate in the toe pulp at and below heart level it is possible to distinguish between normals, claudicants, and patients with critical ischaemia.

Peripheral blood flow rates and microvasdular respons to orthostatic pressure changes in claudicants before and after revascularisation

The present study was undertaken to: (a) assess absolute (resting) blood flow rates in toe pulp skin positioned at heart level before and after vascular surgical intervention for intermittent claudication due to atherosclerosis, and (b) to study the microvascular responses to orthostatic pressure changes before and after surgery.

Patients

The examinations were performed in a prospective, open study on 11 non-diabetic patients (five men; mean age 68, range 54 - 77 years) with intermittent claudication in the calf (Fontaine group II a) (Fontaine et al., 1954), and an ankle blood pressure index (API = segmental systolic ankle blood pressure/systolic arm blood pressure) above 0.30 on the symptomatic side (European working group on critical leg ischaemia, 1992). The median API was 0.47 (0.38 - 1.00). The examinations took place just before surgery, and on average 7 (2 - 11) months after surgery. The intervention included five aortobifemoral prosthetic grafts, three femoropopliteal grafts with distal anastomosis above the knee, one femoropopliteal above the knee *in situ* graft, one femorofemoral crossover prosthesis, and one percutaneous transluminal angioplasty with stent in the supragenicular popliteal artery. Only the most symptomatic side was chosen for study. After operation the ankle blood pressure index, API, was in median 0.69 (0.46 - 1.08) on the side of interest, and pulse could be palpated in at least one artery at ankle level or on the back of the foot. None of the patients had clinically detectable leg oedema at the time of postoperative examination.

A subgroup of a previously published study (Midttun et al., 1996) consisting of six normal subjects (two males; median age 43 years (33 - 62)) without symptoms or clinical signs of arterial disease acted as a control group. All had four pedal pulses and normal systolic ankle blood pressure. In these individuals measurements were made on both feet.

Methods

The subjects were in a positive heat balance and resting on an examination couch in supine position in a room with a temperature of 21 - 24°C. Blood flow rate was measured with the ***heat-wash-out method*** in the pulp of the **first toe** (a) with the toe **at heart level**, and (b) with the toe passively positioned 50 cm **below heart level**.

Results

In the control group (normal subjects), blood flow rate in the pulp skin of the first toe at rest did not change during 50 cm lowering in relation to the heart in the supine individual. The 25/75 quartiles were 44.5/52.0 ml(100 g · min)$^{-1}$ at heart level and 46.0/56.6 ml(100 g · min)$^{-1}$ when lowered, giving a blood flow ratio of 0.97/1.10 (N.S., ANOVA, logarithmic, paired t-test).

Before reconstruction, blood flow rate in claudicants was 31.7 (27.9/46.1) ml(100 g · min)$^{-1}$ at heart level. Blood flow rate increased by a factor 1.79 (1.50/1.87) (ratio of (50 cm down)/(heart level)) when the toe was lowered to 50 cm below heart level, where blood flow rate was 57.0 (50.1/73.8) ml(100 g · min)$^{-1}$. After reconstruction, resting blood flow rate at heart level was 51.8 (47.2/94.8) ml(100 g · min)-1, and at 50 cm down blood flow rate was 65.6 (49.1/74.0) ml(100 g · min)-1. The ratio of (50 cm down)/(heart level) was 0.93 (0.77/1.52).

The Mann-Whitney test showed that resting blood flow rate at heart level was significantly lower in the claudicants before operation than in the group of normal subjects ($p = 0.0076$). Blood flow rate at heart level increased postoperatively by a factor of 1.63 ($p = 0.0128$) to normal values (n.s.). Before surgery, blood flow rate increased (by a factor of 1.79) during lowering as compared to the value at heart level ($p<0.0051$), but after surgery blood flow rate was the same at heart level and at 50 cm delevation (n.s.) - and like that in normal subjects (n.s.) (see figure 18). It is seen that the response to lowering was less pronounced after operation as compared to the preoperative measurement in all cases.

Discussion

Our findings show that the resting blood flow rate in pulp skin at heart level was significantly reduced in claudicants before surgery as compared to normals. It is interesting that although the material in a certain sense is heterogenous (proximal or distal reconstructions), the pathophysiological variables in terms of ankle blood pressure and blood flow rates were comparable. The reduction in blood flow rate is probably due to the larger

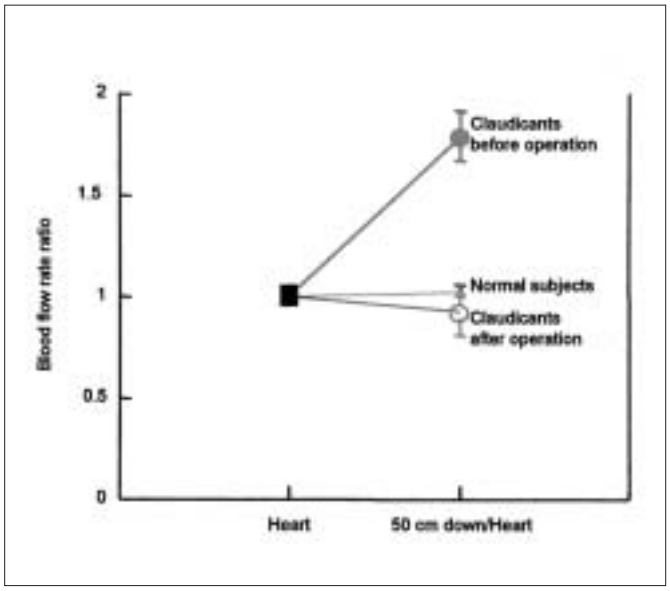

Fig. 18. Blood flow rate was measured with the heat-wash-out method in the first toe pulp skin of normal subjects (x), claudicants (Fontaine IIa) before revascularisation (•), and claudicants 7 (2-11) months after the procedure (°). The blood flow ratio, as illustrated in the figure, was calculated by dividing the blood flow rate measured after lowering the foot 50 cm down by the value measured at heart level. In this way a relative measurement of the response to lowering is obtained. The preoperative response to lowering in claudicants is markedly different to normal subjects, since an increase in blood flow rate by a factor 1.79 was observed in claudicants during dependency, whereas the blood flow rate in normals are identical at heart level and during 50 cm dependency. The preoperative pathological response in claudicants reverted towards normal after surgery. (Midttun et al., 1999).

resistance in major arteries which will tend to give smaller shunt vessel blood flow rates at a given blood pressure. This finding is of interest since nutritional blood flow rate through capillaries is the same at heart level in normals and claudicants (Strandell & Wahren, 1963, Henriksen & Paaske, 1980, Midttun et al., 1997). This means that the capillary circulation is able to maintain normal perfusion rates through modulations in arteriolar tone, but in claudicants there is a reduction in overall pulp perfusion due to decreased AVA-blood flow rate at heart level.

During lowering, blood flow rate through AVA's increased in claudicants. This was presumably due to increased compliance in the AVA's by atrophic adaptation of the vascular smooth muscles to lower systemic arterial blood pressure in the periphery of the extremities. This theory is in accordance with observations by Popoff (1934) who found the AVA's to be wide open channels in patients with senile atherosclerosis. The elastic fibres were thickened, fragmented and distorted. These anatomical changes must be taken as an indication of increased compliance. Arteriolar contraction and dilation are not compromised in claudicants in spite of the reduced absolute blood flow rate, so it is reasonable to believe that myointimal cell metabolism concerning vasoreactivity is not deranged in claudicants. Since loss of flow mediated vasodilation reflects endothelial dysfunction, it seems as if the endothelium is not damaged in this respect in non-diabetic claudicants even though endothelial dysfunction is associated with atheroma formation. This is in contrast to a recent study in patients with non-insulin dependent diabetes, where signs of endothelial dysfunction were present before the appearance of microalbuminuria (Goodfellow et al., 1996). The role of important vasodilators (such as nitrous oxide) and vasoconstrictors (e.g., endothelin-1) for modulation of AVA tone remains to be examined in detail, but a resent study demonstrated that endogenous nitric oxide production may be more important in regulating microvascular skin blood flow rate in regions rich in AVA's than in areas containing mainly nutritive vessels (Noon JP et al., 1996).
The theory of increased compliance in AVA's (atrophic adaption to lower systemic arterial blood pressure in the low pressure distal vascular bed of claudicants) is also supported by the increased blood flow rate during dependency.
After surgery, skin pulp circulation in claudicants reverts towards normal in two ways: both with respect to absolute blood flow rate, but also with respect to a normalisation of the response to passive dependency. This signifies that the atrophy of the AVA vessel wall is reversible when the distal arterial perfusion pressure is normalised and that permanent damage has not been induced by the chronic claudication state. The smooth vessel wall of the AVA's is richly supplied with nerve fibres (Molyneux, 1977). It is generally assumed that the diameter of these vessels is influenced neither by local metabolites nor by regional temperature changes (Hales et al., 1978), consequently the nervous control of smooth muscle tone should be normal even in AVA-areas with low systemic blood pressure, so the fundamental disturbance in these vessels is probably smooth muscle atrophy. This would imply that the smooth muscle cell contraction at a given nervous stimulus would be less pronounced in claudicants as compared to normals (Paaske & Henriksen, 1975). This has no metabolic consequences during rest, but it might

be speculated that this could probably lead to a suboptimal redistribution of blood flow during walking and thus augments the severity of the claudication symptoms.

In conclusion measurements of absolute blood flow rates in toe pulp skin and of perfusion response to passively induced orthostatic pressure changes are, in combination, able to identify patients with intermittent claudication. Vascular surgical intervention normalises both pulp skin perfusion and the responses to orthostatically induced pressure changes.

Is non specific aneurysmal disease of the infrarenal aorta also a peripheral microvascular disease?

The tunica media of the infrarenal aortic wall of patients with non specific abdominal aneurysm exhibits chronic inflammation and degradation of the extracellular matrix with disorganization and disruption of the elastic fibres (He & Roach, 1994, Rizzo et al., 1989, Newman et al., 1994, Satta et al., 1998), so the normal vessel architecture is destroyed (Wills et al., 1996) with thickening of the intima and the medias as part of the remodelling

Accumulating evidence suggest that the vessel wall is being degraded by a synergistic combination of macrophages (Elmore et al., 1998, Curci et al., 1998), plasminogen activators (Reilly, 1996), the elastolytic matrix metalloproteinases (Elmore et al., 1998, Patel et al., 1996, Sakkalihasan et al., 1996), and other proteolytic enzymes, unbalancing the protease- antiprotease system (Curci et al., 1998, Rao et al., 1999). Since both genetic, anatomic, mechanical, biochemical, and acquired factors contribute to the degenerative process, it is no longer tenable to consider the development of abdominal aortic aneurysms as being simply due to atherosclerosis (Sonesson et al., 1997).

The reduced elastin contents causes a stiffer - less compliant - vessel wall of the dilated and elongated process (Sumner et al., 1970). The results of a series of examinations of the common carotid artery in patients with abdominal aortic aneurysms showed that the abdominal aortic aneurysm is a generalized process of the arteries with focal manifestation in the abdominal aorta (Sonesson et al., 1997), since carotid stiffness - as determined by ultrasound echo tracking technique and (auscultatory) systemic blood pressure measurements - was significantly increased in both sexes.

Normal arterioles in the peripheral tissues such as skin, subcutaneous adipose tissue, and skeletal muscles have numerous elastic fibres which are the effector organ for local blood flow rate modulation and control. AVA's have a wall with well developed smooth muscle cells and a rich supply of muscle fibres (Midttun et al., 1999). The difference in the structure of the walls of the arterioles and the AVA's presented an opportunity to examine whether aneurysmal disease of the aorta is a generalized disease in the major arteries, or whether the disorder has a functional component in the peripheral microvasculature, too.

Patients

The examinations were performed in a prospective, open study on two groups of subjects: a) **ten normal subjects** (mean age 70 years, range 64 - 78; three females), and b) **fifteen patients** who had been previously operated for ruptured non-specific infrarenal aortic aneurysm (mean age 69 years, range 59 - 82; three females). All subjects were without signs of venous or peripheral atherosclerotic disease and had normal distal segmental arterial blood pressure and four pedal pulses. None had hypertension or diabetes mellitus.

Methods

The subjects were resting on an examination couch in supine position in a room with a temperature of 21 - 24°C. Blood flow rate was measured by 1) the ***^{133}Xe-washout method*** in the subcutaneous tissue of the **first interstice between the first and second toe**, and in 2) the cutaneous tissue of the pulp of the first toe by the ***heat-washout method.*** With both methods blood flow rate was measured with the foot fixed and immobilised at a) **heart level**, with the foot passively positioned b) 30 cm **below heart level**, and with the foot passively positioned c) 30 cm **above heart level**. The ^{133}Xe-washout registrations were initiated 35 - 40 min after labelling, and made for 7 minutes at each level. A λ -value of 10 ($ml \cdot g^{-1}$) was used for subcutaneous tissue (Sejrsen, 1971).

Results

The results are summarized in table 6, and figure 19a and b .

Capillary blood flow rate in subcutaneous adipose tissue of the forefoot at **heart level and outside heart level** was four times higher in patients with previous rupture of an abdominal aortic aneurysm than in normal subjects ($p = 0.005$; Wilcoxon signed-rank test). Blood flow rate in **AVA's** did not differ at heart level between normal subjects and patients (n.s.).

Capillary blood flow rate 30 cm **below the heart** was reduced in both normals ($p = 0.008$) and patients ($p = 0.01$) as compared to the values obtained at heart level, but the blood flow rate through **AVA's** was not reduced in this position.

Blood flow rate 30 cm **above heart level** did not fall neither in normal **capillaries** nor in the capillaries of patients with aneurysmal disease. Blood

	30 cm above heart level	Heart level	30 cm below heart level
Normal capillaries	2.8 [1.6]	3.7 [1.6]	2.0 [0.9]
Normal AVA's	50.7 [6.8]	66.2 [10.2]	66.4 [11.2]
AAA capillaries	10.4 [6.4]	14.7 [4.1]	10.5 [4.7]
AAA AVA's	48.4 [12.3]	67.5 [16.7]	67.5 [15.7]
Blood flow rate (ml(100 g · min)$^{-1}$) mean (S.D.) (Midttun et al. 2000)			

Table 6. Results of the study: The blood flow rates in capillaries of the subcutaneous tissue of the forefoot, and in AVA's of the pulp of the first toe were measured in 10 normal subjects and in 15 patients who had been previously operated for ruptured abdominal aortic aneurysm (AAA). (Midttun et al., 2000.)

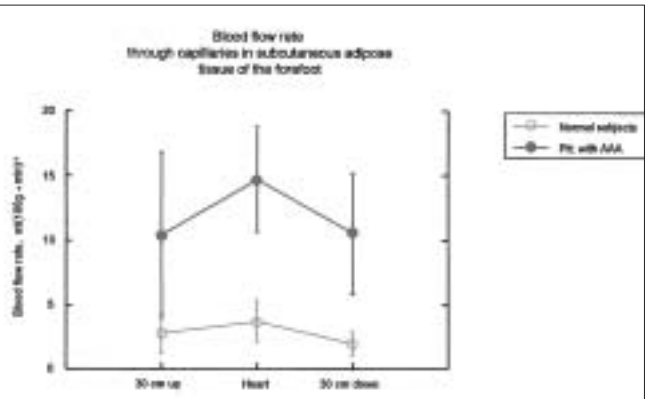

Fig. 19a

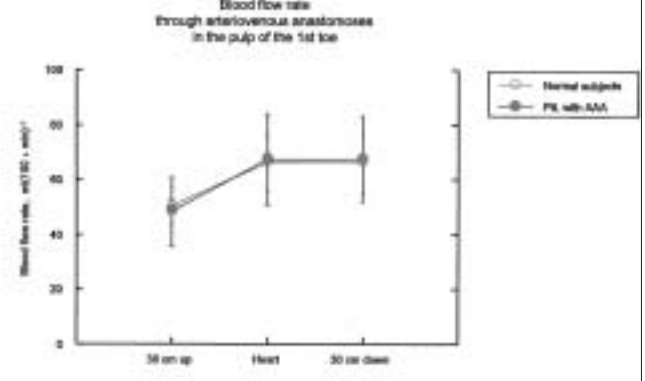

Fig. 19b

Fig. 19 (a and b). Graphic representation of the study results. Heart denotes that the results were obtained with the patient in supine position and with the foot at a level with the heart; 30 cm down and 30 cm up signifies passive elevation of the foot to a level 30 cm below, respectively above, the heart level in the supine subject. (Midttun et al., 2000).

flow rate through **AVA's** decreased significantly by elevation to 30 cm in both groups (p = 0.01 and p = 0.001, respectively).

Discussion

Blood flow rate in subcutaneous adipose tissue of the distal part of the leg in young, healthy subjects is under normal circumstances about 2 - 4 ml(100 g · min)$^{-1}$ (Henriksen et al., 1973).

In the present study the mean value is 3.7 ml(100 g · min)$^{-1}$ in a population with a mean age of 70 years, indicating that blood flow rate in this tissue does not decrease with age in healthy subjects.

In the normal subjects the local sympathetic veno-arteriolar axon reflex, and autoregulation of blood flow were present (Henriksen et al., 1973, Henriksen, 1977), and like in previous examinations blood flow rate in normal AVA's did not show neither autoregulation nor veno-arteriolar reflex (Midttun et al., 1996 and 1997).

In the patients with previously ruptured aneurysm, the basic blood flow rate of subcutaneous adipose tissue was around 15 ml(100 g · min)$^{-1}$ which is four times higher than in normal age and sex matched controls without vascular disease. The only conceivable explanation for this finding is that the arterioles must be more dilated during resting conditions in patients with aneurysm, and the peripheral resistance is diminished. A theoretical objection might be that the increased blood flow rate was due to sequelae of the operation itself, for example damage to the sympathetic nerves. Previous studies have shown though that a sympathetic lesion abolishes the veno-arteriolar reflex for at least ten years post operatively (Henriksen, 1977).

Normal arterioles have a well developed internal elastic membrane (Sleek & Duling, 1986), and the formation of periluminal corrugations of the elastic elements during vasoconstriction is not a random or passive phenomenon, but results from a highly organized smooth muscle cell ultrastructure. There is evidence to suggest that the regular formation of ridges along the intimal border of the smooth muscle cells allows the lumen of an arteriole to maintain an approximately circular profile during vasocontriction (Sleek & Duling, 1986). The ultrastructure of arterioles in peripheral tissues of patients with aneurysmal disease is not known, but the results of our investigations clearly point towards an increase in arteriolar luminal radius under baseline conditions due to defective and disrupted elastin elements in the tunica media.

The results of our study further suggest that the elastic fibres are determinant neither for the operation of the veno-arteriolar axon reflex, nor for the

blood flow rate modulation by autoregulation since both these responses are in operation in aneurysm patients at the much higher blood flow rate level than in normal subjects. Since both mechanisms are present in patients with aneurysmal disease we infer that the function of the smooth muscle cells of the arteriolar wall is not affected by the disease which shows that they have adapted to the change of diameter as well as circumferential shear stress acting on the arteriolar wall. Our study showed identical qualitative and quantitative findings in AVA's in normal subjects and in patients with aneurysmal disease, so the AVA's are functioning normally in aneurysm patients.

Previous studies have shown that blood flow rate in AVA's increases below heart level in patients with intermittent claudication (Midttun et al. 1997, and 1999). In the present study blood flow rate was the same in aneurysm patients at and below heart level. This can be interpreted as absence of functional atherosclerotic components in these aneurysm patients.

Others have claimed that the aortic wall of patients with infrarenal abdominal aneurysm is stiff and less compliant that healthy vessel walls due to elastin disturbances (Sonesson et al., 1997). Furthermore the carotid arteries in patients with aortic aneurysm have showed increased stiffness taken as an evidence for the disease being a generalised structural and functional disorder of the arteries (Sonesson et al., 1997). In the present study the elastic fibres of the peripheral arterioles seemed to be defective as well. It is therefore concluded that non specific aneurysmal disease of the infrarenal oarta seems to have a peripheral arteriolar component.

General conclusion

1) The heat-washout method was described.
2) The heat-washout method was compared to the ^{133}Xe-washout method and seemed to be useful for measuring local, cutaneous capillary blood flow rate at local temperatures between 37 and 45°C. The method was compared to venous occlusion plethysmograhy on the thumb and was not found useful for measuring blood flow rate in areas with AVA's as it measures an average blood flow rate in the part of the finger included in the plethysmogragh.
3) The heat-washout method was examined during a series of normophysiological studies, advantages and disadvantages of the method were described, and it was found useful for measuring blood flow rate in areas with AVAs.
4) Blood flow rate in AVA's of the thumb pulp and the pulp of the first toe were studied, and did not show autoregulation, veno-arteriolar reflex, or hyperaemia, whereas autoregulation of blood flow was present in the arterioles supplying the capillaries of the proximal phalanx of the thumb, first toe, and the pulps. Veno-arteriolar reflex was present in arterioles supplying the capillaries of the pulp and in the skin fold. Reactive hyperaemia was registered in the arterioles supplying the capillaries of the pulp, and in the skin fold. AVA seem to be present in the ear lobe, nose, and presumably sometimes in the forehead as well.
5) Blood flow rate in the AVA's of the thumb pulp and the capillaries of the skin fold between the thumb and the index finger were studied during exercise in healthy subjects. AVA blood flow rate decrease at the onset of moderate exercise, and increased to the initial level after 4.6 min, whereas capillary blood flow rate remained unchanged.
6) AVA blood flow rate was studied in the toe pulp of 15 children and in the toe and thumb pulp of 16 adults showed a decreasing blood flow rate with increasing age, a higher blood flow rate in the thumb pulp than in the toe pulp, but no difference between sexes were found.
7) Comparing blood flow rate in the pulp of the first toe in normals, claudicants, and patients with critical ischaemia showed a significant increase in AVA blood flow rate in claudicants when the foot was placed 50 cm below heart level. Patients with critical ischaemia had a low AVA blood flow rate at heart level and it was unchanged 50 cm below heart level. Capillary blood flow was the same in all groups and remained unchanged at all levels examined.
8) AVA blood flow rate measured before and after vascular reconstruction in claudicants showed a normalisation of blood flow rate in the AVA's of the toe pulp.
9) Capillary blood flow rate increased with a factor four in forefoot subcutaneous tissue in patients with earlier ruptured non-specific abdominal aorta aneurysm, but autoregulation and veno-arteriolar reflex operated as in normals. AVA blood flow rate reacted as in normals.

English Summary

The *heat-washout method* was developed, validated, and found useful for measuring total cutaneous blood flow rate in the forearm and in the pulp of the thumb in absolute values. Blood flow rate in the AVA's can be estimated by subtracting the capillary blood flow rate measured by the ^{133}Xe-washout method, from the total cutaneous blood flow rate measured by the heat-washout method. During heat-washout measurements the local skin temperature is increase a few degrees above normal skin temperature. Local heating increases blood flow rate in local capillaries due to arteriolar dilatation, but not in AVA's, and AVA's do not show reactive hyperaemia. During measuring with the heat-washout method in areas with AVA's, a heat gradient is created during pre-heating, and is subsequently washed away by blood of a lower temperature passing under the probe during washout.

As *venous occlusion plethysmography* used on the finger measures an average blood flow rate of the tissue included in the plethysmograph, this method is unable to measure blood flow rate in cutaneous tissue with AVA's. A correction for the squeezing effect of the finger cuff was recorded during blood flow cessation and is therefore recommended.

Further examinations showed that *autoregulation* of blood flow rate was not present neither in the AVA's of the pulps, nor in the skinfold between the thumb and the forefinger. However it was present in the arterioles supplying the proximal phalanx of the thumb, first toe, and the pulps. The *Veno-arteriolar reflex* did not exist neither in the AVA's, nor in the arterioles supplying the capillaries of the pulps or the skinfold, but in the arterioles supplying the proximal phalanx of the thumb and first toe. Reactive *hyperaemia* was not registered in the AVA's but in the arterioles supplying the capillaries in the pulp, and in the skin fold. Indirect cooling resulted in a significantly reduced blood flow rate in the AVA's of the thumb of the cooled hand as well as in the contralateral. Examinations of regions of the *face* showed that AVA's most probably are present in the ear lobe, nose, and presumably sometimes in the forehead as well.

At the onset of *exercise* with a moderate load, blood flow rate decreased in the finger pulp, a region with AVA's as well as capillaries. After about 4.6 min of exercise, tympanic temperature increased and subsequently blood flow rate in the AVA's increased to permit elimination of the surplus of heat. In contrast, blood flow rate in the capillaries of the skin fold between the thumb and the forefinger remained constant during 11 min of exercise.

AVA blood flow rate measured in the toe pulp of *subjects between 3 and 93 years old*, and in the thumb pulp of adult men and women showed a decrease in AVA-blood flow rate with increasing age, and the difference between children and adults was highly significant. Blood flow rate in the finger pulp was higher than in the toe pulp, but no significant differences in AVA blood flow rate was found in either thumb pulp or toe pulp between men and women.

Comparing *normals, claudicants, and patients with critical ischaemia* showed that the AVA's exhibit a distinct, characteristic reaction as response to passive elevation and lowering of the extremity in the three groups. Determination of the local blood flow responses to changes in orthostatic pressure changes might permit objective assessment of patients with arterial insufficiency.

Vascular surgical intervention normalises both pulp skin perfusion and the responses to orthostatically induced pressure changes.

Capillary blood flow rate is increased with a factor four in forefoot subcutaneous adipose tissue in patients with earlier ruptured non-specific *abdominal aneurysm* as compared to normal subjects. Consequently arterioles are more dilated, have higher compliance in aneurysm patients, and the smooth muscle cells behave normally. Autoregulation of blood flow and the local veno-arteriolar reflex operate in these patients as in normals. AVA's are functionally unaffected by aneurysmal disease.

Danish Summary

Ved hjælp af Radiometers tc-PO_2-elektrode, der er konstrueret med en termostaseret kappe, er det muligt at måle blodgennemstrømningshastigheden i huden. Blodgennemstrømningshastigheden i hudens arteriovenøse anastomoser (AVA's) kan beregnes ved at måle hudens samlede blodgennemstrømningshastighed med varmeudvaskningsmetoden og derfra trække blodgennemstrømningshastigheden målt i hudens kapillærer ved ^{133}Xe-udvaskningsmetoden. Da varmeudvaskningsmetoden påvirker blodgennemstrømningshastigheden i kapillærerne under proben, er metoden mest anvendelig i områder domineret at AVA's, som ikke påvirkes at lokal opvarmning.

Interessen har været rettet mod måling af blodgennemstrømningshastigheden i hudens AVA's under normofysiologiske og patofysiologiske forhold. Undersøgelserne viste, at AVA's ikke udviste autoregulation af gennemblødningen, og at en veno-arteriolær refleks ikke var til stede, i modsætning til de arterioler, der forsyner kapillærerne i de undersøgte områder. Reaktiv hyperaemi var heller ikke til stede i AVA's. Indirekte køling resulterede i en signifikant reduktion i blodgennemstrømningshastigheden i AVA's i såvel den afkølede hånds tommel-pulpa som i den modsidige hånds AVA's. Yderligere undersøgelser har vist, at ved påbegyndelse af et moderat tungt fysisk arbejde falder blodgennemstrømningshastigheden i tommelens AVA's for atter at stige til normale værdier efter ca 4 1/2 min arbejde, hvorimod blodgennemstrømningshastigheden i hudens kapillærer i hudfolden mellem tommel- og pegefinger er konstant og uforstyrret gennem hele perioden. Desuden er det vist, at blodgennemstrømningshastigheden i AVA's i tommel og storetå falder med stigende alder. Der er ingen forskel på mænd og kvinder, men blodgennemstrømningshastigheden er signifikant højere i tommelfingerens pulpa end i storetåen og højere i storetåespulpa hos børn end hos voksne.

Ser man på de patofysiologiske undersøgelser, hvor blodgennemstrømningshastigheden i storetåens pulpa sammenlignes hos normale, patienter med claudicatio og patienter med kritisk iskæmi, udviser AVA's en helt karakteristisk reaktion på ortostatiske ændringer, hvilket muliggør en objektiv klassificering af patienterne med arteriel insufficiens. Efter karkirurgisk intervention normaliseres både gennemblødningen og det karakteristiske reaktionsmønster.

Undersøgelser af forfodens subkutane kapillærer og storetåspulpa AVA's hos patienter, der tidligere er opereret for rumperet abdominalt aortaaneurisme sammenlignet med normale viste, at patienterne havde en fire gange så høj blodgennemstrømningshastighed i deres kapillærer som raske, som tegn på et reduceret elastinindhold i karvæggen, men at karrene i øvrigt reagerede normalt på ortostatiske ændringer. De AVA's fungerede normalt i begge grupper.

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