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Central and peripheral control of finger blood flow in the cold

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CONTENTS

Chapter 1

General Introduction

The main objective of this thesis is to investigate the interaction of central and peripheral effects on the vascular reaction of the hands to cold. In a nutshell, the main central and peripheral effects on the hand skin vasculature are:

Central effects
The temperature of the blood in the body core is sensed in the hypothalamus. The lower the blood temperature, the higher the sympathetic output to the peripheral blood vessels. Sympathetic activation constricts the blood vessels in the skin and thus retains body heat.

Peripheral effects
A low skin temperature activates thermoceptors and, at very low skin temperatures, nociceptors (Guyton and Hall, 1996). These receptors evoke local vascular reflexes and modify sympathetic output at the spinal and central level.

The majority of the scientific publications concerning the regulation of skin blood flow focus on either the central or the peripheral effects. This is understandable, since partial problems are less complicated, but regrettable because it is well known that both central and peripheral effects are acting simultaneously.

In this study, the interaction between central and peripheral effects is investigated for two particular situations: a situation in which the hand is exposed to mild cold (water temperature 15 - 25°C) so that the cold thermoceptors are activated, and a situation in which the hand is exposed to severe cold (water of 10°C or less), which triggers the cold-pain nociceptors.

Exposure of the hand to mild cold
When the hand is exposed to mild cold by immersion in water of 15 to 25°C, the hand skin temperature slowly decreases to values slightly above water temperature. In this condition, the blood flow in the hand is mainly determined by the temperature of the body core (Wenger et al., 1975; Wyss et al., 1975). Plethysmographic measurements showed that the blood flow in the fingers increased and decreased concomitant with fluctuations in body core temperature around a fixed threshold in esophageal temperature. However, this threshold was difficult to determine since the plethysmographic method is unreliable at low blood flows. Therefore, another method was used in this study, in which finger heat flux in stead of blood flow as measured by plethysmography was the dependent variable. Moreover, the stability of the esophageal temperature threshold was investigated and the influence of mean body skin temperature and hand temperature on the determined

threshold. The latter is important for modelling the blood flow in the hands and feet (e.g., Lotens, 1989, Shitzer et al., 1996).

Exposure of the hand to severe cold

Exposure of the hand to severe cold is immediately followed by a strong vasoconstriction in the skin. Cold-pain sensors in the skin transmit impulses to the Central Nervous System that reacts with an increased sympathetic output resulting in vasoconstriction.

The ensuing low tissue temperatures in the hand may lead to hampered dexterity and, in a later phase, irreparable cold injuries. Cold Induced Vasodilation (CIVD) is supposed to play an important role in the prevention of these threats (Iida, 1949). About five to ten minutes after the initiation of cold exposure of the hand, the blood vessels in the finger tips suddenly open up, which increases the temperature of the finger tips (Fig. 1.1). The vasodilation is followed by a new phase of vasoconstriction. This process repeats itself and is called 'the hunting reaction' (Lewis, 1930). The mechanism of this phenomenon is still in debate. Some authors consider its regulation as a purely peripheral phenomenon, for instance due to a cold induced paralysis of the vascular muscle coat (Guyton and Hall, 1996), while others were able to show a systemic control based on body heat content (Zanick and Delaney, 1973).

In this thesis several experiments are reported which show that both central and local mechanisms are involved in the hunting reaction. Some indicators for the relative importance of central versus local control are the amount of correspondence in hunting between the fingers, the occurrence of synchronization in non-simultaneously immersed hands, and the relation between hunting parameters and core temperature.

All experiments in the international literature investigating central effects on hunting, lack adequate data on the actual core temperature. Therefore, the core temperature was measured in all but one experiment in this study. Since only a minimal amount of data on reproducibility is present in the literature, a special experiment was devoted to this issue.

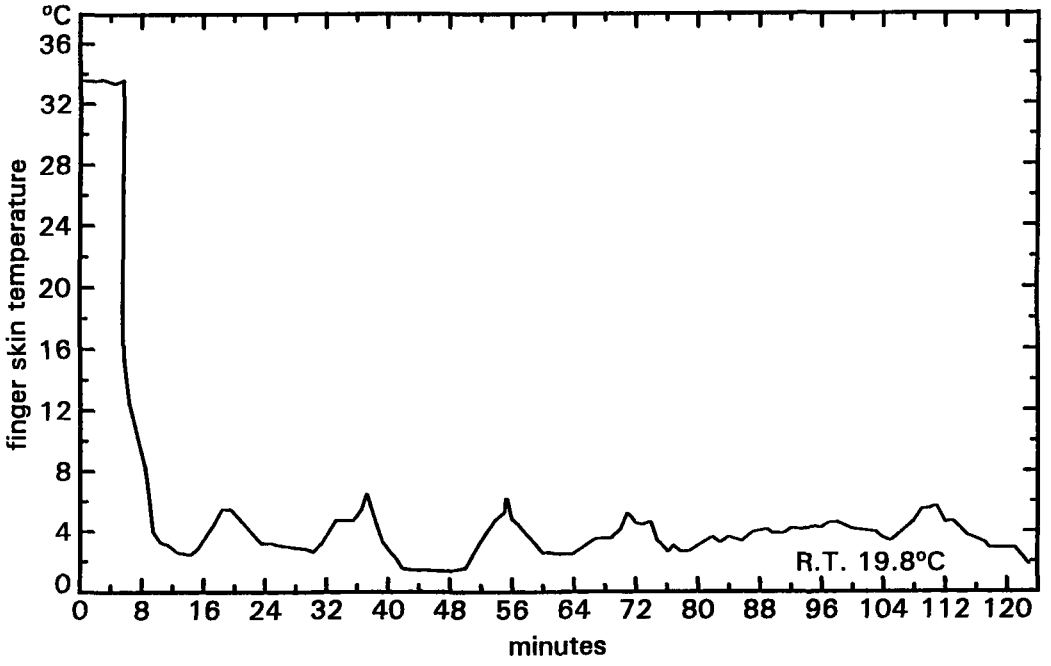

Fig. 1.1 Temperature profile of a finger tip immersed in ice-water (Lewis, 1930). R.T. stands for Room Temperature.

Chapter 2 provides a literature review on the physiological processes that occur in the hand when the human body or the hands are exposed to cold. Arteriovenous anastomoses (AVA's) are assumed to play a major role in thermoregulation, hence, their structure and function are dealt with in more detail. The practical significance of the vascular reactions of the hands to cold to prevent the impairment of the normal dexterity and the occurrence of local cold injuries is also discussed.

Chapter 3 presents the methodology used in the experiments. Temperature measurements and calorimeter determinations were used to analyse the heat transfer between the hands or part of the hands and the environment. These measurements were combined with assessments of blood flow by either the laser Doppler technique and/or strain-gauge plethysmography.

Chapter 4 describes the magnitude and time profile of heat loss of hands and feet to a relatively cold environment. Both hands and feet were immersed in a calorimeter water bath of about 25°C. The heat transfer of the hand and feet to the environment was quantified and related to local blood flow.

Chapter 5 addresses the vascular reaction to mild cold and presents a study on the relationship between hand blood flow and core temperature. Depending on the thermal status of the body, the hand was either comfortable (above 30°C) or cold (about the ambient temperature). It seems as if there is an on-off mechanism which regulates the blood flow to the hands. In this study the core temperature was raised by exercise in order to investigate at what core temperature the finger suddenly got warm.

Chapter 6 is dealing with the vascular reaction to severe cold (Fig. 1.1). The interplay between body temperature and local (finger) skin temperature was investigated in an indirect way. Twelve subjects immersed their left hands in cold water for 40 minutes. The temperature profile of every fingertip was measured. The profiles of the fingertips were interrelated by correlation analysis. The amount of synchronization between the fingertips indicates the relative contribution of central and local mechanisms in the hunting reaction.

Chapter 7 not only investigates the synchronization of hunting in one hand, but also looks closely at the amount of correspondence in finger temperature fluctuations between two immersed hands. The hands were immersed simultaneously in one experiment and five minutes after each other in a second experiment. If a central regulatory component is predominant, synchronization of the hunting reaction is expected to occur also in the non-simultaneously immersed hand.

Another way of investigating the central influence on CIVD is to immerse one hand in cold water and determine the temperature fluctuations in the non-immersed hand. This is described in **chapter 8**. If the temperature fluctuations of the non-immersed hand are similar in shape and phase as those of the immersed hand, a central nervous component in the regulation is rather likely. If, however, the temperature fluctuations of both hands are out of phase, a possible relation with body core temperature exists. Each time a vasodilation in the fingers of the immersed hand occurs, heat is transferred to the water and the body core is cooled. The relatively cold core in turn causes vasoconstriction in the non-immersed hand. Thus, vasodilation in the immersed hand may be followed by vasoconstriction in the non-immersed hand. The esophageal temperature was measured as an indicator of central blood temperature.

By combining the results of chapters 6 and 7, it became clear that the central component in the hunting reaction becomes more dominant when the body core temperature and water temperature of the immersion bath were higher. Unfortunately, both core and water bath temperature were raised at the same time in chapters 6 and 7 and were not investigated separately. Therefore, an experiment was conducted in which the core temperature and water bath temperature were varied independently (**chapter 9**). The body core temperatures were related to the individual thresholds in core temperature for finger vasodilation (see chapter 5) in order to find out if this might be an explanation for the large interindividual differences found in chapter 6 and 7.

Exposure to different ambient temperatures changes the body core temperature and the mean body skin temperature simultaneously, which makes it impossible to investigate their relative contributions to the hunting reaction. In **chapter 10** an experiment is described in which the body core temperature and mean body skin temperature were varied independently and their effects on the hunting reaction were investigated.

In all performed experiments it was shown that the hunting reaction differed vastly between subjects. In order to quantify the variations within subjects, an experiment was conducted in which the hunting reaction was investigated three times on the same subjects under identical conditions (**chapter 11**).

Results of all previous experiments showed that the hunting reaction was triggered at low finger skin temperatures and became more pronounced when the body heat content was higher. This means that both local and central control play a role. Recently, Hornyak et al. (1990) found that local and central control interact since the axon reflex is modified by the amount of sympathetic activity.

In **chapter 12** it is investigated if and how the interaction between local and central control takes place during the hunting reaction. In a complex experiment the body was cooled or warmed to induce different amounts of central vascular control on finger blood flow. The importance of neural control for the hunting reaction was investigated by measuring the effect of a neural block on finger skin blood flow. The plausibility of the axon reflex as an explanation for cold induced vasodilation was tested by electrically evoking axon reflexes during the hunting reaction.

The thesis ends with a general discussion (**chapter 13**).

Chapter 2

Vascular reactions to cold: an overview

This chapter presents an overview of the literature concerning the physiological processes that occur in the hand when the whole human body or one or two hands are exposed to cold. The possible mechanisms for the changes in fingertip temperature during whole body or local cold exposure are discussed, as well as the role of arteriovenous anastomoses in thermoregulation. The last part of this chapter outlines the relevance of thermal physiological research of hand blood flow for practical applications.

2.1 The hand and its circulation

2.1.1 Anatomy of the hand

In this thesis the hand is defined as the structure distal to the styloid processes of the ulna and radius. The hand basically consists of bones, joints, muscles, tendons and skin.
The percentage of skeletal muscle in a hand is relatively low. This means that not much heat can be generated in the hand itself. Raman and Vanhuyse (1975) estimated its metabolic heat production under resting conditions to be about 0.25 W.
The hands have a total skin surface area of about 400 cm^2 (Molnar, 1957); this is about 5% of the body surface area. The surface to mass ratio in the hand is 10 times larger than in the trunk (Hirata et al., 1993). The skin of the hand has a strong capability to vasoconstrict and vasodilate and is therefore important for thermal regulation. Hirata et al. (1993) illustrated this in a recent experiment in which subjects exercised with and without occluded hands. In the occluded state the core temperature was 0.2°C higher, due to the hampered heat transfer.

2.1.2 Blood vessels of the hand

Blood is supplied to the hands by two main arteries: the radial and ulnar artery. These arteries anastomose in the deep palmar arch and to a lesser extent in the superficial palmar arch (Gray, 1980). The finger arteries arise mainly from these arches. Dorsal and palmar digital arteries run parallel to the phalanges on both sides. The palmar digital arteries are the main supply vessels, the dorsal digital arteries being very small.
The veins of the hand are also divided into superficial and deep. The palmar digital veins mainly open into superficial arches and the palmar metacarpal veins into deep arches. The superficial

arches continue in the cephalic, basilic and median antebrachial veins, the deep arch drains into the radial and ulnar veins, which unite in the brachial vein.
The most common connection between the arterial and venous network is formed by the capillaries. A small artery splits up in even smaller arterioles which feed the capillaries. In some tissues, e.g., mesentery of connective tissue, the first part of a capillary still has a coat of smooth muscle. Such a structure is named a precapillary sphincter. However, Currie (1990) disputes the existence of these structures. The capillaries end in venules (small veins) which have a thin muscular coat. In some finger skin area's other arteriovenous connections are known, which will be discussed in par. 2.4.

2.1.3 Vascular innervation in the hand

innervation of blood vessels in general
Blood vessels respond to both nervous and hormonal influences. Several systemic hormones have an influence on vasomotor tone. In this thesis, however, the emphasis will be on nervous control, since this is more important in short term reactions to cold.

In the reticular substance of the pons, located in the central nervous system (CNS), a special area is designated for neural control of the circulation. This area is called the vasomotor centre. It receives inputs from the hypothalamus, which signals deviations in central blood temperature and integrates information from thermosensors throughout the body. Other higher nervous centres also give input to the vasomotor centre, such as those involved in stress-reactions. The vasomotor centre sends nerve impulses to the spinal cord, were they exit via the sympathetic part of the autonomic nervous system. The vasomotor centre has a basal firing rate, which leads to a basal vasomotor tone. The vast majority of the nerves to arterial and venous vessels is autonomic, but some nerves may be sensory, for example to subserve arterial pain (Nelms, 1963).

The efferent part of the autonomic nervous system can be divided into a parasympathetic and sympathetic part. The parasympathetic nerves mainly release acetylcholine (ACh) at their endings near the effector, the sympathetic nerves mainly (nor)adrenaline, which is equivalent to (nor) epinephrine. Activation of the parasympathetic nerves results in dilatation of blood vessels. The parasympathetic nerves, however, do not extend to the skin and skeletal muscles.

The sympathetic nervous system includes two gangliated sympathetic trunks (Gray, 1980). Pre-ganglionic fibres arising in the lateral column of the grey matter connect the spinal cord to the sympathetic trunk. The blood vessels of the hand are mainly innervated by the postganglionic fibres arising from the three cervical ganglia. The sympathetic nerves pass through the grey rami communicantes and join the mixed peripheral nerve. About 8 percent of the fibres in the mixed nerve consists of sympathetic nerve fibres (Guyton and Hall, 1996).

The action of the sympathetic nerves depends on the receptors in the vessel wall. Stimulation of α-receptors leads to vasoconstriction, and of β-receptors to vasodilatation. These receptors can be subdivided into α_1 and α_2 or β_1 and β_2, characterized by a different reactivity to vasoactive drugs.
In summary, vasodilation in the hands can be caused by stimulation of β-adrenoceptors ('active' dilation) or by a decrease of α-stimulation (passive dilation). Vasoconstriction can be caused by stimulation of α-receptors (active constriction) or by a decrease of the activity of the β-receptors ('passive' constriction).

innervation of the blood vessels in skeletal muscles
The sympathetic nerves to skeletal muscles carry sympathetic vasodilator fibres as well as constrictor fibres. The predominant receptors for (nor)epinephrine are of the α- and β_2-type. This means that both active vasoconstriction and active vasodilation can be accomplished. It depends on the relative distribution of the adrenoceptors in the muscle wall whether constriction or dilation is the primary response to local cold. The terminal arterioles, which are the functional capillary sphincters in this tissue (Tangelder et al., 1984), probably have α-receptors. Receptors in the venules and veins are of both α- and β-subtype. However, the opening of resistance vessels in the muscle also depends on local metabolism (Shepherd, 1983).

innervation of the blood vessels in the skin of the hand
The arterioles in the human skin are innervated by sympathetic constrictor as well as vasodilator nerves (Guyton and Hall, 1996). Capillaries are not innervated. However, sensory endings are so close that the somatic system may play an indirect role in the regulation of blood flow through the capillaries (Nelms, 1963).
The blood vessels of the hand skin are normally subjected to a high degree of vasoconstrictor tone, even though the subject is comfortably warm. For instance, Wilkins et al. (1938) observed a 100-fold increase in finger blood flow during body heating when sympathetic activation gradually decreases. This large increase in hand blood flow during body heating seems to be due entirely to release of vasoconstrictor tone. No evidence exists that vasodilator fibres contribute to this increase. This is consistent with the finding that the norepinephrine receptor in the skin of the hands is mainly of the α_2-type (Ekenvall et al., 1988; Freedman et al., 1992). Warren et al. (1942) found that the hand blood flow was maximal after sympathectomy, and suggested that no active vasodilation occurs in the hand. Recently, Johnson et al. (1995) showed that active vasodilation occurs in the back of the fingers and hands. The mechanism of active vasodilation is still subject to debate. Kellogg et al. (1995) showed that cutaneous active vasodilation is mediated by cholinergic nerve co-transmission. Although cholinergic sympathetic pathways are involved, the responsible neurotransmitter is still unknown and is probably not ACh. Blood vessels in ears and lips are innervated like hands, but other parts of the body show a different pattern.

specific innervation of the skin blood vessels in the hand
The structures of the hand are innervated by the median, ulnar and radial nerve, which come from the brachial plexus. These mixed nerves contain:

- efferent myelinated moto-nerves, which innervate the muscles,
- afferent non-myelinated and myelinated sensory nerves from various sensors in the skin and ligaments,
- efferent non-myelinated sympathetic nerves, which innervated the blood vessels.

The skin of the little finger tip is mainly innervated by the ulnar nerve, the tip of the ring finger by the ulnar and median nerve, and the remaining finger tips by the median nerve (Guyton and Hall, 1996). The ulnar part of the palmar and dorsal side of the hand is innervated by the ulnar nerve. The radial part of the dorsal side is innervated by the radial nerve; the radial part of the palmar side by the median nerve.

2.2 Whole body cooling and hand blood flow

During whole body cooling, the blood vessels in the skin of the hands constrict in order to retain heat for the body core. This results in a decrease of the local skin temperature, which will approach ambient temperature. Thus, the finger temperature of a subject during an overall day in a moderately cold environment may vary widely depending on his situation. One extreme is a local skin temperature of about 35°C, which is fairly close to the core temperature, when the subject is relatively warm; the other extreme is a finger skin temperature close to the low ambient temperature when the subject is relatively cold. There appears to be a certain threshold in core temperature above which the hand is warm and below which the hand is cold. The literature concerning this threshold is discussed in paragraph 2.3. In chapters 5 and 8 this threshold is examined in more detail.

2.2.1 Short term circulatory adjustments to cold

As soon as a subject enters a cold environment several mechanisms are triggered to prevent heat loss to the surroundings and to increase metabolism. The reduction in heat loss is achieved in four different ways (Raman and Vanhuyse, 1975):

1 vasoconstriction in the skin and muscles
During exposure to a cold environment the skin blood vessels of the hands constrict (see also Fig. 1.1). Burton and Edholm (1955) suggested that vasoconstriction in the peripheral musculature also contributes to the prevention of heat loss. Indeed, Ducharme and Tikuisis (1991) observed that the effective insulation of the forearm muscles increased manyfold during cold exposure due to vasoconstriction in this tissue.

2 change of circulation-pattern

Normally, the connection between the arterial and venous circulations is brought about by capillaries. In some parts of the human body such as fingers, lips, cheeks, nose and elbows (Sucquet (1862) in Hale and Burch, 1960), direct connections between the arterial and venous network are found. These connections are called arteriovenous anastomoses (AVA's) (See Fig. 2.1 and paragraph 2.3 for more details).

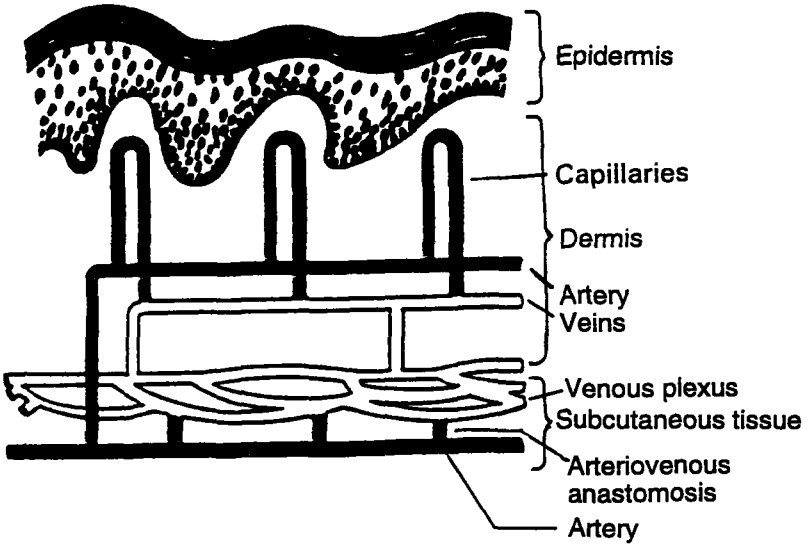

Fig. 2.1 Diagrammatic representation of the skin circulation. The feeding arteries are depicted dark. The capillaries have diameters of about 5 - 10 μm. (From: Handbook of Physiology).

Grant and Bland (1931) investigated the role of AVA's in thermoregulation. They found a relation between the number of AVA's in a body part and the occurrence of cold induced vasodilation. Since this discovery, the importance of AVA's for local temperature regulation has been stressed by many authors (e.g., Livingstone et al., 1989a). Solid evidence, however, is hard to find because blood flow through the AVA's can not be measured in a simple way.

The circulation pattern thus can be changed by a different distribution of blood flow through AVA's and capillaries. Since the AVA's have a relatively large diameter, the total blood flow in that skin part will increase, and so will the heat transfer to the surrounding tissue and eventually the environment (see par. 2.4.7.1).

3 counter current heat exchange (CCHE)

CCHE means that two adjacent vessels with opposite direction of blood flow interchange heat (Fig. 2.2).

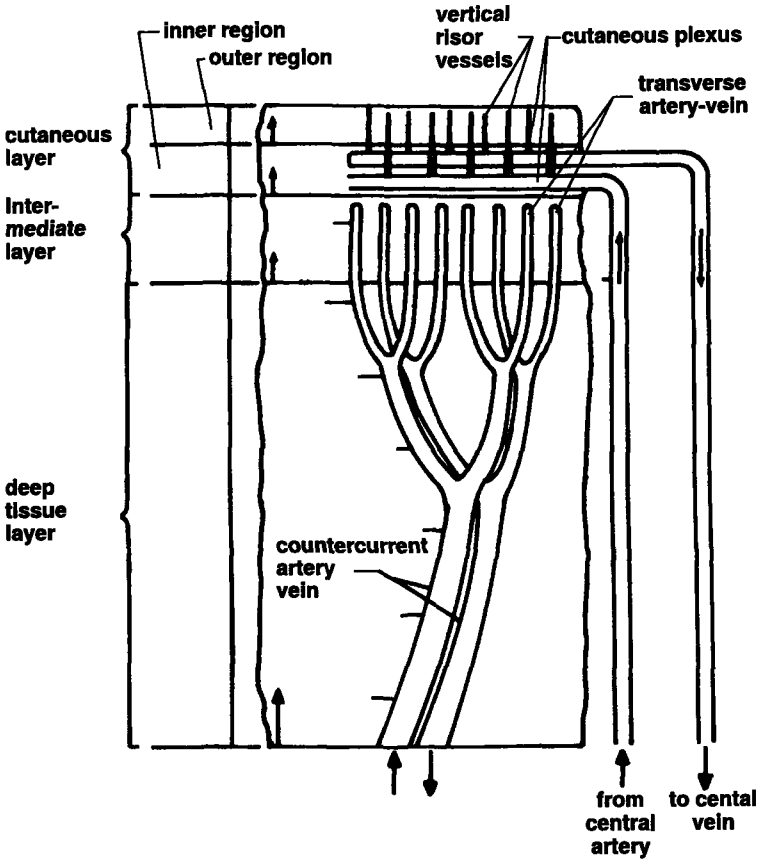

Fig. 2.2 Schematic representation of Counter Current Heat Exchange (Song et al., 1987).

CCHE in humans was first described by Bazett et al. (1948) who determined the temperature of the blood inside the radial artery. Following Bazett, the contribution of CCHE to the reduction in heat loss has been mainly investigated with analytical models. Those analytical models show conflicting results due to differences in the assumptions. Also, verification of the models is a problem for technical reasons.

Mitchell and Myers' (1968) analytical model revealed that probably no significant counter-current effect occurs in the arm of man. It is reasonable to assume that for these large vessels the distance

between the arterial and venous vessels is too great, the blood flow too fast, and the length of the vessels too short to ensure CCHE of sufficient magnitude.

In the skin, the arterial and venous vessels are rather close. However, the difference in temperature between these vessels is so small that almost no CCHE occurs, even though the heat transfer surface is large. Song et al. (1987) consider micro-vessels as insignificant in this respect when their dimensions are less than 50 μm. According to Jiji et al. (1984), the thermally significant counter-current arteries and veins are located in the deep tissue (more than 4 mm under the skin surface) and are 50 to 300 μm in diameter. In this area the combination of vessel length and distance between arterial and venous vessels is optimal for CCHE. Jiji et al. (1984) stress the influence of CCHE by pointing at the small arteriovenous temperature difference of only 0.1 to 0.2°C, while the difference between the temperature in the major supply vessels and the skin temperature amounts to 5-10°C. Hence, effective rewarming of the blood must have occurred on its way back to the heart.

Raman and Roberts (1989) estimated that the effectiveness of CCHE in reducing heat loss had a maximum of 30% at a hand temperature of 25°C. Tikuisis and Ducharme (1990) calculated a 53% efficiency for CCHE in the forearm.

Vanggaard (1975) argues that CCHE in the arms is of minor importance in total heat exchange. In his experiments he found no difference in temperature decay when a hand was cooled in an occluded or non-occluded situation. He came to the conclusion that CCHE either had to be always 100% effective or negligible, and naturally opted for the latter. However, it is questionable if temperature decay is a good indicator for CCHE. The real parameters of importance are the blood temperature in the arteries and veins, which are not easy to measure.

4 combination of change in circulation pattern and CCHE

It is likely that both CCHE and a change of circulation pattern occur simultaneously to prevent heat loss. Vanggaard (1975) and Burton and Edholm (1955) suggested that the blood leaving the capillaries drains into the deeper veins, while blood leaving the AVA's enters the superficial venous circulation. In favour of this, is the finding that the oxygen content of superficial veins is close to arterial values. This, however, can also be explained if the skin drains in the superficial veins and the muscles in the deeper veins.

The deep venous blood flow is expected to have more CCHE than the superficial venous blood flow, because the superficial veins are located far from the arteries. Unfortunately, Raman and Roberts (1989) have not incorporated this phenomenon in their model, which makes their results questionable for low skin temperatures.

2.2.2 Central influence on short term circulatory adjustments in the cold

The peripheral blood flow in the cold is determined by humeral factors, including blood temperature, and by nervous factors.

humeral factors
Cold blood impairs peripheral circulation by its direct effect on the blood vessel wall (Keatinge, 1970) and by its increased viscosity (Burton and Edholm, 1955).
In the cold, the adrenal medulla releases more adrenalin in the blood due to increased sympathetic activity. The higher concentration of adrenalin reduces peripheral blood flow since adrenalin is a strong vasoconstrictive agent for blood vessels in the skin (Guyton and Hall, 1996).

nervous factors
During whole body exposure to cold, peripheral vasoconstriction reduces finger temperatures to values close to ambient temperatures. When the body core is returned to normal after rewarming, the temperature of the finger tips increases again. The mechanism by which these peripheral temperature changes are brought about is likely to be associated with the opening and closure of arteriovenous anastomoses (Hales, 1985). Opening of the AVA's markedly increases blood flow, due to the large diameter of these vessels as compared to capillaries. Clark (1938) estimated that volume blood flow through an AVA is a factor 250 greater than through a capillary, while Nelms (1963) even reports a 1000 fold difference. Unfortunately, there is a gap in our knowledge about the number of AVA's in the extremities (see par. 2.4.4). Nevertheless, even with small numbers of AVA's present, they seem to play a crucial role in thermoregulation of the hand, although direct evidence is not available.

Passive heating of the body core reduces the amount of sympathetic outflow to the periphery. Zanick and Delaney (1973) cooled and heated the body cores of dogs and observed respectively a decrease and increase in blood flow through the AVA's. This was measured by the amount of 28±3 μm polystyrene particles retrieved from the venous network after injection into the femoral artery. They proposed that the temperature of the blood at the level of the CNS determined the sympathetic outflow and thus the opening and closure of the AVA's.

Exercise (active heating of the body core) increases sympathetic nerve activity and leads to peripheral vasoconstriction in the blood vessels of the hand, and also of the AVA's (Seals and Victor, 1991). Eventually, the increase in core temperature will cause a decrease in sympathetic activity.

2.2.3 Reflex vasodilation

As stated in the introduction of par. 2.2, the hand is relatively cold if the core temperature is below a certain threshold. However, if heat is applied to another part of the body, such as a leg, the vessels open up and the hand gets warm (Gibbon and Landis, 1932). This phenomenon is called reflex vasodilation. Sensors in the skin react to the external stimulus and transfer information to the vasomotor centre. This centre integrates the information and sends an adequate response to the effector organs. Pickering (1932) showed that blood temperature also plays an important role in this mechanism. He found no reflex vasodilation when the venous return of a heated hand was blocked. Many experiments are described in the literature in which a specific body part or the body core is heated or cooled and the effects on hand blood flow are investigated. This approach is essential for the development of computer models for thermoregulation.

From their experiments in sheep, Hales et al. (1985) concluded that peripheral blood flow (more particular AVA blood flow) is low at a core temperature 0.5°C below normal. Once the body core is at a level requiring increased heat loss, the skin temperature exerts an extremely potent influence on the nature and magnitude of changes in skin blood flow. This mechanism seems to be present in man also, as is illustrated by Cooper et al. (1964). They investigated the effect of radiant trunk heating on hand blood flow. If the core temperature was below 36.5°C, reflex vasodilation was inhibited. The body was not warm enough to eliminate heat by the hands. If the core temperature exceeded 36.8°C, reflex vasodilation occurred within 2 minutes. Similarly, a 'threshold' for trunk skin temperature existed: if the trunk skin temperature fell below about 33°C - regardless of the core temperature-, no reflex vasodilation occurred. However, if the investigated hand was immersed in 40°C water, reflex vasodilation was restored. In summary, the occurrence of reflex vasodilation or vasoconstriction depends on the core temperature and several skin temperatures, including the skin temperature of the investigated hand.

Hales and Iriki (1977), Hales et al. (1978) and Hales (1985) found that direct heating of a body part in sheep or rabbits increased the capillary blood flow by local reflexes, while sympathetic output and AVA flow remained constant. However, when the CNS or another body part (reflex vasodilation) was heated, the blood flow increase was brought about by the AVA's with minimal changes in capillary blood flow. They concluded that alterations in blood flow through the AVA's are effected by variations in sympathetic vasoconstrictor tone and that the AVA's are less involved in local reflex mechanisms.

Blumberg and Wallin (1987) described reflex vasodilation in the foot. They stimulated the peroneal nerve intra-neurally and measured the vascular response by laser Doppler flowmetry. Stimulation of the afferent Aδ fibres caused dilation in the stimulated foot and to a lesser extent in the opposite foot. The reflex dilatation is probably caused by a reduction in sympathetic activity.

Reflex vasodilation and -vasoconstriction are also noted during the hunting reaction (see also par. 2.3). Immersion of the feet in cold water during the hunting reaction in fingers, reduced the magnitude of the hunting reaction (Keatinge, 1957). Lewis (1930) observed that cooling the forearm suppressed CIVD in the fingers. Page and Brown (1953) and Livingstone et al. (1978) observed that Eskimos had less reflex vasodilation in the fingers upon cold water immersion of a foot than control subjects. Thus, Eskimos are able to maintain a good dexterity when the feet are cold.
Werner (1983) shows that reflex vasodilation or -constriction not only depends on the skin and core temperatures but also on the rate of change of these temperatures.

2.2.4 Long term circulatory adjustments to cold

The term acclimatization refers to physiological changes which occur in a slowly changing environment. Unlike the powerful acclimatization of human beings to heat, the ability to acclimatize to cold is limited. Several mechanisms are proposed, but the magnitude of the effects is small and a large inter-subject variability exists. In some subjects an increase in insulative capacity is found after prolonged exposure to cold environments (Young et al., 1986), which is often combined with the ability to live with lower core temperatures (Hong, 1963; Radomski and Boutelier, 1982). The combination is called insulative-hypothermic acclimatization (Livingstone et al., 1989b). Others claim an increase in metabolism after long term cold exposure (Bittel, 1987; Bittel et al., 1989; Golden and Tipton, 1988). Investigating long term adjustments to cold is complex, because it is difficult to control human behaviour during cold exposure.
The effects of whole body exposure to cold on the blood flow through the hands are controversial. Elkington (1968), Hampton (1969), Wyndham et al. (1964) and Livingstone (1976b) found no difference or increased vasoconstriction in the hands after prolonged cold exposure, but Livingstone et al. (1989b) found an enhanced hunting reaction in the fingers. In par. 2.3.2 the relative importance of whole body acclimatization versus hand acclimatization is discussed.

2.3 Effects of local cold on hand blood flow - The hunting reaction

When an extremity is exposed to a cold environment, the blood vessels in the skin initially constrict in order to prevent heat loss to the surroundings (see Fig. 1.2a). In a severely cold environment, such as water immersion below 15°C or exposure to freezing air, the vessels open up again after about 5 to 10 minutes. This is called cold induced vasodilation (CIVD). A common teleological explanation of this phenomenon is that it prevents the occurrence of local cold injuries and maintains sufficient dexterity. In chapters 6 to 12 several experiments are described in an attempt to elucidate the mechanism behind this reaction.
Immersion in cold water is often a painful experience. LeBlanc (1975) and Heus and Daanen (1993) noted that the most painful period occurred during vasoconstriction, and that the vasodilation phase

was often felt as a relief. The pain during strong vasoconstriction may be seen as a warning for exceptional cooling. Kreh et al. (1984) found a close relationship between pain intensity and degree of vasoconstriction. If the cooling continues, the tissue temperature may decrease below the threshold for nerve conduction. If that threshold is reached no information from the periphery can reach the central nervous system and the extremity feels numb.

2.3.1 Terminology of the hunting reaction

Lewis (1930) was the first to describe the phenomenon of CIVD. The vasodilation and vasoconstriction were derived from the recorded temperatures of the finger tips. Lewis (1930) called the repeated fluctuations of finger temperature 'hunting': "it is frequent for the temperature reaction to be repeated over and over again during immersion; this slow 'hunting' of temperature is never quite rhythmic and the rises for the most part are irregular in time and form". Later, other methods, such as laser Doppler, were added as an indicator for blood flow and diameter changes of the blood vessels.

The temperature response during cold exposure can be distinguished in several phases (Fig. 2.3):

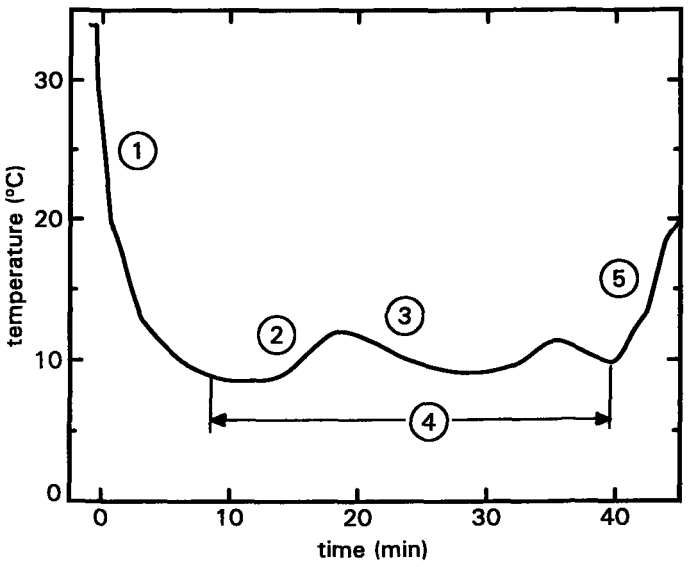

Fig. 2.3 *Schematic representation of the temporal evolution of finger tip skin temperature* during cold water immersion, including CIVD. See text for explanation of the numbers and Fig. 3.1 in the Materials and Methods section for a description of the parameters which can be derived from the temporal evolution of the hunting reaction.

1) Initial cold vasoconstriction.

   This is the phase that is of interest for most psychologic experiments since it is known that the sympathetic system is activated during this stressful phase. The duration of standard cold pressure tests for stress research are therefore limited to only a few minutes (e.g., Boutouyrie et al., 1994, who used a 2 minute cold pressure test).

2) Cold induced vasodilation (CIVD).

   The blood vessels dilate and the local skin temperature increases. This phase starts about 10 minutes after cold water immersion.

3) Vasoconstriction.

   After the cold induced vasodilation, the vessels start to contract again during the immersion phase.

4) Hunting reaction.

   Repetition of the period with vasodilation and vasoconstriction.

5) Final vasodilation.

   After removal of the extremity from the cold environment, vasodilation is found, often resulting in eventually higher skin temperatures than before immersion of the hand in cold water (e.g., Lewis, 1930; Wolff and Pochin, 1949). The magnitude of the final vasodilation seems to depend on the phase in the hunting reaction at which the hand or finger is removed from the water bath.

In the literature the term CIVD is also often used in a similar meaning as the hunting reaction i.e. it includes the vasoconstriction phases (e.g., Purkayastha et al., 1992). Another term for the hunting reaction is the 'Lewis-reaction' (Kramer and Schulze, 1948, Werner, 1977). In this thesis the hunting reaction will refer to the vasodilation and vasoconstriction phases during cold exposure and the term CIVD will be limited to the vasodilation phase during cold exposure.

Purkayastha et al. (1992) argue that the hunting reaction, shown in Fig. 2.3, is only one out of four possible reactions to local cold, which are depicted in Fig. 2.4.

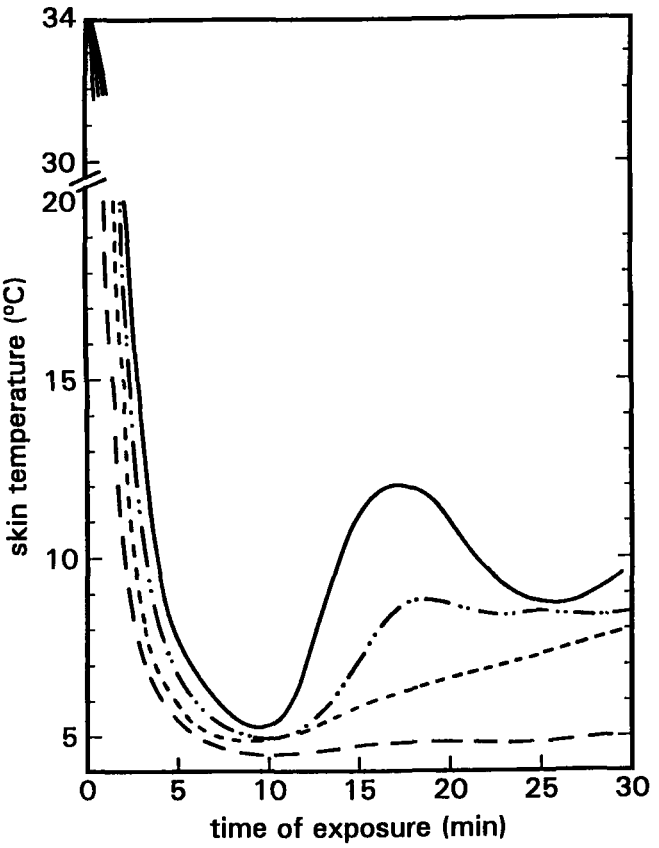

Fig. 2.4 Responses to local cold according to Purkayastha (1992).
1. Solid line = hunting reaction;
2. _.._ = proportional control form;
3. ---- = slow steady and continuous rewarming;
4. _ _ = absence of CIVD response.

Response 2 occurs mainly at relatively high core temperatures (e.g., in fever and on a hot summer day). The initial vasoconstriction is often of short duration and the finger temperature may stay constant at a relatively high temperature, even for several hours (Kramer and Schulze, 1948).
Response 3 has not been seen in our study.
Response 4, absence of CIVD, can occur when the mixed peripheral nerve is degenerated or when the body core is extremely cold.

In this thesis all four responses are considered as different manifestations of the same mechanism. The parameters chosen to quantify the hunting reaction (par. 3.3.1) guarantee that all these different manifestations can be identified.

2.3.2 Influences on the hunting reaction

Many factors are known to alter the hunting reaction. An overview of the factors investigated sofar is given below.

body temperature

The regulation of blood flow to the extremities is, at low ambient temperatures, primarily determined by the thermal state of the body as a whole. Even at air temperatures below -30°C, the skin temperature of bare hands can be sustained above 21°C (Rapaport et al., 1949). Therefore, it is rather likely that the body core temperature influences the hunting reaction. In Table 2.1 results of relevant articles in the literature are summarized.

Table 2.1 Influence of body temperatures on the hunting reaction. T_{re}: rectal temperature (°C), $\bar{T}_{sk}$: mean body skin temperature (°C), $\bar{T}_{fi}$: mean finger skin temperature (°C), T_{min}: minimum temperature of finger skin during immersion (°C), Δt_{onset}: time from immersion to T_{min} in minutes.

Author(s)	Body temperatures			Hunting reaction		
	Induction	Measurement		Induction	Measurement	
		Method	Value		Method	Value
Adams and Smith, 1962	Room temp. 7 and 22°C for 1 hour	-	-	index finger for 20 minutes in 0°C	finger skin temp.	Δt_{onset} increased in cool subjects
Bader and Mead, 1949	Room temp. 13 and 32°C	-	-	terminal phalanx in ice water or 0°C air	finger skin temp. and plethysmography	blood flow not dependent on local temp. (cold water or air) but on ambient temp.
Blaisdell, 1951	Room temp. 28, 25, 15 and 12°C for 2 - 3 hours	T_{re}, $\bar{T}_{sk}$	T_{re} not different between room temp. $\bar{T}_{sk}$ at 28°C: 33.1°C. $\bar{T}_{sk}$ at other room temp.: 25.-9°C.	hand in 0, 5, 10 and 15°C air	finger nail bed temp. and plethysmography	T_{min} lower when chilled (3.8°C versus 7.8°C at 28°C room temp.), no differences in frequency and amplitude
Edwards and Burton, 1960	Room temp. 'neutral' and 9-17°C	-	-	finger in ice water	plethysmography, calorimetry	reduced blood flow and heat transfer in cold room
Elsner et al., 1960	Room temp. 18°C unclothed and 22°C clothed	-	-	hand for 30 minutes in water of 5°C	calorimetry	more heat loss in warm room
Folkow et al., 1963	Indirect warming and cooling	-	-	hands in ice water	venous occlusion plethysmography	more blood flow when indirectly warmed
Greenfield et al., 1951b	Room temp. 14.5°C, 20.5°C and 22.5°C	-	-	toes in water 0-6°C	calorimetry	more heat loss when room temp. increases

Author(s)	Body temperatures			Hunting reaction		
	Induction	Measurement		Induction	Measurement	
		Method	Value		Method	Value
Keatinge, 1957	6°C water bath; Room temp. 5-6°C (1 hour) and 17-18°C with clothing and exercise	-	-	index finger in ice water	calorimetry	finger heat loss hot: 65% of max. cold: 5% of max. cold bath: 13% of max.
Kramer and Schulze, 1948	Room temp, hot drinks, daily and seasonal variations	-	-	hands in cold air of -18 to 10°C	finger skin temp.	mean finger skin temp. increased when warm
Lee et al., 1996	30 minutes in 27°C air (N), 60 minutes in 20°C water (H)	T_{es}, T_{re}	N: T_{es}: 36.85; T_{re}: 37.02 H: T_{es}: 36.18; T_{re}: 36.29	right middle finger in 4°C water	finger skin temp.	mean finger skin temp. lower in H. amplitude also lower
Spealman, 1945	Room temp. 16, 24 and 32°C for 3 hours	-	-	hands for 3 hours in water of 2 to 35°C	blood flow by venous occlusion plethysmography	blood flow higher at high ambient temp. and when water temp. is higher or lower (CIVD) than 15°C.
Tanaka et al., 1971b	Room temp. 25, 30 and 35°C	-	-	middle finger for 30 minutes in 0°C	finger skin temp.	with increasing room temp.: higher T_{min} and $\bar{T}_{fi}$ and shorter Δt_{onset}.
Werner, 1977	Room temp. 15 (for 0.5 hours), 30 and 45°C	T_{re}	-	hands in air at 0.5 $m \cdot s^{-1}$ at -5, 0 and 5°C	finger skin temp.	$\bar{T}_{fi}$ higher when ambient and hand temp. increase. No fluctuations at 45°C ambient temp.
Yoshimura and Iida, 1950	Room temp. 4 - 36°C	-	-	middle finger for 30 minutes in 0°C	finger skin temp.	T_{min} increases with room temp. $\bar{T}_{fi}$ increases with room temp. Δt_{onset} decreases with room temp.

Generally, a higher core temperature leads to higher mean finger skin temperatures during the hunting reaction. Elsner et al. (1960) found that the onset of skin warming due to CIVD was not much different between a cold and warm body, in contrast to many other studies. In par. 2.3.4 the possible explanations for the effect of body temperature on the hunting reaction will be discussed.
In most investigations the effects of body temperature were investigated by putting subjects in a relatively cold or warm room. Unfortunately, the resulting core and mean body skin temperatures were seldomly measured. In the experiments in the chapters to come, body temperatures and peripheral responses have been determined in all but one experiment.

The core temperature is changing during the day and during the year (seasonal). The effects of these changes in core temperature on CIVD, as reported in the literature, are:

- The hunting reaction is more pronounced in the afternoon, than in the morning or the night (Kramer and Schulze, 1948).
- In the summer the amplitude of the hunting reaction is higher than in the winter (Tanaka, 1971b). Schulze (Kramer and Schulze, 1948) measured himself several times throughout the year and found an average maximal finger skin temperature of 28°C in the summer and 16°C in the winter. Elkington (1968) showed that the finger blood flow during immersion in cold water was less during the Antarctic winter than during the summer.

In summary, it appears that in the afternoon and in the summer, when the core temperature is relatively elevated, the hunting reaction is more pronounced.

cooling medium

To evoke CIVD two media are commonly used: water and air. Immersion in cold water is used most often. The thermal conductivity of water is about 25 times higher than that of air, so cooling is rather quick.
Kramer and Schulze (1948) cooled fingers in cold air, and compared the results with publications concerning water cooling. Cooling characteristics were almost the same for water of 0°C and air of -18°C with minimal wind speed. Kramer and Schulze (1948) also showed that the frequency of the hunting reaction increased when the air temperature in the cooling box around the hand decreased. At an air temperature of -18°C a hunting period lasted 20 - 35 minutes and at +10°C it lasted 80 to 130 minutes.
There is no agreement in the literature concerning the water temperatures at which CIVD occurs. The lower limit, of course, is 0°C. Lewis (1930) and Yoshimura (1960) performed their experiments at this temperature, since they expected a maximal response. Lewis (1930) did not see a hunting reaction in water temperatures above 18°C. Hirai et al. (1970) saw no response at 15°C and advised an optimal temperature for investigation of 5°C, since the differences between two investigated populations were optimal then.
The discrepancies in the literature can partly be explained by the differences in core temperature. At a low core temperature hunting is less likely to appear.

acclimatization to cold

In contrast to the conflicting results concerning 'overall' acclimatization to cold (par. 2.2.4), the long term effects of regular local cold exposure show more agreement. People working with their hands in a cold environment (e.g., fish-filleters) show an increased blood flow through the hand in the cold as compared to unacclimatised subjects (Krog et al., 1960, LeBlanc et al., 1960). CIVD occurs at an earlier stage of cold exposure in the acclimatized subjects (Nelms and Soper, 1962). Tanaka (1971a) found that ice chamber workers had a higher mean finger temperature, a higher minimal finger temperature and shorter onset-time of CIVD than cool room workers. Purkayastha et al. (1992, 1993) showed that tropical residents developed a more pronounced hunting reaction seven weeks after an airlift to an arctic region and that the response was even indistinguishable from the response of arctic residents. In Table 2.2 the findings on local cold acclimatization are summarized.

adaptation to cold

The term adaptation refers to genetic changes that occurs by natural selection due to long lasting cold exposure. Most often a comparison is made between populations who inhabit different locations. Studies on cold adaptation are included in Table 2.2.

Table 2.2 Summary of investigations concerning acclimatization and/or adaptation of finger temperatures to local cold exposure. CA = Cold Adapted / Acclimatized; N-CA = Not Cold Adapted / Acclimatized. The data of Yoshimura and Iida (1950) could not be presented, because they are recalculated in a Frostbite Resistance Index. Brown and Page (1952) and Hellström and Andersen (1960) measured only blood flow or heat transfer, not finger temperatures.

Authors	Population		Onset time (min) of CIVD		Minimal finger temperature (°C)		Mean finger temperature (°C)		Experimental setup
	CA	N-CA	CA	N-CA	CA	N-CA	CA	N-CA	
Bridgman, 1991	Divers	Non-divers	9.4	9.1	-	-	-	-	index finger at 0°C
Elkington, 1968	After Antarctic trip	Before Antarctic trip	7.4	7.3	-	-	-	-	index finger at 0°C
Elsner et al., 1960	Arctic Indians	Scientists	4.7	7.5	2.3*	0.6*	-	-	index finger at 0°C
Elsner et al., 1960	Arctic Indians	Scientists	2.3	3.3					index finger at 4-5°C
Hirai et al., 1970	Japanese	Caucasians	6.5	9.1	9.7	6.9	10.5	8.3	middle finger at 5°C - both groups actually not CA
Iampietro et al., 1959	Caucasians	Negros	9.2	15.9	2.9	1.0	7.2	2.7	all fingers at 0°C
Itoh et al., 1970	Hokkaido natives	Main island natives	6.2	7.8	2.3	1.2	5.9	4.2	middle finger at 0°C
Jackson et al., 1989	Caucasians	Negroes	4.2	6.6	6.5	5.7	7.6	6.8	middle finger at 5°C
Krog et al., 1960	Laps	Norwegian students	5.4	9.1	1.6	1.2	-	-	middle finger at 0°C
Krog et al., 1960	Fishermen	Norwegian students	6.9	9.1	1.7	1.2	-	-	middle finger at 0°C
Leblanc et al., 1960	Fishermen	Labourers	-	-	-	-	> 4.0	≤ 3.5	index and middle finger at 0°C; only 10 min. immersion
Livingstone, 1976b	Military personnel after 2-week arctic stay	Military personnel before arctic stay	9.3	12.4	5.4	3.9	9.8	7.5	middle finger at 0°C

Authors	Population		Onset time (min) of CIVD		Minimal finger temperature (°C)		Mean finger temperature (°C)		Experimental setup
	CA	N-CA	CA	N-CA	CA	N-CA	CA	N-CA	
Livingstone, 1976b	After 7 days of cold exposure	Before cold exposure	10.4	13.3	4.6	3.5	7.5	5.5	middle finger at 0°C
Meehan, 1955	Alaskan Natives	Caucasians	-	-	4.2	2.2	5.9	4.4	median of index finger at 0°C
Meehan, 1955	Caucasians	Negroes	-	-	2.2	0.0	4.4	1.4	median of index finger at 0°C
Miller & Irving, 1962	Cold accustomed whites	Not cold accustomed whites	-	-	6.3	5.6	-	-	mean of 5 fingers at about -7°C air
Miller & Irving, 1962	Eskimo	Not cold accustomed whites	-	-	15.2	5.6	-	-	mean of 5 fingers at about -7°C air
Nelms & Soper, 1962	Fish filleters	Technical staff officers	4.5	9.9	2.0	0.4	-	-	middle finger at 0°C
Purkayastha et al., 1992	Arctic natives	Tropical residents	8.2	11.1	8.0	5.6	10.3	6.6	index finger at 4°C
Takeoka et al., 1993	Tibetans	Japanese	-	-	-	-	9.2	12.0	middle finger at 0°C at 4860 m altitude
Takeoka et al., 1993	Tibetans	Japanese	-	-	-	-	8.3	9.0	middle finger at 0°C at 2260 m altitude
Tanaka, 1971a	Ice chamber workers	Cool room workers	6.7	8.9	7.6	1.7	11.5	6.9	middle finger at 0°C

* These results are indirectly derived from Nelms and Soper (1960).

The results of the studies mentioned in Table 2.2 that measured blood flow or heat transfer, showed ambiguous results. Brown and Page (1952) showed that Eskimos had a higher blood flow of the hand than Canadian students. Hellström and Andersen (1960) found no differences in heat output between Arctic fishermen and controls. Also, Krog et al. (1960) found no differences between Laps and Norwegian controls in blood flow, but noticed that CIVD occurred more vigorously in Laps.

The results were unambiguous when finger temperatures were measured. It was generally found that the Cold Adapted/Acclimatized (CA)-subjects had a shorter onset time and a higher minimal and

mean temperature (Table 2.2). Only few publications were not consistent with this statement. Takeoka et al. (1993) found that the cold adapted Tibetans had a lower $\bar{T}_{fi}$ than the Japanese controls. In this case however, hypoxia coexists with cold, which may alter the response. Bridgman (1991) found no differences between divers and non-divers, probably due to an insufficient stimulus for acclimatization. The other publications, in which finger temperatures were measured, were in general agreement. Meehan (1955) found that the mean temperature of the fingers during hunting was highest for Alaskan natives, followed by Caucasians and Negroes respectively. Elsner et al. (1960) showed an earlier onset of vasodilation in arctic Indians as compared to a control group. Itoh et al. (1970) showed that natives of the colder Hokkaido island had a more pronounced hunting reaction (earlier onset, higher mean finger temperature and higher minima) than subjects born on the main island. Iampietro et al. (1959) showed that Negroes and Caucasians reacted similarly to whole body cold exposure, but that Negroes had a reduced hunting reaction to local cold exposure. Yoshimura and Iida (1952) showed that the Resistance Index for Frostbite (see par. 2.5.3) was higher for Chinese, Mongol and Orogon people (6.2 - 8) than for Japanese (5.8). Analogous to the findings in the fingers, Elsner (1963) showed that foot temperatures were higher in Australian aboriginals and Indians as compared to Caucasians during cold exposure.

In most investigations, differences between groups could not be attributed to either genetic differences or acclimatization, since one of the ethnic groups is usually also exposed to more intense cold. However, there are a few investigations in which the distinction between the two could be made, but the results of these investigations are conflicting.
The Negroes and Caucasians in the survey of Meehan (1955) had similar cold exposure, but different genetic background. The persisting differences in hunting reaction between both groups favours an adaptation hypothesis over acclimatization. However, Purkayastha et al. (1993) found that acclimatized tropical residents showed the same hunting reaction as arctic residents and this favours an acclimatization hypothesis over adaptation.
Hirai et al. (1970) investigated differences in hunting reaction between two populations who were both not exposed to cold on a regular basis: Japanese and Caucasians. In a water bath of 5°C they found that Japanese showed a more pronounced hunting reaction (earlier onset, higher mean finger temperature and higher minimum). If, however, Japanese and Caucasians living in the same area are compared, no differences were found. This leads to the conclusion that ambient factors, such as diet and acclimatization, may be of greater importance than ethnic differences.

In some experiments, the subjects were not only exposed to local cold, but also to general body cooling. In these investigations the results may have been dependent on the most severe stress. When general cold exposure was the dominant stress, whole body acclimatization effects may prevail (par. 2.2.4), while local cold acclimatization dominates in local cold stress. Recently, Livingstone et al. (1989b) measured the acclimatization in four subjects who crossed the North Pole on skis. Both an enhanced hunting reaction and insulative-hypothermic acclimatization were shown. Recently, Savourey et al. (1996) immersed both legs of eight subjects in 0-5°C water twice a day for

a month. Again, both local cold acclimatization (higher leg skin temperatures) and general insulative-hypothermic cold acclimatization occurred. Elkington (1968), Hampton (1969), Wyndham et al. (1964) and Livingstone (1976b) found no difference or even increased vasoconstriction in the hands after prolonged cold exposure. Here, whole body cold exposure might have been predominant.

hypoxia

A significant reduction in the hunting reaction is found during exposure to high altitude, where cold co-exists with systemic hypoxia (Mathew et al., 1977). Takeoka et al. (1993) showed that $\bar{T}_{fi}$ during the hunting reaction was lower in seven Japanese men at an altitude of 4860 m (ambient temperature 9°C) as compared to 2260 m (ambient temperature 12°C). Therefore, it seems that systemic hypoxia reduces the magnitude of the hunting reaction.

sex

Hand and finger blood flow in thermoneutral conditions is higher for men than for women as measured by laser Doppler flowmetry and plethysmography, due to an increased vasomotor tone in women (Cooke et al., 1990). By contrast, after total body warming of both genders, the blood flow was greater in females than in males.

When warm hands (about 32°C) are exposed to cold, women show an enhanced vascular reactivity as compared to men, which causes a more pronounced decrease in peripheral blood flow and skin temperatures in females (Bartelink et al., 1993, Pollock et al., 1993). The reactivity is most pronounced in women using oral contraceptives, followed by premenopausal women and postmenopausal women (Bartelink et al., 1993). These three different hormonal conditions thus have a strong impact on vascular reactivity. However, Cooke et al. (1990) found no relation between female hand blood flow and levels of serum oestrogen or progesterone.

Miller and Irving (1962) found no differences in finger temperature response to cold air between three Eskimo women and eight Eskimo men and between eight Eskimo boys and four Eskimo girls. Also, Yoshimura and Iida (1952), Tanaka (1971b) and Yoshimura et al. (1958) found no sex differences in the hunting reaction.

In summary, females tend to have lower hand blood flows when exposed to cold, but in the temperature profiles of the hunting reaction no differences are found.

age

Yoshimura and Iida (1952) found the highest reactivity to cold water at the ages of 25 to 29 years old. At younger age, or when older, the reactivity decreased generally more and more, except that in childhood it was higher than in puberty. Miller and Irving (1962) found that the finger temperature of Eskimo children dropped more than that of adults during cold exposure. However, this may probably be attributed to their drop in body temperature, which was not controlled for.

cold resistance training

Several authors tried to increase the resistance against cold by daily cold water immersions.

Yoshimura and Iida (1952) describe an experiment in which boys and soldiers immersed their legs in ice water for 15 or 30 minutes daily for one month. Adams and Smith (1962) immersed the terminal two phalanges of the index finger in ice water four times daily for one month. In both experiments, an increased mean toe or finger temperature was found during immersion at the end of the training phase. These effects were not found when the peripheral cold exposure was limited to one minute at 4°C daily for 9 days (Glaser and Whittow, 1957). In all experiments the pain at the end of the training was less than at the start.

In summary, an intense cold stimulus that is repeated on a regular basis may lead to a more vigorous hunting reaction and reduced pain. However, Yoshimura and Iida (1952) warn that these methods of training may have side effects: pain and nausea occurred during the training. A milder training regime might have the same beneficial results without these side-effects.

diet

Ingestion of a meal increases the core temperature. The increased core temperature leads to an increased finger blood flow (Hirai et al., 1991).

Yoshimura et al. (1952) showed that a daily intake of excessive protein (150 - 200 g/day) or excessive salt (>45 g/day) increased the reactivity of the hunting reaction after about one week. These changes were explained by influences of diet on metabolism, which in turn affected the thermoregulatory centre.

Also, Vitamin C intake (2 g/day for one month) enhances the hunting reaction (Livingstone, 1976a). In particular, the onset time is shortened.

Thus, dietary changes may improve the resistance against frostbite.

alcohol

Granberg (1991) reviewed the effects of alcohol on human responses in the cold and concluded that experimental studies on humans during relatively short exposure to moderate cold have given inconsistent results concerning heat balance. Longer exposure (several hours) to colder environments has revealed enhanced heat loss. Alcohol delays the onset of shivering and gives a feeling of bravery. Vasoconstriction after exposure of the hands to cold occurs rather slowly due to alcohol (Kramer and Schulze, 1948; Mills et al., 1986). However, Mills et al. (1986) found no differences in hunting frequency between sober and intoxicated subjects, but reported higher finger skin temperatures when intoxicated. Kramer and Schulze (1948) observed that the onset of CIVD occurred sooner when alcohol had been taken.

The use of alcohol thus increases the risk for hypothermia, but on the other hand seems to have some positive effects on finger blood flow in the cold. Granberg (1991) observed that intoxicated subjects are less likely to suffer from severe freezing cold injuries.

mental stress

Meehan (1957) showed that the hunting reaction was abolished in a stressed subject who has just completed an exam, in contrast to three previous experiments in which the hunting reaction had been clearly present. This finding of Meehan (1957) was confirmed by Adams and Smith (1962). They showed that a strong emotional stress given during the vasodilation phase led to an immediate strong vasoconstriction. This demonstrates the functional integrity of efferent vasomotor nerves and receptors during CIVD. Mental stress increases the activity of the vasomotor centre which increases the amount of vasoconstriction in the skin (Marriott et al., 1990). When the sympathetic vascular tone is high, however, mental tasks may lead to paradoxical vasodilation (Cooke et al., 1990, Halperin et al., 1983). Also, man is able to voluntary vasodilate the blood vessels in the finger pad, and thus increase his finger temperature (Carter, 1978).

pathology

Jobe et al. (1985) investigated the hunting reaction of the right middle finger in eight subjects with Raynaud's disease type I, an idiopathic vasospastic disorder of the peripheral vasculature, and in nine normal subjects. At 10°C and 15°C water bath temperature, the Raynaud's disease subjects showed a less pronounced hunting reaction as compared to the normal subjects (e.g., longer time to the first rise of finger skin temperature). At 5°C water temperature, the differences were marginal.

Jobe et al. (1982) showed that the digital temperatures during cold exposure of subjects suffering from Raynaud's disease could be increased by 2.2°C with adequate training. The training consisted of a 10-minute hand immersion in hot water (43°C) while the dressed body was exposed to cold (0°C). The training was repeated three times a day, three days a week for three weeks. The success was ascribed to a Pavlovian reaction (classical conditioning) in the extremity.

Gasser et al. (1992) compared the reaction to cold in 39 subjects with general complaints of cold hands, but absence of vasospastic disease, with a control group of similar size. The contra lateral hand was immersed in water of 4°C for 30 seconds. The Doppler blood flow was continuously higher in the control group. The reactivity of the vessels was not different from controls, but an increased vasomotor tone seemed to be present.

2.3.3 Explanations for the central influence on the hunting reaction

The body core can influence the hunting reaction by humeral factors, including blood temperature, and nervous factors.

humeral factors

Edwards and Burton (1960) combined plethysmographic and calorimetric measurements during the hunting reaction in the finger. From the blood flow and heat transfer they calculated the arteriovenous (A-V) temperature difference. They estimated that in a warm environment and with a warm body core, the digital arterial blood temperature almost equalled the body core temperature, and that

the venous blood temperature almost equalled the local skin temperature. However, in a cold environment and with a cold body core, the digital arterial blood temperature was far below the body core temperature. In one case the calculated arterial blood temperature was as low as 7.3°C. The increase in viscosity associated with such a low arterial blood temperature impairs blood flow and may partially explain the faint CIVD response in a cold environment when the body core is cold. Cooling of the arterial blood can thus explain differences in hunting reaction with a cold and warm body core.

A decreased body temperature is accompanied by an increased sympathetic activity which releases mainly adrenalin but also noradrenalin from the adrenal medulla (Guyton and Hall, 1996). The vasoconstriction caused by the increased concentration of (nor)adrenalin leads to a decreased peripheral blood flow. This limits the amount of adrenalin that reaches the peripheral muscles and may thus result in peripheral vasodilation. This mechanism might explain the hunting phenomenon during cold immersion of an extremity, but is contradictory to the finding that the hunting reaction is almost absent when the body is cold.

nervous factors

Impairment of the sympathetic vasoconstrictor nerve conduction might also trigger CIVD (Hertzman and Roth, 1942). Cold reduces nerve conduction velocity (Vanggaard, 1975) and thus reduces the amount of norepinephrine secreted at the junction between nerve ending and smooth muscle. This leads to an increased diameter of the peripheral blood vessels, and an increase in blood flow (CIVD). However, the unmedullated sympathetic nerves have been shown to be among the last nerves to be affected by cooling (Douglas and Malcolm, 1955), and sympathetic paralysis is therefore not likely.

In order to elucidate the role of the sympathetic nerve system in vascular control, several experiments have been reported in the literature in which the sympathetic nerve or mixed nerve was blocked. Thus, the central nervous input to the peripheral blood flow was eliminated. The results of these experiments are summarized in Table 2.3. From this table it can be concluded that a block or section of the sympathetic or mixed nerve releases the constrictor tone and leads to vasodilation, even when the hand is immersed in cold water. The temperature fluctuations in the finger tips during immersion are reduced in magnitude, because the vessels are already opened up.

Table 2.3 Overview of literature data in which the effects of sympathetic block on peripheral blood flow were investigated with the axon reflex intact.

Denerv. = Denervation of peripheral nerve;
Symp. = Sympathectomy (ganglia or dorsal root);
C = Chemical agent
Vasodil. = Vasodilated during immersion

Author(s)	number of subjects	Type of neural block	Thermal conditions	finger blood flow response
Freeman, 1935	1	C - 1% novocain in sympathetic ganglia	hands in 17.5°C water	increased blood flow
Gemne et al., 1986	13	C - 5 ml of 2% lidocaine in finger base	body in 5°C air, finger cooled by 5°C water	increased blood flow
Greenfield et al., 1951a	3	C - 2 - 5 ml of 2% procaine in wrist	finger in 0-6°C water	increased heat loss
Greenfield et al., 1951a	2	ganglionic symp.	finger in 0-6°C water	increased heat loss
Greenfield et al., 1951a	4	denerv.	finger in 0-6°C water	increased heat loss immediately after denervation
Lewis, 1930	1	denerv.	finger in 0°C water	higher finger skin temperatures immediately after denervation
Lewis, 1930	1	13 days after ganglionic symp.	finger in 0°C water	normal hunting reaction
Thomsen et al., 1988	8	C - 0.25 mg/kg body weight Guanethidine in vein of the hand	hand in 21°C air	increased skin perfusion
Warren et al., 1942	1	C - novocain in sympathetic ganglia	body in 21°C air, feet in 43°C water	vasodil. (increased blood flow)

2.3.4 Peripheral mechanisms explaining the hunting reaction

2.3.4.1 Vasoconstriction phase

Prior to the hunting reaction a strong vasoconstriction is observed in the first minutes of cold exposure. This strong vasoconstrictor response is caused by several factors. The most important mechanism is a reflex excitation of vasoconstrictor fibres (Folkow et al., 1963). The thermoceptors

in the cooled skin transmit afferent signals to the thermoregulatory centre in the brain. The centre increases the vasomotor tone and transmits signals to the periphery by the sympathetic nerves. Increased sensitivity of the vascular smooth muscle cells to norepinephrine may contribute to the neurally mediated vasoconstriction (Shepherd and VanHoutte, 1978). The α_2-receptors, located in the vessel muscle wall are most important. Ekenvall et al. (1988) showed that the cold induced vasoconstriction was completely abolished after administration of the α_2-adrenoceptor antagonist rauwolscine. Cooling augments α_2- and suppresses α_1-adrenergic vasoconstriction, whereas warming produces the opposite effects (Freedman et al., 1992).

The cold can also act directly on the smooth muscle surrounding the blood vessels (Keatinge, 1970). Folkow et al. (1963) also mention a decrease in the formation of vasodilator metabolites in the immediate environment of the vascular smooth muscles, leading to chemical changes which increase the muscular tone.

The local blood flow is not only affected by the vascular lumen but also by the intrinsic properties of the circulating blood. The viscosity of the blood increases when the blood is cold, and thus may add to the impairment of the local circulation (Burton and Edholm, 1955).

2.3.4.2 Vasodilation phase

Several hypotheses have been formulated to explain the mechanism of the hunting reaction. In 1963 Folkow et al. summarized the operative hypotheses and experimental support. He suggested that the mechanism was a combination of several hypothesized processes. An updated list of most important hypotheses for CIVD includes five hypotheses. These hypotheses are illustrated in Fig. 2.5.

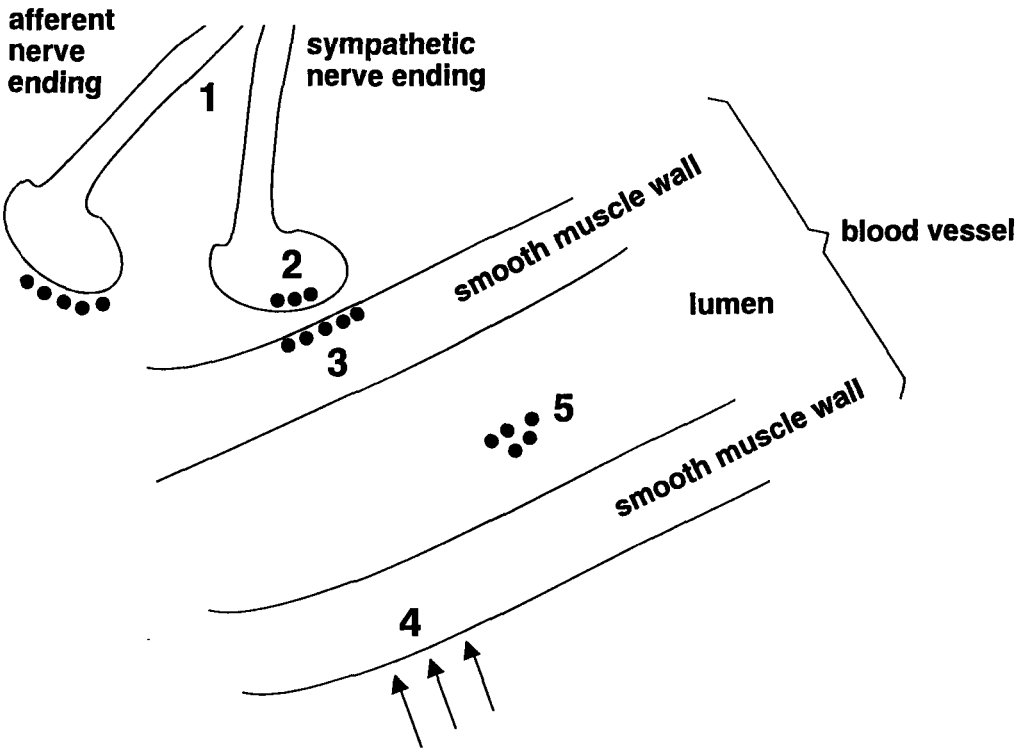

Fig. 2.5 Illustration of current hypothesis on CIVD. Numbers correspond with hypothesis in the text.

1 "axon reflex initiated by a local substance"

Several weeks after denervation of a peripheral nerve, degeneration of the nerve axons distal to the lesion is complete. However, the peripheral vessels regain their contracted state, sometimes above pre-operative levels due to up-regulation of the α-receptors (Guyton and Hall, 1996). In the degenerated state, Lewis (1930) found absence of CIVD. The difference between denervation and degeneration of the somatic nerve indicates that the distal end of the nerve plays a crucial role, which led to the concept of an axon reflex as explanation for CIVD.

An axon reflex or antidromic vasodilation is a reaction in which:

1. noxious stimuli (including cold) excite receptive nerve endings of unmyelinated neurons,
2. the evoked impulses are conveyed centrally and antidrommically via the axon branches,

3. the exited sensory nerve endings release vasoactive substances, which cause cutaneous vasodilation (Hornyak et al., 1990).

The axon reflex takes place entirely within a single sensory neuron. It is initiated in thin afferent fibres, in particular by C-polymodal nociceptors (Izumi and Karita, 1991). These free nerve endings are present at all levels of the epidermis from the stratum granulosum through the stratum germinativum, dermis and subdermis to the deeper layers (Nelms, 1963). The axon reflex can be invoked by cold (Lewis, 1930), electrical stimulation on the skin (Hornyak et al., 1990; Westerman et al., 1987; Magerl et al., 1987), intra-neural stimulation (Ochoa et al., 1993), electrophoresis of acetylcholine (Walmsley and Wiles, 1990), injection of histamine (Hovell et al., 1987; Izumi and Karita, 1991), injection of substance P (Izumi and Karita, 1991) and injection of nicotine (Izumi and Karita, 1992). The evoked vasodilation is most often assessed by laser Doppler flowmetry. The vasodilation area of an axon reflex extends about 9 ± 3 mm outside the stimulating electrode for a strong stimulus (20 pulses of 1 ms duration at 2 Hz and 20 mA current) (Wårdell et al., 1993). The axon reflex is often used as an indicator for the integrity of the nerves to the region under investigation.

The afferent signals are supposed to inhibit the sympathetic nerves which lie in close vicinity (Schadé and Ford, 1973). The AVA's, richly innervated by sympathetic nerves and having α-receptors in the muscle wall, react by subsequent relaxation.

Kramer and Schulze (1948) found that CIVD was abolished after infiltration of the finger tip with a local anaesthetic, which would block any axon reflex mechanisms. However, Greenfield et al. (1951a) found that CIVD persisted after complete degeneration of the mixed nerve, although with diminished magnitude and only after pre-immersion of the fingers in warm (42°C) water. They concluded that non-nervous mechanisms also had to play a role. Some of the patients in the latter study were reexamined by Shepherd and Thompson (1953). They found that in some of the patients the sensation returned, and so did CIVD.

Keatinge (1961) transferred by iontophoresis adrenalin and noradrenaline (NA) through the palmar side of the distal two phalanges of the left index finger. The concentration was raised until the contraction state of the fingers was so high that blood flow was minimal. Hereafter, they immersed the finger in ice water and found a CIVD response with an amplitude of about one third of the normal response. Webster (1974) found that CIVD disappeared after infusion of NA in sheep.

In summary, it can be concluded that the major part of the CIVD response is abolished when the axon reflex is blocked. The remaining vasodilation as seen by Keatinge (1961) may be attributed to a direct effect of cold on the smooth muscle wall of the arteriovenous anastomoses and small arteries (Keatinge, 1970) or an indirect effect through the release of vasodilatory agents, such as NO (Umans and Levi, 1995).

In Table 2.4 the experiments are summarized in which a total peripheral nervous block was achieved, i.e. not only the central sympathetic activity is blocked, but also axon reflexes are abolished. Comparison with Table 2.3 shows that a peripheral nervous block with the axon reflex intact leads to vasodilation, while a peripheral nervous block including blockade of the axon reflex abolishes CIVD. The abolishment of CIVD after complete degeneration of the peripheral nerve was confirmed in cats (Folkow et al., 1963) and rats (Gardner and Webb, 1986).

Table 2.4 Overview of experiments in which peripheral nerve blocks were applied, which abolished both the central sympathetic influence and the axon reflex.

Degen. = Degeneration of peripheral nerve;
C = Chemical agent

Author(s)	Number of sub-jects	Type of neural block	CIVD-response	Remarks
Greenfield et al., 1951a	4	degen.	reduced	CIVD absent when fingers are pre-immersed in cold (15°C) water
Keatinge, 1957	7	C - 2% lignocaine	sometimes present	
Keatinge, 1961	11	iontophoresis of (nor)adrenalin	reduced	
Kramer and Schulze, 1948	1	C - novocaine	none	
Lewis, 1930	3	degen.	none	

A point of discussion is if the vasomotor centre discharges as a complete unit like in an alarm response, or if the neural vasomotor control is spatially organized, like in the sensory and motor cortex. In the process of temperature regulation, the sympathetic system controls blood flow in the skin without affecting other organs innervated by the sympathetic system (Vissing et al, 1991; Guyton and Hall, 1996). This, however, may be mainly due to the higher sensitivity of the skin to sympathetic stimulation than the muscles. In cats, Kocsis (1994) showed that the sympathetic output of the vertebral, cardiac and renal nerve was rather similar. Oberle et al. (1988) showed that intra-neural electrical stimulation produced more vasodilation in hands than in feet in cold subjects and concluded that this indicated a spatial organization of neural vasomotor control. However, the influence of peripheral and geometric factors may also play a role.
Therefore, the issue is still not completely resolved, and for our study it is assumed that a vasomotor discharge affects all vessels of the hand in about the same manner.

It still is unclear which vasoactive substance in the sensory nerve endings causes the vasodilation. Lewis (1930) proposed that *H*-substance (*histamine*; *β-imidazolylethylamine*) is released in the skin as a reaction to the damage caused by the cold. Histamine affects the free nerve endings and initiates the axon reflex. The results of Yoshimura et al. (1962) supported his results: they found that histamine-salves applied to the skin improved the hunting reaction and that an anti-histaminic agent

reduced the response. However, Duff et al. (1953) found that the onset of the CIVD reaction was not advanced after intra-arterial injection of histamine directly after immersion of a finger tip in cold water. Also, Fox et al. (1961) found that antihistaminics had no effect on cold vasodilation in the skin, and they proposed that the polypeptide bradykinin played a major role. More recently (Chahl, 1988) reviewed the hypothesis concerning antidromic vasodilation. The current hypothesis (Fig. 2.6) is that a stimulus (like local cold) releases Substance P (SP), neurokinin A (NKA) and Calcitonin gene-related peptide (CGRP) from the endings of the unmyelinated primary afferent fibres. All chemicals have a direct vasodilating effect on local blood vessels. Moreover, SP and NKA trigger the release of histamine from mast cells. Mast cells are located immediately outside the microvasculature and play an important role in some types of allergic reaction (Guyton and Hall, 1996). The released histamine may also cause vasodilation. It is interesting to note that Leblanc et al. (1960) found more mast cells in local cold acclimatized subjects (92 ± 6 per mm^2) than in controls (68 ± 2 per mm^2), which might explain their enhanced vasodilatory response to cold.

The review of Chahl (1988) shows that the agent that may invoke vasodilation is not unambiguously determined. Probably, several agents play a role simultaneously and the relative contribution may vary depending on the experimental conditions and characteristics of the individual.

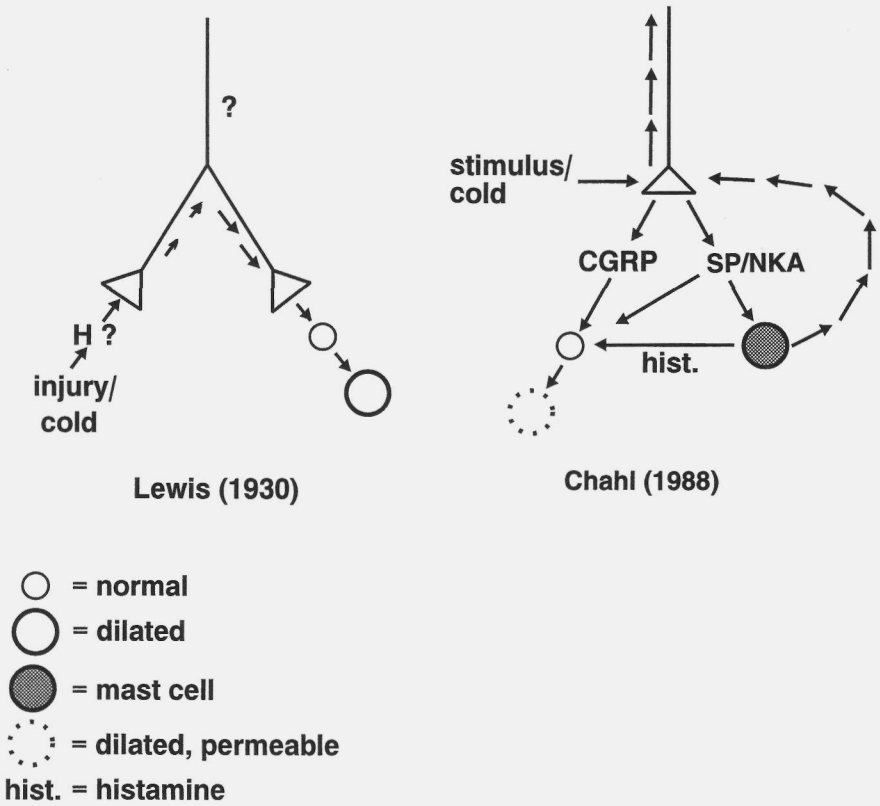

Fig. 2.6 Comparison of the concept of Lewis (1930) and of Chahl (1988) (Modified from Chahl, 1988).

2 "decreased release of norepinephrine from adrenergic nerve endings"

Gardner and Webb (1986) observed that CIVD did not occur in a rat tail when norepinephrine was continuously perfused. This led them to the conclusion that CIVD is caused by a cessation of transmitter release from adrenergic nerve endings. The resulting renewed blood flow warms the vessel wall past the critical temperature for sympathetic nerve activity and catecholamine release resumes, initiating a period of vasoconstriction.

3 "altered sensitivity of the vessels for catecholamines in the cold"
This hypothesis states that the sensitivity of the vessels to catecholamines is altered in the cold. Folkow et al. (1963) suggested that the sensitivity of the vessels to catecholamines was reduced when cooled. This reduced sensitivity would lead to the vasodilation. However, more recent experimental results show that the sensitivity of the α-receptors for norepinephrine increases in the cold (Shepherd et al., 1983), in particular the predominant α_2-receptors (Freedman et al., 1992) (see par. 2.3.4.1). The cold induced vasoconstriction induces a decrease in tissue temperature which may become so low that a nervous blockade occurs. Thus, norepinephrine is not released and the contractile apparatus of the smooth muscle wall stops (see hypothesis 2). This in turn causes vasodilation, the blood flow increases again, nerve conduction is restored and the contraction force of the smooth muscles takes place again. These consecutive changes are supposed to explain the hunting phenomenon.

4 "effect of cold on vascular smooth muscle activity"
Folkow et al. (1963) hypothesized that "it is not unreasonable to assume that the inherent smooth muscle activity will be considerably depressed or even abolished when the tissue temperature is reduced to low levels, producing a vasodilation". Keatinge (1970) showed that low tissue temperatures enhanced the contractile status of the blood vessel wall. Below a certain threshold, however, the contractile system relaxes and CIVD occurs (Keatinge and Harman, 1980). The formation of cross-bridges in the contractile system is inhibited. This hypothesis is frequently mentioned in physiology hand books (e.g., Guyton and Hall, 1996). Keatinge (1961) showed that a decrease in NA-release due to the local cold (hypothesis 2) could not be responsible for CIVD: iontophoreses of NA still produced CIVD in humans.

5 "dilating substance entering the blood"
This hypothesis has been put forward by Aschoff (1944). He postulated that a dilating substance (yet unknown) was formed when local temperature decreased under a certain threshold. The increased blood flow washed the substance away. The concentration of the substance should be dependent on the temperature.
Most experiments point out that CIVD only occurs when the peripheral nerves are intact (Table 2.4). This means that the vasodilating substance should be related to the nervous system as described by Chahl (1988) (see hypothesis 1).

2.3.5 Interaction between central and peripheral mechanisms

Hornyak et al. (1990) investigated the effect of the sympathetic system on the axon reflex. An axon reflex was elicited by electrical skin stimulation. The effect was measured by laser Doppler flowmetry. It was shown that cooling the skin from about 32 to 27°C reduced the axon reflex. Regional blocking of the mixed nerves by mepivacaine enhanced the reflex. From this experiment

and others they concluded that the axon reflex and sympathetic control have a competitive interaction. This conclusion was confirmed by experiments of Ochoa et al. (1993). Unfortunately, the interaction of the sympathetic nerves and the axon reflex has not yet been investigated during the hunting reaction. Therefore, chapter 12 of this study is devoted to this topic.

2.4 The role of arteriovenous anastomoses (AVA's) in thermoregulation

2.4.1 Definition and description of anastomoses

An anastomosis is a natural or acquired connection between two organs, spaces or parts of the same organ (Holboom, 1974). In the human lymphatic and circulatory system numerous anastomoses are present. Anastomoses can be detected in the arterial network as well as in the venous network. The larger superficial and deeper veins form anastomoses. In the arterial network an example of an anastomosis is the basilary artery which forms the point of connection of both vertebral arteries. If one vertebral artery closes, the other takes over and blood can still flow to the crucial basilary artery. In this way the anastomosis forms a kind of protection. If one vessel becomes blocked and the other takes over, the blocked vessel may degenerate, while the other dilates and strengthens. Therefore, anastomoses are no fixed structures, but may come and go on demand. Clark (1938) developed a double-walled chamber for implantation in the ear of rabbits to study the development of AVA's. In one chamber he counted 40 AVA's. 39 Days later 41 AVA's were counted: two AVA's had subsided and three new ones developed.

2.4.2 Arteriovenous connections and glomera

The most common connection between the arterial and venous network is formed by the capillaries. Besides these capillaries, the following vascular connections were also observed between the arterial and venous network in the skin (Gray, 1980):

- preferential channels,
- (simple) arteriovenous connections,
- specialised arteriovenous connections, also called glomera.

An almost identical classification is made by Staubesand (1950) (in Hale and Burch, 1960). He distinguishes between three types of arteriovenous connections: bridge-anastomoses, arteriovenous connections and glomus organs. His classification is derived from Schumacher (1938) (In Hale and Burch, 1960). Schumacher distinguished type I and type II anastomoses and glomera. Masson (1937) introduced the term 'glomus'. He was dissatisfied with the name 'arteriovenous anastomosis' because of the confusion with traumatic and other unusual connections which have received the

same name. This new name had at that time the remarkable effect of a renewed interest in AVA's. A few decades later a distinction was made in structure between AVA's and glomera. The terminology of Gray has been generally adopted.
Currie (1990) indicates that this terminology may be oversimplified. He distinguished 19 types of blood vessels in the tip of the toes, mainly based on histology and discusses the existence of preferential channels. In particular the presence of AVA's in the skin alters the functional characteristics to a large extent.

According to Hale and Burch (1960) arteriovenous connections originate from preferential channels. Preferential channels are vessels with a wall consisting only of endothelial cells and their basement membranes. However, their diameter is greater than that of capillaries: about 10 to 20 μm in the skin as compared to a maximum of 10 μm for capillaries. The development of smooth muscle cells around such channels marks the beginning of an arteriovenous anastomose with the potential to regulate flow. Mechanical factors related to dynamics of blood flow in the skin (e.g., arterial pressure) may stimulate the development of these primitive anastomoses, which eventually lead to the formation of highly developed glomus organs.
The best known glomus organs are found in the bifurcation of the carotid artery and the os coccygae. In the human nail bed the AVA's are so elaborated that they can also be called glomera (Fig. 2.7). In the volar finger skin most authors use the term AVA, although some (e.g., Clara, 1939) use the term glomus to describe the arteriovenous connection. Glomera consist of encapsulated arteriovenous connections. In such a glomus, blood vessels, muscle cells and nerve cells are present. Immersion of a finger tip in cold water thus involves the arteriovenous anastomosis of the skin and the glomera in the nail bed. Since the glomera are relatively outnumbered by the AVA's, the accent shall be placed on AVA's in this thesis.

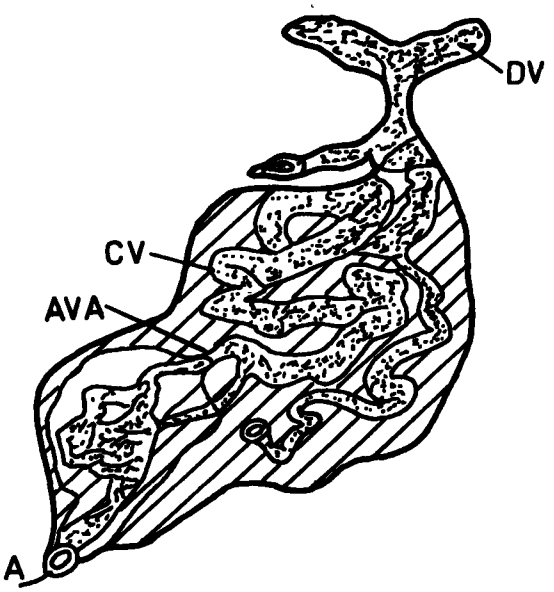

Fig. 2.7 Schematic drawing of a glomus organ from an adult nail bed. A is the feeding artery, AVA the actual arteriovenous anastomosis, CV the collecting vein, DV the dermal vein. Horizontal hatching denotes the connective tissue capsule. The anastomotic segment is encapsulated with epithelioid cells (hatched lines). From Hale and Burch (1960).

2.4.3 Location of AVA's

AVA's can be found at almost any location in the human body (Sherman, 1963). Controversy exists concerning their presence in the lungs, kidneys, muscles and nervous system. Clark and Edholm (1985) state that there is no evidence of arteriovenous shunts being found in the blood vessels supplying the muscles. According to Clara (1939) probably no AVA's are present in the blood supply of the central nervous system.
In the skin, Hale and Burch (1960) and Clara (1939) mentioned the following sites in their review: the skin of the inside of the hand and foot, the nail bed, elbow, lips, cheeks, ears and nose. There is some discussion about the presence of AVA's in the skin of the head. Some authors (as Hoyer (1872) in Clara, 1939) were not able to detect AVA's in the skin of the nose, ears and lips.

Popoff (1934) was not able to find AVA's in premature and newborn infants and related this finding to the poor temperature control mechanisms which are characteristic for these infants. However,

Hale and Burch (1960) did find AVA's, containing smooth muscle, in the newborn. AVA's are difficult to detect, which may explain the inconsistent results (Daanen, 1991a).

2.4.4 Number of AVA's in the skin

The number of AVA's in the skin is not constant. In animals the number of AVA's increases as the need for local blood supply increases, and the number decreases as the stimulus is removed. According to Sinclair (1978), it is unknown if this is also true in humans. However, Hale and Burch (1960) investigated the human fingertip and made it plausible that arteriovenous anastomoses develop if blood requirement increased. Clark and Clark (1934) estimated that the formation of new AVA's lasted two to three days.
Grant and Bland (1931) found 501 AVA's per cm^2 surface area in the nail bed, 236 in the finger tip, 150 on the palmar side of the distal phalanx and 20 for the palmar side of the medial phalanx and 93 for the palmar side of the proximal phalanx. They found no AVA's on the dorsal side of the hand. However, the numbers were derived from only one index finger in only one subject, although they claim that similar results were found in three other subjects. The results of Grant and Bland (1931) are often incorrectly cited. For instance, Hale and Burch (1960) cited the 150 AVA's on the distal phalanx as 50 AVA's. Another citation mistake is made by Burton and Edholm (1955), who state that Clara (instead of Grant and Bland) counted 500 AVA's per cm^2 in the nail bed and 236 in the fingertips.
Masson (1937) only counts 3 to 4 AVA's per cm^2 on the top of the finger and about 10 in the nail bed. Clara (1939) argues that Grant and Bland counted the same AVA several times. AVA's are tortuous and they did not account for that in their counting technique.
The limited information on the number of AVA's, the disagreement in the existing studies and the errors in citation necessitates new research to address this topic. Moreover, there is a strong need for more accurate data on the amount of AVA's in the human body, in particular to improve current computer models on blood flow and heat transfer. However, it is likely that the number of AVA's is greater in the nail bed than on the palmar side of the top of the finger, and that the fingertip has more AVA's than the palm of the hand.

2.4.5 Anatomy and physiology

AVA's have a thick muscular wall and a relatively small lumen, measuring 10 to 30 μm on average (Gray, 1980). Roddie (1983) states that the average lumen is 35 μm. Sherman (1963) gives an average lumen for AVA's in the skin of 50 μm. Under the influence of the sympathetic nervous system, with its rich supply of non-myelinated fibres on the wall of the vessel, they are capable of complete closure. If the AVA's are open, large amounts of blood can pass. Clark (1938) calculated that the volume of blood flow through opened AVA's with an average diameter of 40 μm was 256

times greater than that of a capillary of similar length. He found that AVA's (in the rabbit) rarely exceeded 50 μm inside diameter. Nelms (1963) reports a 1000 fold increase in blood flow for AVA's dilated to 60 μm as compared to a diameter of 10 μm. No actual measurements of blood flow in AVA's have been made. Gray (1980) pointed out that closure of an AVA may not only be caused by contraction of the muscular wall, but also by a swelling of the epithelioid cells of the AVA due to local vasoactive agents.
In the hands and feet AVA's are encapsulated in large numbers of small units (Clara, 1939). The capsule consists of connective tissue covered with a rich network of vessels. In the fingers more collagen is present than in the toes. The structures are located deep in the dermis and nourished by one or more arteries. The feeding arteries come off at right angles from the skin arteries heading for the skin surface. At a short distance from its origin, the afferent artery of a glomus gives off a number of fine 'periglomeral' branches and at once becomes considerably enlarged (Fig. 2.7). It makes an S-shaped curve and then narrows down to become continuous with a short funnel-shaped vein which opens at right angles, into a collecting vein. This vein begins in the middle of the glomus and curves round its outer surface. There it receives venules from the papillary layer of the skin. Finally it joins one of the deeper cutaneous veins.

It is important to note that this general description of a well developed AVA's does not apply to all AVA's in the human body. There are large AVA structural differences throughout the body, for instance regarding the thickness of the muscular wall and the amount of innervation.

2.4.6 Innervation of the AVA's

According to Guyton and Hall (1996) the strong muscular wall of AVA's is innervated by sympathetic nerves using norepinephrine as a transmitter. Nelms (1963) has a different opinion. The constrictive innervation is adrenergic sympathetic, but the anastomotic vessels dilate in response to acetylcholine and contain large amounts of specific anticholinesterase, which may indicate some sympathetic cholinergic, possibly vasodilator, innervation. Currie (1979) finds cholinergic and adrenergic unmyelinated nerve terminals in the adventitial layer of the AVA canal; Böck (1980) on the other hand only finds adrenergic terminals. The nerve terminals are more developed in the arterial segment (Gorgas et al., 1977).

2.4.7 Function of AVA's in thermoregulation

The physiological control of humans at rest, exposed to a cold environment, aims at minimisation of body heat loss, while in a hot environment body heat loss is strived for. There are two important exceptions to this rule, both of which are probably related to the presence of AVA's: cold induced vasodilation (CIVD) and heat induced vasoconstriction (HIVC).

The AVA's are not only important in thermoregulation, but are also held responsible for several other functions. Since AVA's are well innervated (Clara, 1939) and because they have a topographical relation with touch sensors and free nervous endings in the skin (Clara, 1939; Hale and Burch, 1960) it is suggested that they play a functional role in touch sensation, thermoception and pain detection. There is, however, hardly any scientific evidence to support this view.

2.4.7.1 Role of AVA's in CIVD

As far as we know, there is at present no direct evidence that the AVA's are responsible for the increased blood flow during CIVD in man, due to technical difficulties to determine the blood flow in the AVA's during cold exposure. However, there is direct evidence of the involvement of AVA's in thermoregulation and indirect evidence for the involvement of AVA's in CIVD.

Grant and Bland (1931) were able to show AVA's dilatation in rabbit ears as a reaction to central body heating, and thus showed the involvement of AVA's in thermoregulation. Coffman (1972) measured total fingertip blood flow by strain gauge plethysmography and nutritional flow by a $Na^{131}I$ washout technique in ten subjects. The measurements were made in a warm room (28.3°C), cool room (20.0°C) and with and without norepinephrine infusion in a neutral room (25.5°C). Cold exposure and norepinephrine infusion reduced the total blood flow without affecting the nutritional blood flow, except for a slight reduction. The AVA's are the only structures which can explain this difference, and it is concluded that they are actively involved in thermoregulation in humans.

The indirect evidence that AVA's are involved in CIVD is mainly derived from the finding that CIVD occurs only at the AVA locations. Lewis (1930) noted that CIVD was found at sites of the human body with an unfavourably large surface to volume ratio. Grant (1930) observed that AVA's open up in a rabbit ears when the ear had been cooled for a while. In 1931 Grant and Bland suggested that CIVD occurred on those sites in the human body where many AVA's were present. According to Lewis (1930), the CIVD areas are located in the skin of the fingers, toes, nose, ear and chin. Fox and Wyatt (1962) investigated 34 sites in three subjects and found CIVD in the skin of the every part of the head, the neck, the olecranon and the patella, the outside of the anus, the buttocks and the skin around the nipples. If we compare these sites with the body sites where presence of the AVA's was confirmed (par. 2.4.3) we see similarities, but certainly not a perfect correspondence. There is no mention of AVA's in the skin of the buttocks, olecranon and patella. It seems interesting to investigate the presence of AVA's in these regions.
Aschoff (1944) shows that the fluctuations in the hunting reaction are larger in the distal phalanx than in the proximal one. This corresponds with the distribution of AVA's as reported by Grant and Bland (1931).

Another argument for the involvement of AVA's may be that the blood flow through the capillaries is insufficient to explain the magnitude of heat transfer found during CIVD. The periods of vasodilation during the hunting reaction (Fig. 1.3) bring a lot of heat to the finger tips. Spealman (1945) found a blood flow of 5.9 cc per 100 cc hand volume per minute when the hands were immersed in water of 35°C. At a temperature of 15°C the blood flow was only 0.9 cc per 100 cc hand volume per minute. At 5°C the blood flow had increased again to 4.3 cc per 100 cc hand volume per minute! Modelling of blood flow may reveal this issue, but a problem is the lack of accurate data on the number of AVA's (par. 2.4.4).

It has to be noted that CIVD on one location in the human body may influence blood flow and temperature in other body parts. For instance, Ducharme et al. (1991) and Ducharme and Radomski (1990) showed that the fluctuations in blood flow due to CIVD of the hand could also be measured in deep muscle of the forearm. Lewis (1930) even noted that the hunting phenomenon could be detected in the neighbouring non-cooled fingers. CIVD starts distally in an extremity and continues in proximal direction (Aschoff, 1944). Recently, Chen et al. (1996) demonstrated that the highest temperatures were found in the most distal parts of the fingers, where AVA's are most abundant.

2.4.7.2 Role of AVA's in heat induced vasoconstriction (HIVC)

Nagasaka et al. (1987) observed a decrease in finger blood flow using the plethysmography technique as the water bath temperature increased from 37 to 43 °C. This Heat Induced Vasoconstriction (HIVC) may reduce the heat transfer from the skin to the core at extremely high ambient temperatures.

2.4.7.3 The influence of central body temperature on AVA's

Both core and local skin temperature influence the amount of contraction of the wall of the AVA. Grant (1930, in Clark (1938)) found that the anastomoses dilated when the core temperature of a rabbit was raised, and that they closed upon cooling. When he cooled the ear only, the AVA's opened at temperatures below 15 °C, a phenomenon treated under the heading CIVD.
Hales and Iriki (1977) also found in sheep that warming of the CNS produced opening of the AVA's, probably due to a reduction in sympathetic stimulation. Clark and Edholm (1985) state that if body temperature of a human is raised, there is a marked increase in peripheral blood flow even if ambient temperature remains constant. On the other hand, if the ambient temperature is decreased under this condition, the peripheral blood flow also decreases.

2.4.8 Concluding remarks on AVA's

The arteriovenous anastomoses play an important role in thermoregulation. The muscle wall of AVA's is predominantly equipped with α-adrenoceptors and richly innervated by sympathetic nerves. Activation of the sympathetic system leads to active vasoconstriction, and decrease in sympathetic activity leads to passive vasodilation. In a slightly cold environment, the AVA's are almost closed. However, it is likely that the AVA's open up at the start of CIVD. The heat that is brought to the skin causes an increase in local skin temperature. This mechanism may play a role in the prevention of cold injuries in that part of the skin (Iida, 1949). The possible mechanisms are discussed in par. 2.3.4.2.
In a moderately warm environment, the AVA's are open. However, the AVA's close if the tissue temperature exceeds the core temperature, as in the experiments of Nagasaka et al. (1987). This reaction may be helpful to protect the body from hyperthermia. The mechanism behind this phenomenon (HIVC) is still unexplained but a possible explanation may be a sudden increase in sympathetic activity due to activation of hot-pain receptors.

2.5 Relevance of cold hand research

2.5.1 Cooling hyperthermic subjects by hand (or foot) immersion

A limiting factor during work in the heat may be the raise in core temperature. The temperature may become so high that heat collapse occurs. This high risk is especially present when protective clothing has to be worn, like NBC (Nuclear, Biological and Chemical) protective clothing. Intermittent cooling of the hands may be an effective method to reduce heat stress.

The circulation in the hands is elevated during heat stress. When exposing the hands to a cold environment, however, the vasoconstriction may hamper the heat transfer. Allsopp and Poole (1991) immersed hands (with NBC cotton inner gloves under rubber outer gloves) in water of 10 and 25°C after periods of work in the heat. At 10°C up to 200 W of heat was transferred to the water. They assumed that local vasoconstriction did not occur and that the AVA's stayed open. However, this conclusion is insufficiently supported by experimental data. Cooling by this immersion technique is rather effective: the total work time in the heat, limited by aural temperature criteria, was extended with 10 - 20 minutes by immersion. The same positive results were previously reported by Livingstone et al. for working and resting subjects (1989a).
Because immersion of the hands interrupts the task performance, Livingstone and coworkers (Livingstone and Nolan, 1991; Livingstone et al., 1995) cooled the body core by immersion of the bare feet in water of 10, 15, 20, 25 and 30°C. Again, most heat was lost at low water temperatures, up to 151 W at 10°C water.

In summary, cooling hyperthermic subjects by their extremities seems to be an effective technique to prevent overheating.

2.5.2 Rewarming hypothermic subjects by hand immersion

This method is used by the Danish Navy. Vanggaard and Gjerloff (1979) are convinced that rewarming should be carried out through the extremities while keeping the rest of the body insulated from the environment. This method finds its rationale in the observation that the arteriovenous anastomoses in the extremities open up in hot water. Superficial veins carry the rewarmed blood to the body core immediately, leaving the rest of the periphery cold. This method has not been compared to others and deserves more attention according to Livingstone et al. (1986) who stated that "the easy method of Vanggaard of rewarming hypothermic subjects should be considered for more extensive application". However, in a comparison of four rewarming methods it was shown that the heat uptake by the extremities was too low to rewarm the subjects effectively (Daanen and VandeLinde, 1992). It is supposed that the cold body core stimulated the sympathetic pathway, which leads to peripheral vasoconstriction.
Hand immersion is therefore not effective for rewarming. This conclusion is confirmed in a recent review by Tipton et al. (1993).
Although this may seem paradoxical, hand cooling may be a better method to rewarm hypothermic subjects. Van Someren et al. (1982) immersed subjects in water of 29°C and saw a progressive fall in body core temperature. When the hands were immersed in 12°C water the subjects felt cold and started to shiver, which increased the body core temperature or arrested its fall. This method of increasing metabolism is currently under investigation in the United Kingdom (Maidment, 1994). Hales (1985) found in sheep that the opening of the AVA's was related to the difference between deep tissue temperature and skin temperature. Thus, when the difference is high (as in Van Someren's experiment) the AVA's are more likely to open up. However, this phenomenon has never been shown in humans.

2.5.3 Prevention and treatment of local cold injuries

The extensive vasoconstriction induced by an exposure to a cold environment increases the risk of both freezing and non-freezing cold injuries, particularly for the hand and foot. Killian (1981a) reported that nearly 90% of all the cold injuries occur in the extremities, and that the foot is more often affected than the upper extremities.

freezing cold injuries
Frostbite may occur when the unprotected extremity is exposed to environmental temperatures under the freezing point. DeBacker (1989) mentions that frostbite occurs at skin temperatures below

-4°C. However, these low values are often obtained because supercooling occurred. Without supercooling, Keatinge and Cannon (1960) found that the true freezing point of the skin was between -0.53 and -0.65°C.

non-freezing cold injuries

When skin temperatures above the tissue freezing point are maintained for a long time non-freezing cold injuries can occur. The prolonged ischemia leads to pathological changes in the distal portion of somatic nerves (Carter et al., 1988). Francis (1984) reviewed the incidence of non-freezing cold injuries during warfare and found values up to 38 per 1000 in World War I. Chandler (1981) estimated that 60000 American soldiers in Europe during World War II suffered from non-freezing cold injuries. In many cases the affected body part was amputated. If that was not the case, the normal thermoregulatory responses of the injured body part were disturbed and full recovery took several years. See Whayne and DeBakey (1958) and Killian (1981b) for a thorough review of the pathology of cold injuries.

the hunting reaction to prevent cold injuries

Based on years of experience in investigating the hunting reaction, Yoshimura (1960) states that the hunting reaction 'is the essential factor which determines the individual differences of resistance to frostbite'. The preventive action of CIVD for cold injuries is shown in several studies.

Wilson and Goldman (1970) found in their experiments that freezing did not take place when CIVD occurred.

Probably the most elaborate study in this respect is from Iida (1949). He exposed the fingers of 42 subjects to cold air (-21 to -24°C) and determined the time and temperature at which frostbite occurred at the back of the middle finger. Based on these results he classified the group in 9 individuals with high resistance, 21 subjects with average predisposition and 12 individuals with low resistance to frostbite. Later, the hunting reaction of the middle finger in ice water was determined in all subjects. Subjects with a high resistance to frostbite had a much more pronounced hunting reaction (higher maximal and mean finger skin temperature and shorter onset time) than the average and low resistance group respectively.

Based on three hunting parameters, Yoshimura and Iida (1950) developed the 'Resistance Index of Frostbite' (RIF). The middle finger is dipped in ice-water for 30 minutes and the finger tip temperature is measured. The RIF was calculated based on:

- the mean temperature (5 to 30 minutes immersion),
- the maximal temperature of the first CIVD-peak after immersion,
- the time to the first temperature peak after immersion.

All scores were rated on a three point scale, leading to a final score of 3 to 9. During repeated immersions the maximal variation in RIF for a subject was always ± 1 point. This relatively high reproducibility of the RIF does not imply that the hunting reaction is reproducible, however, since the RIF is an artificial derivative from the hunting reaction. The reproducibility of the hunting reaction as a whole will be investigated in chapter 9.

keeping the hands warm with body heat
In order to prevent the occurrence of cold injuries, heat can be applied to the human body. Goldman (1965) found that it was most practical to supply the heat directly to the extremity surface, since hot air supplied continuously to the torso was inadequate to maintain the integrity of the circulation to the hands. Brajkovic and Ducharme (1996), however, found that heating the torso using an electrical heated vest was effective in keeping the hands warm. The reasons for these conflicting results are as yet not clear.

treatment of cold injuries
Several methods are used for early treatment of cold injuries, varying from slow to fast rewarming of the frozen tissue (Killian, 1981b). The benefits and disadvantages of slow versus fast rewarming form a continuous source for discussion. However, it is without discussion that during treatment of a cold injury, the central body temperature should be elevated to enable warming of the extremities via the bloodstream (Killian, 1981b).

2.5.4 Improvement of dexterity in the cold

The first problem encountered during prolonged exposure to a cold environment is a decreased dexterity. People can not perform their tasks any more and the number of accidents increase (Müller, 1982).
The relation between a cold environment and the decrease in dexterity has been thoroughly investigated. This interest can be explained by the impetus on productivity in commercial and civilian settings. A general overview of the relation between dexterity and cold is given by Daanen (1991b) and Daanen (1993). Heus et al. (1995) presented a general review focusing on the physiological limits of dexterity. The relation between CIVD and dexterity has been investigated by Bensel and Lockhart (1974). They showed that subjects with a short onset time had initially superior performance and subsequently inferior performance on specific manual tasks with increasing durations of whole-body cold exposure.

2.5.5 Clinical applications

Werner (1977) mentions that the hunting reaction can be used for clinical applications, for instance in plastic surgery for flap transplantations and in oedema prophylaxis. Moreover, the therapy of patients with Raynaud's phenomenon (Wollersheim, 1988) and reflex sympathetic dystrophy (Drummond et al., 1991) may benefit from new knowledge on the regulation of vascular reactions in the cold.

2.5.6 Model construction

Computer models are widely used in thermal physiology to improve the understanding of the underlying physiological processes and to make the knowledge applicable to a wider audience. The hunting reaction is included in some of these models (e.g., Lotens, 1989; Tikuisis, 1995; Shitzer et al., 1994), but prediction is not easy due to large inter- and intra-individual differences. Current models mostly use deep body temperature, mean skin temperature and peripheral temperatures as independent variables. To improve the models predictive performance, accurate data have to be available. At present, the literature primarily contains descriptive information and a lack of precise quantitative data (see for instance Table 2.1).

2.6 Research questions

From the preceding literature overview, it may be concluded that several mechanisms underlying cold responses are still unresolved. Some of these issues are addressed in this thesis, with the focus on central and peripheral control of finger blood flow. The following research questions are addressed in this thesis:

1. What is the time course and magnitude of heat transfer from hands and feet to a moderately cold environment (Chpt. 4) ?
2. How stable is the threshold in core temperature above which the blood flow in the hands increases ? What is the influence of mean (body) skin temperature and local hand temperature on this threshold (Chpt. 5) ?
3. How much synchronization occurs between the temperature profiles of the finger tips in one hand (Chpt. 6) and between two hands (Chpt. 7) ? The amount of synchronization gives information about the central or peripheral influence on the hunting reaction.
4. Do the temperature fluctuations in a non-immersed hand correlate to those of the immersed hand (neural influence) or to the blood temperature (Chpt. 8)?
5. What is the magnitude of the influence of body temperature and hand temperature on the hunting reaction ? Is the individual threshold in core temperature related to the magnitude of the response (Chpt. 9) ?
6. What is the magnitude of respectively body core temperature and mean (body) skin temperature on the hunting reaction (Chpt. 10) ?
7. What is the reproducibility of the hunting reaction (Chpt. 11) ?
8. How is the hunting reaction modified in hypothermia and hyperthermia? How does an axon reflex in the fingers depend on body temperature and water temperature (Chpt. 12) ?

Chapter 3

Instrumentation and methods

In this chapter the instrumentation and methods used in this thesis are described. In Table 3.1 a general overview is presented of the determined variables and used measurement techniques.

Table 3.1 Overview of the determined variables and used measurement techniques.

(physiological) variable	measurement technique
blood flow	strain gauge plethysmography
skin perfusion	laser Doppler flowmetry
temperatures	
- local skin temperature	thermocouples and/or thermistors
- mean skin temperature	thermocouples and/or thermistors
- core temperature (rectal, esophageal, ear canal)	thermistors
finger heat flux	heat flow discs
hand heat transfer	calorimetry
pain rating	modified 'Borg'-scale
temperature sensation	thermal sensation scale

Temperature measurements of the skin of the hands were combined with calorimeter determinations, laser Doppler blood flow techniques and strain-gauge plethysmography. In this way information was gathered on heat transfer of the total hand and of specific portions on the hand. This information was related to the core temperature, measured in the rectum, esophagus and/or ear canal.

The instrumentation used in the experiments which were performed in Canada (chapter 10 and 12) differed somewhat from the Dutch instrumentation, described in this chapter. The Canadian instrumentation is described in more detail in the instrumentation part of chapters 10 and 12. Main differences are the use of ear canal temperature as an estimator of core temperature in chapter 10 and the use of more skin sites to determine the mean body skin temperature in chapter 12.

3.1 Strain gauge plethysmography

An indirect estimator of the blood flow in the hand, middle finger, foot and middle toe was derived by the plethysmograph Whitney gauge technique using mercury-in-silastic circumference gauges (type SG6 and SG24, Vasculab company, P.O. Box 7268 Mountain View California 94039, USA; Whitney, 1953). The technique provides absolute measurements of blood flow in $ml \cdot min^{-1} \cdot 100\ ml\ tissue^{-1}$.

The principle of this technique is that proximal to the measuring site a cuff is placed and inflated in such a way that blood is still allowed to enter, but not to leave the measured extremity. During the obstruction a linear increase is seen in circumference due to the accumulating blood. The increase in circumference is an estimator of blood flow. See Elkington (1968) for a detailed description of the use of the technique.

The gauges were attached around the wrist, finger, ankle and toe respectively. Since the fingers and toes are almost free of muscle tissue, their volume changes mainly represent alterations in the blood volume in the cutaneous blood vessels (Okuda, 1942). The plethysmograph gauges were calibrated before each measurement using an electronic calibration signal (1% deflection). A pressure cuff was placed on the upper arm or on the thigh, and inflated to a pressure of 50 mm Hg for 5-10 s. The resistance output generated by the stretching of the gauge was then read by a plethysmograph (Vasculab II strain gauge plethysmograph SPG 16). The deflection angle was measured on the charts with a protractor.

3.2 Laser Doppler flowmetry

The skin blood flow at the tip of the middle finger and toe was estimated by using a laser Doppler flowmeter (Periflux PF 2B, Perimed company, P.O. Box 857 501 15 Boras, Sweden). Light from a 2 mW He-Ne laser with a frequency of 15.8 MHz enters the skin and is backscattered from moving red blood cells or static skin structures. Light scattered from moving objects is shifted in frequency (Doppler-shift) in proportion to the velocity of the moving target. A photodetector, located closely to the laser beam end, measures the backscattered light.

All measurements were performed within a frequency range of 20 Hz to 12kHz, an output circuit time constant of 3.0 seconds and a gain of 3 or 10. Öberg (1990) showed that a linear relation between blood cell flux and output voltage exists in the selected frequency range. A PF110 angle probe (fibre separation 0.26 mm) was used in a special frame (PF 114) with a thickness of about 0.2 mm. This means that there is an air gap of about 0.2 mm between the end of the glass fibre and the surface of the skin.

Skin perfusion is often related to total blood flow. For instance, Johnson et al. (1984) found a good relationship between laser Doppler flow and forearm blood flow ($r = 0.94 - 0.98$). However, there are also situations, such as reflex vasodilation, in which skin perfusion is regulated independently (Hales, 1985; Hirata et al., 1988).

There is some discussion on the penetration depth in the skin of the laser Doppler method. Penetration depth is determined by the wavelength of the laser Doppler system, the fibre separation and local properties of the skin.
Nagasaka et al. (1987) assumes that only capillary flow is measured in Doppler flowmetry. Nilsson et al. (1980) and Öberg (1990) show that the maximal sensitivity of the Periflux is found at a penetration depth of about 0.6 mm. Kolari (1985) shows that only 40% of the He-Ne laser light reaches a depth of 0.5 mm in the skin, and only 5% reaches a depth of 1.77 mm. The average thickness of the cutaneous plexus is 1 - 2 mm (Roddie, 1983). How deep the AVA's are located is difficult to determine. Jiji et al. (1984) locate them at 0.5 to 1 mm from the skin surface. Based on these data Nagasaka et al. (1988) argues that only a minimal part of the AVA's can be 'seen' by laser Doppler flowmetry. Wollersheim (1988), however, shows that at least part of the shunt flow is included in the volume measured by laser Doppler.
Different optic fibre separations give different penetration depths (Hirata et al., 1988) and may discriminate between nutritional and total blood flow. The maximum sensitivity at the fibre separation used in this thesis was estimated to occur at a depth of about 0.8 mm (Hirata et al., 1988).
Another factor which is related to penetration depth is the tissue that is measured (Tenland, 1982). In highly perfused tissue, like the dilated finger tip, a shorter light penetration depth can be expected, since the light absorption in red cells is higher than in surrounding tissue and since the red cells "stand in the light for each other" (Tenland, 1982).
In conclusion, laser Doppler flowmetry, as used in this thesis for the assessment of skin blood flow, was determined by blood flow in the small arterioles, venules, capillaries and AVA's.

During the laser Doppler measurements, the subject was sitting comfortably. The hand under investigation was resting on a surface at the level of the heart or the hip. The foot under investigation was placed on the floor. The laser Doppler flowmeter was calibrated at the beginning of each study, in the way described in the Perimed documentation. The Doppler probe was connected to a small elastic band and fixed around the finger by Velcro tape. Care was taken that the probe was not fixed too tightly. The Doppler signal was sampled continuously.

In Chapter 11 a comparison is made between finger skin temperature and laser Doppler signal. It was shown that the Doppler signal preceded the temperature signal by about 90 ± 48 sec.

3.3 Temperature

Temperatures were measured of the calorimeter water bath used for immersion of a hand or foot, of the environment, body core, skin and finger tips. All thermocouples and thermistors were calibrated prior to the experiment with a certified mercury thermometer. The error in absolute temperature for the thermocouples was about 0.1°C.

3.3.1 Local skin temperature

The temperature of the palmar side of the distal phalanx of every finger was measured by copper-constantan (type T) thermocouples, with the exception of chapter 4 in which only two fingers were measured. Each of the two wires of the (standard) thermocouple had a core diameter of 0.5 mm. The two wires were twisted. The sensors were placed directly on the skin and fixed with 25 mm wide air-permeable tape (Leucoplast, Beiersdorf corporation). All copper/constantan ends were sealed with PVC. The PVC socket increased the total diameter to about 3.2 mm. Sealing was necessary to reduce cross-talk between the thermocouples, in particular when the water bath became polluted with electrolytes. The PVC ends may have delayed the temperature response by a few seconds, but guaranteed reliable operation under extreme conditions.
In the literature the nail bed is also often used as a measuring site, since it is known that AVA's in glomera are abundant there. However, Yoshimura (1966) showed that the temperature reaction measured on the pad of the finger was more sensitive and reproducible than on the nail bed. Therefore, the temperature was only measured on the finger tips in this study.

From the temporal evolution of the finger tip skin temperature during immersion, several parameters were derived (Fig. 3.1).
The **first minimum temperature** (T_{min}) was calculated by a computer algorithm as the first data point for which temperature values in the two time-periods of four minutes before and after were higher.
The **maximum temperature** (T_{max}) was calculated as the finger skin temperature exceeding all temperatures in the preceding and following four minutes, respectively.
The **onset time** (Δt_{onset}) was defined as the time from immersion to first minimum.
The **amplitude** was defined as the difference between the first minimum temperature and the maximum temperature.
The **peak time** (Δt peak) was defined as the time interval between first minimum temperature and maximum temperature.
A second minimum was calculated the same way as for the first to determine the **period** (Δt period, i.e. time to second minimum minus time to first minimum).
The **mean finger temperature** ($\bar{T}_{fi}$) denotes the average finger skin temperature starting 10 minutes after the immersion.
The results of the computer algorithm were always visually checked with the raw data, to ensure that no true minima or maxima were excluded.

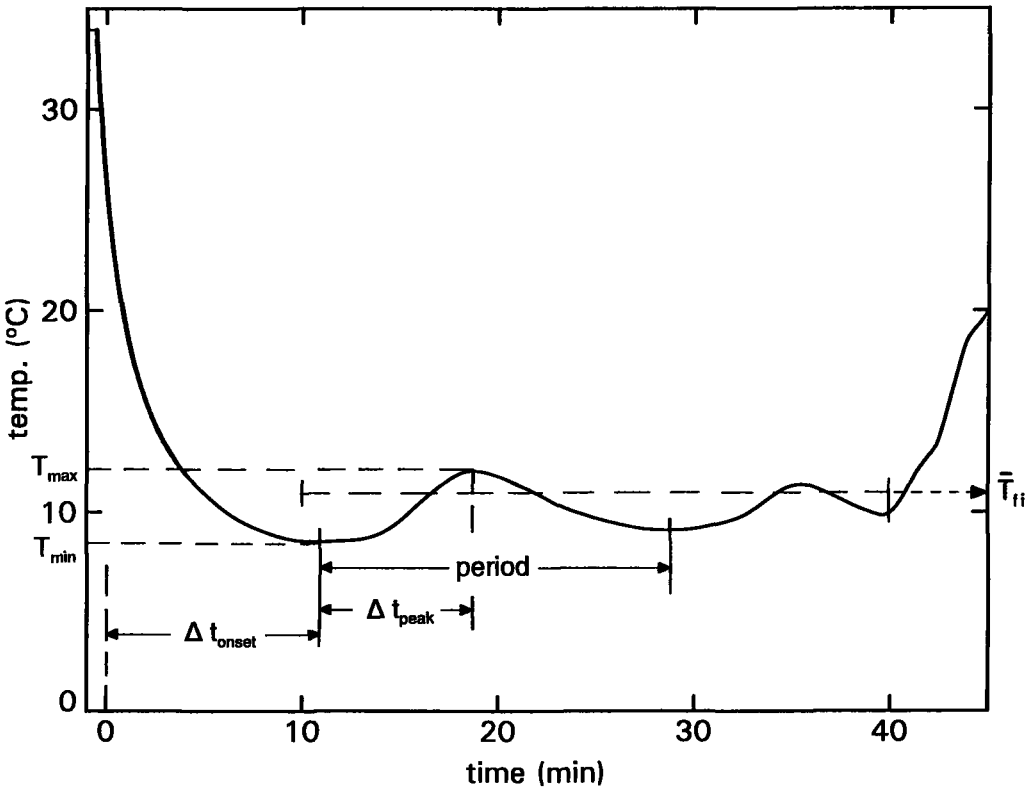

Fig. 3.1 Parameters derived from a temperature profile of a finger tip immersed in cold water. See text for the description of these parameters.

The calculated parameters are not independent. They are closely related to each other e.g., a short onset time is highly correlated to a high T_{min} (Tanaka, 1971b).

3.3.2 Mean (body) skin temperature

Three thermocouples were used to calculate the mean skin temperature ($\bar{T}_{sk}$). The thermocouples were positioned on the sternum (chest), and on the belly of the biceps brachii muscle (arm) and vastus medialis muscle (thigh). $\bar{T}_{sk}$ was calculated as 0.36 arm + 0.25 chest + 0.34 thigh + 1.19 (Lund and Gisolfi, 1974). This formula was validated against surface weighted calculation at 10 sites for a temperature range of 18 to 36°C and at three exercise levels.

3.3.3 Core temperature

During the experiments, rectal temperature of the subjects was measured by a thermolinear probe (YSI 701) inserted 120 mm beyond the rectal sphincter. In addition, an esophageal thermolinear probe (YSI 702a) was inserted through the nasal passage. Sometimes, on request of the subjects, the mucosa of the nose and throat were anaesthetized with 10 mg lidocaïne spray prior to insertion. The insertion depth beyond the external nares was based on sitting height, as determined prior to the experiments (Mekjavic and Rempel, 1990). In the experiment described in Chapt. 5 the insertion depth was fixed at 41.5 cm, since it was performed before the results of Mekjavic and Rempel were published. In chapter 10, the core temperature was assessed by the ear canal temperature.
In some subjects, the esophageal recording in a cold environment showed artifacts. These artifacts were due to the swallowing of cold saliva, which caused a short reduction in esophageal temperature. When this occurred, the negative deflections were removed from the recording and the missing points were interpolated.

In this thesis the body core temperature was manipulated in four ways:

1. The core temperature shows a normal fluctuation during the day and fluctuates between days. Thus, repeated measurements yield varying core temperatures. This leads to uncontrolled experiments and can not really be used to study the effect of core temperature on the hunting reaction. Therefore, except for the three manipulations described below, it was tried to keep the core temperature as constant as possible. The inevitable variations in core temperature were not included in the analysis of the hunting parameters.

2. The core can be actively warmed by exercise. Exercise, however, also leads to vasoconstriction of the skin and evokes reflexes that interfere with thermoregulatory control. Therefore, hunting reactions were only investigated after exercise and not during exercise.

3. Passive heating of the body core was achieved by a high ambient temperature or by wearing insulative clothing. In chapter 12 passive heating was accomplished by a special designed suit. Low ambient temperatures and wearing clothing with low insulation were used for passive cooling.

4. Drinking hot or cold liquids. The vasomotor centres may be affected not only by temperature, but also by the altered information from the stomach and intestines. However, Kramer and Schulze (1948) found similar effects on core temperature of passive heating and drinking hot fluids. In chapter 8, hot or cold drinks were only used prior to an evoked hunting reaction and not during the immersion period.

3.3.4 Body heat content

The body heat content is calculated as:

$$Q_b = 3.48 * (0.8 * (T_{re} + T_{es})/2 + 0.2 * \bar{T}_{sk}) * M_b \quad [3.1]$$

in which:

Q_b = body heat content in kJ
T_{re} = rectal temperature in °C
T_{es} = esophageal temperature in °C
$\bar{T}_{sk}$ = mean body skin temperature in °C
M_b = mean body mass in kg.

The weighing factors of 0.8 for core temperature and 0.2 for mean body skin temperature are representative for thermoneutrality and are used for both thermal states of the body. Farnworth and Havenith (1987) showed that a slightly more accurate assessment of mean body temperature can be obtained by incorporating extra weighing factors for toe and leg temperature. These variables, however, were not measured in this thesis for practical reasons.

3.3.5 Ambient temperature

The ambient air temperature was determined by a copper-constantan thermocouple placed outside the calorimeter in the open air, away from the subject and technical instruments.

3.3.6 Water bath temperature

The water temperature was determined by a copper-constantan thermocouple placed just below the stirrer of the calorimeter.

3.4 Heat flux

Heat flux (HF) was measured by 2 calibrated heat flux transducers (Ducharme et al., 1990) with a diameter of 17 mm (ITI company). Heat flux discs enable the measurement of local heat transfer from the extremity to the environment. Specific locations of the human body can be investigated, such as finger tips, which is almost impossible with calorimetric methods. However, these transducers are often questioned because of their reliability and accuracy (Ducharme et al., 1990), and the disks were carefully located on the skin to reduce the occurrence of erroneous measurements.

The sensors were placed directly on the skin and fixed with surgical tape (Blenderm, 3M Corporation). On the dorsal side of the hand the disc was applied between the fourth and the fifth metacarpal. On the ventral side the disc was located on the belly of the abductor pollicis brevis muscle. On the foot, the discs were fixed between the fourth and the fifth metatarsal on the dorsal side and on the belly of the flexor digitorum brevis muscle on the ventral side.

Heat flux (HF) from the volar surface of the left index finger during the threshold determination, as described in chapter 5 and 8, was measured by miniature heat flux sensors (9.5 mm diameter; 1.8 mm thickness; Concept Engineering type FRM-200-T). The sensor was placed directly on the skin and fixed with 25 mm wide air-permeable tape (Leucoplast, Beiersdorf corporation).

3.5 Calorimetry

Heat transfer was determined by calorimetry with the system shown in Fig. 3.2. An Iwaka magnet pump (MD-30R) circulates the water to a heat exchanger (HE), which is immersed in a glycerol bath (Tamson TLC 3). Hereafter, the water flows through the calorimeter bath and through the guard box, which includes a cover, back to the pump. Proportional valve K regulates the relative flow through the calorimeter and guard. The difference in temperature between the incoming and outgoing water of the calorimeter (ΔT) was determined by a thermopile, which consists of 40 thermocouples in series. The resolution of the thermopile is 0.0025°C.

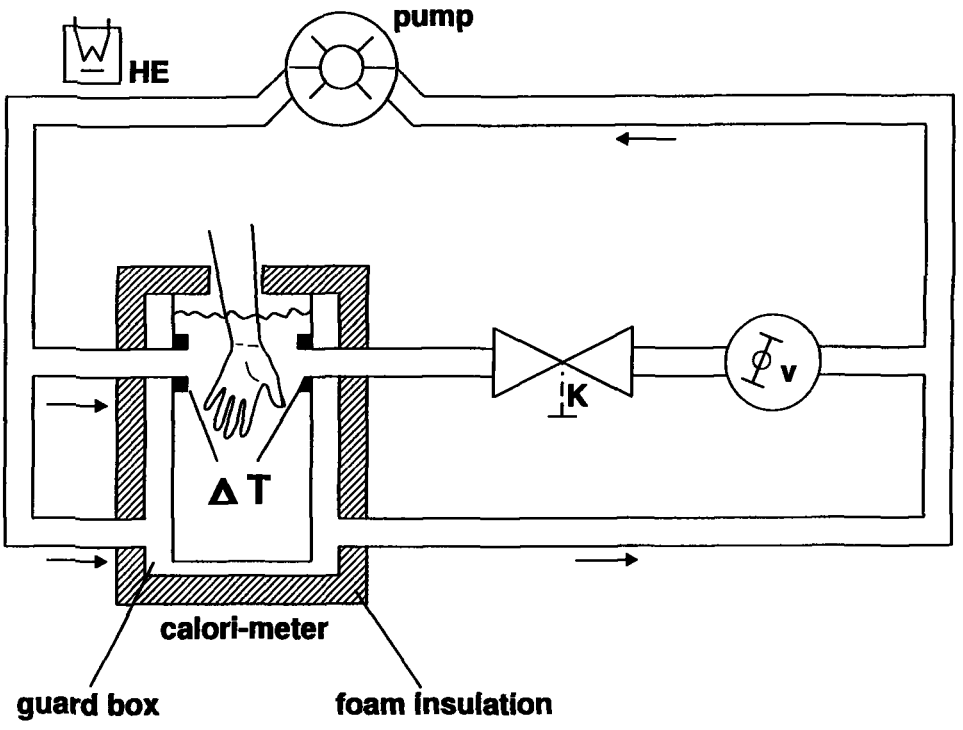

Fig. 3.2 Schematic overview of the calorimeter set-up. K is an proportional valve to regulate the flow of the water. HE is a heat exchanger and Φ_v is a flow meter. The direction of flow is indicated by arrows.

The calorimeter is an insulated metal box with an internal dimension of 45 x 15 x 15 cm. The calorimeter is encapsulated in a guard box that is kept at the same temperature as the water calorimeter bath by means of a water circuit, thus preventing heat loss to the environment. Foam insulation is added to the outside of the guard.
Two foam inserts are placed in the calorimeter to reduce the water volume. A volume of 3.5 l water is required to accommodate the hand and a volume of 4.5 l to accommodate the foot.
A metal stirrer is mounted on the inside of the hood of the calorimeter to stir the water over the hand or the foot. The stirrer is activated at the beginning of every immersion.

The flow of the water is kept constant at 1.5 $l \cdot min^{-1}$ and controlled by a Rota KL1 flow meter.

The power transferred from the hand or foot to the water is calculated according to the formula:

$$\text{Total power transferred} = \rho \cdot C_p \cdot \Phi_v \cdot \Delta T + \rho \cdot C_p \cdot V_0 \cdot d\Delta T/dt \text{ (W)} \quad [3.2]$$

in which
- ρ = density of water, being 998 $kg \cdot m^{-3}$
- C_p = specific heat of water, being 4.180 $kJ \cdot kg^{-1}$ per °C
- Φ_v = flow of water in $m^3 \cdot s^{-1}$
- ΔT = temperature difference in °C
- V_0 = volume of water in m^3
- t = time in seconds.

The calorimeter was calibrated with a coil with a fixed power output (Daanen et al., 1990). The difference between the power as measured in the coil and the power as calculated for the calorimeter did not exceed 0.15 W. The transferred heat (kJ) is calculated as the transferred power, integrated over the immersion period.

The time constant of the calorimeter can be calculated as:

$$\text{Time Constant} = V_0 / \Phi_v \text{ (sec)} \quad [3.3]$$

and is about 140 sec for the measurement of the hands (Daanen et al., 1990). Adding the second part of formula [3.2], also called the instationary component, reduces the time response slightly more, which makes the calorimeter a relatively fast instrument to measure overall heat transfer.

3.6 Thermal and pain sensations

Subjective sensations were scored just before immersion, at the moment of immersion, every five minutes during immersion of the hands in the water-bath and finally after ten minutes of recovery. Pain sensation could be scored on a 11-point modified Borg scale ranging from "no pain at all" (1) to "unbearable pain" (11) (Havenith et al., 1993) and thermal sensation on a 13-point scale from "comfortable warm" (2) via "neutral" (0) to "very, very cold" (-10) (Havenith and Van Middendorp, 1985). The scales are shown in Appendix 2.

3.7 Climatic chamber

All experiments were performed in a climatic chamber with a fixed air temperature (accuracy better than 0.2°C over time and place) and fixed relative humidity (accuracy better than 2% when the

ambient temperature is higher than 20°C). The setting varied from experiment to experiment and is mentioned where appropriate.

3.8 Subjects

All subjects were male or female students or employees of the TNO Human Factors Research Institute. None of them had a previous history of cold injuries. The subjects were not allowed to smoke or drink coffee less than two hours prior to immersion of the hand(s). All subjects were fully informed about the purpose of the investigation, and signed an informed consent. The ethical committee of the TNO Human Factors Research Institute approved all protocols.
The volume of the hand was estimated by the water displacement when the hands were immersed to the level of the styloid processes of the ulna and radius. The palmar side of the hand was photocopied. The contours of the hand were marked and the surface area was determined by a computerized planimeter to get a rough indication of the surface area of the hands. The body surface area was calculated according to Dubois and Dubois (1916).

3.9 Procedures

pretest conditions
The hunting reaction was investigated when the subjects were thermoneutral, slightly hypothermic or slightly hyperthermic. In the experiment of chapter 12, it was ensured that the subjects were in a stable thermal condition before the hand was immersed in the cold water. However, in the preceding chapters, thermal stability was not always ensured, since this would extend the duration of some experiments to intolerable long time spans. In the standardization protocol of Carlson (1966) for hunting reaction research, he proposed a neutral thermal state of the subject for 30 minutes prior to immersion as measured by hand (30-32°C), skin (mid medial thigh 34 ± 0.5°C) and core temperature (oral temperature >36.0°C, dependent on time of day).

test conditions
In our experiments the room temperature varied from 12 to 31°C, and relative humidity from 21 to 60°C (Table 3.2). The air movement was minimal. The subject was seated with the hands at heart level (chapters 4, 5, 10 and 12), or at the level of the hips (chapters 6, 7, 8, 9 and 11). One or two hands were immersed in water of 4 to 10°C to evoke the hunting reaction. Immersion was done to the level of the styloids, except for chapter 12, where, for practical reasons, the immersion was about 5 cm less deep. Immersion lasted at least 40 minutes, except for the experiment in chapter 10 were the immersion time was limited to 30 minutes.

Carlson (1966) proposed a room temperature of 27 ± 0.5°C, relative humidity <50%, minimal air movement, seated posture of the subject with hand at heart level, immersion of the first two

phalanges of the middle finger in stirred ice water. The thermocouple should be located at the nail bed. However, the finger pad is shown to give better reproducible results than the nail bed (Yoshimura, 1966); since there are large differences in the hunting reaction between fingers, the use of only one finger supplies limited information and it is better to immerse all fingers; immersion of the entire hand causes no more pain than immersion of a finger, since pain is not spatially summated (Burton and Edholm, 1955); relative humidity has been shown to be of minor importance to skin temperatures as compared to ambient temperature (Roth et al., 1940); and the medium temperature of 0°C is known to be very painful for the subjects. It is shown that a water temperature of 5°C is less painful and gives similar or even better results (Elsner et al., 1960; Hirai et al., 1970; Kregel et al., 1992). Carlson proposed an immersion time of at least 15 minutes. This is too short to determine the hunting frequency.

data recording

The data recording interval varied from 16 to 60 seconds. Carlson (1966) proposed a 15 s recording interval, but since the frequency of the hunting reaction is several minutes, no aliasing will occur in our experiments.

The experimental conditions of the experiments described in this study are summarized in Table 3.2. The table is divided in five main parts.

In the upper part of the table, the number of subjects participating in a given study is provided as well as the number of sessions every subject had to participate in and the number of days he or she had to come to the laboratory.

The next part of the table concerns the immersion procedure. It is shown which hand was immersed first, how long the hands were immersed and in the case of non-simultaneous immersion how much the time delay was in between immersions.

Hereafter, the ambient settings are shown: ambient temperature, relative humidity (RH) and water bath temperature.

Next, the measurements performed are shown and the sites on the body.

The last part contains a list of other variables which were encountered in the experiments e.g., if pain was measured or extra radiation applied.

Table 3.2 Experimental conditions for the experiments described in this study. See text for the description of the five main areas in this table.
Finger codes: 1 = right thumb, 2 = right index finger, 3 = right middle finger, 4 = right ring finger, 5 = right little finger, 6 = left thumb, 7 = left index finger, 8 = left middle finger, 9 = left ring finger, 10 = left little finger;
RH = relative humidity;
Core temperature codes: R = rectal, E = Esophageal, C = Ear Canal;
Other codes: Le = left, Ri = right, - = not measured, x = measured, Le-Ri = half of the subjects started with the left hand, half with the right hand.

CHAPTER	4	5	6	7	8	9	10	11	12
Keyword	heat loss	thres-hold	one hand	two hands	one hand out	body temp	skin and core	repro-duction	axon reflex
# subjects	5	6	12	8	7	8	9	8	6
# session/subj.	8	4	1	2	2	4	5	3	3
# days/subject	4	2	1	2	1	1	5	3	3
first immersion	Le-Ri	Le-Ri	Le	Le-Ri	Ri	Le-Ri	dominant	Ri	both
immersion time (min)	60	120	40	47	40	40	30	40	40
time between imm. (min)	-	-	-	5	-	3	-	2	-
ambient temp. (°C)	25	12-26	22	31	31	25	15-30	27	15-30
RH (%)	50	21	22	52	40	50	50	40	60
water temp. (°C)	25	15-25	5	10	5.4	4,8	8	6	5,35
core temp.	R	ER	-	R	ER	ER	RC	R	RE
finger temp.	3,8	9	6-10	1-10	1-10	1-10	3,8	1-10	1-10
hand temp. palm / back	Le/Ri	Le	Le	-	-	-	-	-	-
skin temp.	-	x	-	-	x	x	x	x	x
skin perfusion	3,8	8	-	-	8	-	-	3	3,5,8,10
finger blood flow	x	x	-	-	-	-	-	-	-
hand blood flow	x	x	-	-	-	-	-	-	-
finger heat flux	-	7,9	7	2,7,8	-	-	-	-	-
hand heat flux palm/back	x	Le	Le	-	-	-	-	-	-
foot blood flow and heat transfer	x	-	-	-	-	-	-	-	-
surface area hands	-	x	x	x	x	-	-	x	x
volume hands	-	x	x	x	x	-	-	x	x

CHAPTER	4	5	6	7	8	9	10	11	12
Keyword	heat loss	thres-hold	one hand	two hands	one hand out	body temp	skin and core	repro-duction	axon reflex
pain rating	-	-	-	-	x	x	-	x	x
temp. sensation	-	-	-	-	x	x	-	x	-
comfort sensation	-	-	-	-	x	-	-	-	-
extra radiation on back	-	-	-	x	-	x	-	-	-

premature termination of the experiments

The experiment was stopped prematurely if:

- either the subject or the experimenter requested it,
- the subject complained of intolerable pain,
- the subject was feeling sick,
- the core temperature (esophageal temperature when available) exceeded 38.5°C during exercise or 38°C during rest,
- the core temperature (esophageal temperature when available) dropped below 35.5°C during rest.

The latter two criteria were not applied in the experiment, described in chapter 12, since the purpose was to induce hypothermia and hyperthermia.

3.10 Data processing

The signals from the thermocouples, thermistors, heat flux discs, calorimeter flow meter and thermopile were scanned continuously during the experiments by a data acquisition system (Fluke 2400 B). Corrected values were calculated from the raw signals and the calibration constants. These corrected values were sent to a PC every 16 to 60 seconds by means of a RS 232 port. The data were stored on a digital computer. The data were smoothed by a moving window (time constant of 2 min 24 s), using SYSTAT software, to eliminate the signal noise. The time constant was based on repeated visual inspection of the signal.

The heat transfer from the hand to the calorimeter was smoothed twice. The right term of formula [3.2] contains a derivative, which increases experimental noise. Therefore, smoothing of this term was performed with a time constant of 4 minutes. The combined result of both terms (the total transferred power) was smoothed afterwards with a time constant of 2 min 24 s. This double smoothing technique may change the correlation with single filtered signals, due to distortion of the shape of the signal, and the time lag between the compared signals.

3.11 Statistical processing

In this thesis five calculation methods are used to evaluate the central / peripheral influence on the hunting reaction. These methods are illustrated in Fig. 3.3, with the numbers corresponding to the description given below:

1. (Cross)correlation of the hunting patterns of the immersed fingers of one hand (SYSTAT statistical package, module CORR). When all fingers have about the same hunting pattern, a common influence for the hand is likely.

2. (Cross)correlation of the hunting patterns of an immersed fingers of each hands. When the hunting patterns of the fingers of different hands are much alike (high correlation), central influence is likely.

3. Comparison of the hunting patterns of the finger tips of two hands which are not immersed simultaneously i.e. one hand is immersed first, and the other somewhat later while the first hand remains immersed. When a central component is important, the hunting patterns are supposed to get synchronized.

4. Comparison of the temperature fluctuations of the immersed fingers to the overall heat transfer as measured by a calorimeter. For this purpose the coefficient of variation (CV) is used, i.e. the standard deviation within subjects divided by the mean. When the CV of the calorimeter heat transfer is large as compared to the finger CV's, this means that the temperature fluctuations of the fingers are summed, indicating central control. If, however, the CV of the calorimeter is low as compared to finger CV's, the hunting patterns of the finger are relatively independent, indicating local control. In order to have a correct zero baseline for the comparison, the water bath temperature is subtracted from the finger temperatures.

5. Comparison of the amount of correspondence of the hunting pattern of one immersed hand with the temperature fluctuations of a non-immersed hand. When the patterns are alike, central (nervous) influence is likely.

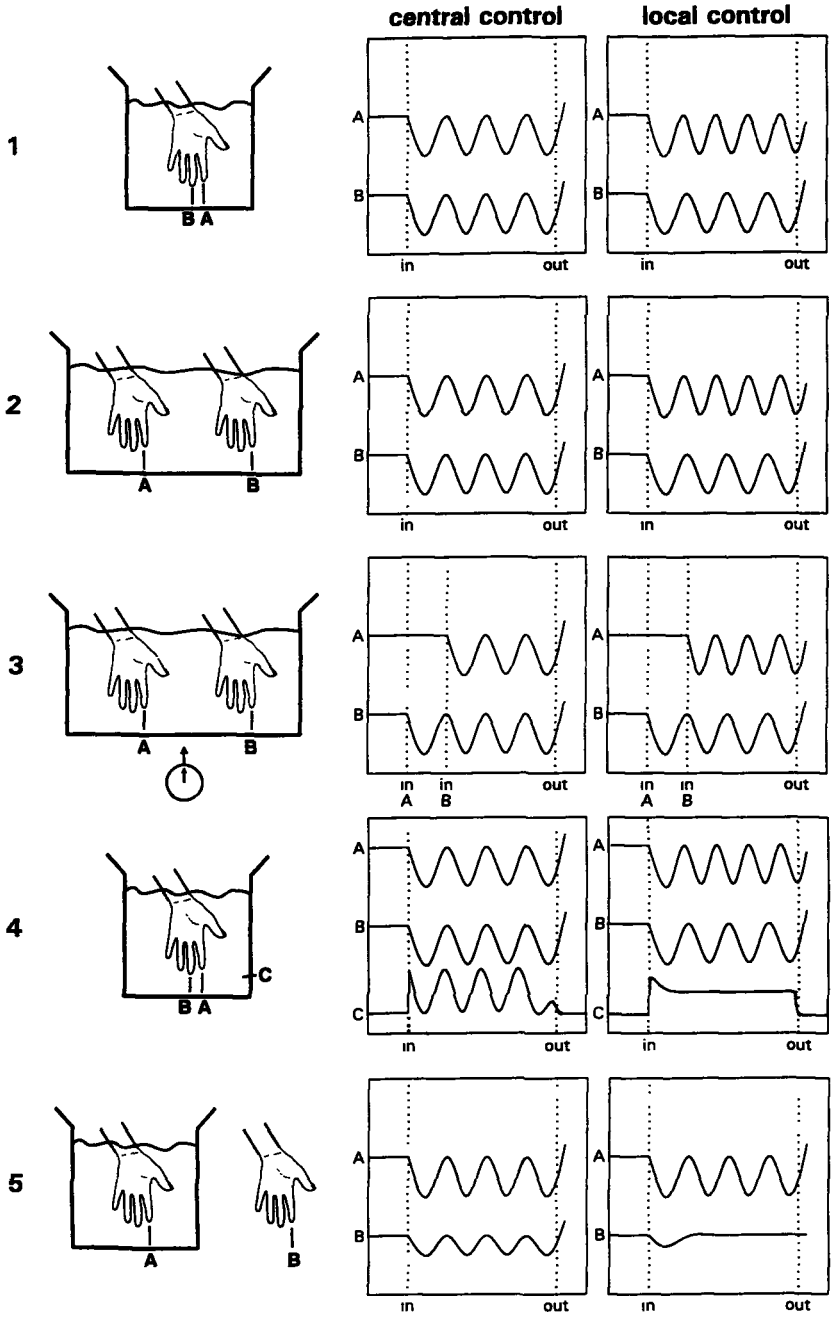

Fig. 3.3 Schematic representation of the statistical methods used in this thesis to evaluate the central and peripheral influence on the hunting reaction. C stands for the power calculated by the calorimeter. See text for a description of the five situations.

To perform the calculation correctly, the initial 10 minutes of the immersion were removed from the data set, because during this period the major part of the heat content of the hand is transferred to the water and the finger skin temperatures are not dependent on blood flow. The characteristic hunting reaction is only seen in the remaining time period. A period of about 30 minutes then remained for subsequent analysis.

Pearson correlation coefficients (PCC) were calculated for the skin temperatures of the fingers. The PCC is a sensitive estimator of the amount of correspondence. If one of the two compared temperature measurements shows a sudden increase while the other remains unchanged, a large reduction in the PCC occurs. The mean PCC was calculated by averaging all PCC's of every possible combination of finger pairs. For ten fingers 45 PCC's were averaged. Statistical testing of differences between PCC's was performed non-parametrically by Kruskal-Wallis one way analysis of variance (SYSTAT, module NPAR), because the PCC values are expected not to be normally distributed. This certainly holds when the PCC values are approaching 1.
The PCC is only a good estimator of the amount of correspondence between two signals if no time lag is present. The presence of a time lag and its influence was quantified by the cross correlation coefficient function (CCCF). If a time lag was present, the maximal cross correlation coefficient (MCCC) was used as an indicator for the amount of correspondence between the compared signals and the time at which the MCCC occurs was used as an indicator for the time lag between the compared signals. There was no systematic time lag between the temperature registrations of the fingers of one hand as investigated in the experiments described in Chpt. 6.
A disadvantage of the PCC is that outliers have a strong influence on the correlation. Therefore, attention was paid to the correctness of the signal. Moreover, all data were smoothed in an equal manner.

The coefficient of variation (CV) was calculated for skin and water temperature and heat transfer. This parameter indicates the amount of fluctuation and can be seen as an estimate for the magnitude of the hunting reaction.

In this thesis, a distinction is made between synchronization and correspondence. The amount of correspondence between two signals has to do with the similarity in shape, and is estimated by the calculation of the PCC, after verification that the time lag of the MCCC was close to zero. Synchronization is a timing parameter and denotes the similarity in time when changes occur in the signal (e.g., vasodilation) (chapter 7).

Chapter 4*

Heat loss of hands and feet in moderate cold

4.1 Introduction

Maintaining a fixed core temperature is so important for the human body that, in extreme cases, peripheral damage may occur due to a change of the circulation pattern (Raman and VanHuyse, 1975) and a low circulation. In the latter the hand and foot play a major role: the blood flow through the fingers for example may vary a 100-fold or more from full vasodilation to full vasoconstriction (Robinson, 1963). The extensive vasoconstriction induced by a exposure to a cold environment increases the risk of both non-freezing and freezing cold injuries, particularly for the hand and foot. The purpose of the present study was to investigate the physiological responses of the hand and foot to moderately cold water immersion (one hour at 25°C) in a population with no history of cold injuries. The time course and magnitude of heat transfer from hands and feet are determined and may serve as a reference for subjects with local cold injuries.

4.2 Materials and methods

subjects

Five healthy male subjects, aged 18 to 24 years, participated in the study. The subjects were asked to abstain from smoking and using any medication, drug or other stimulant (including caffeine and alcohol) for at least 12 hours before the experiments.

The anthropometry of the subjects is presented in Table 4.1.

* The study described in this chapter has been published in Arctic Medical Research 50 (Suppl. 6): 115 - 121, 1991 and as TNO report IZF 1991 A-15.

Table 4.1 Age, mass, stature and body surface area of the investigated subjects.

subject	age	mass	stature	body surface area
	years	kg	cm	m^2
1	18	67.9	170	1.79
2	20	55.9	177	1.69
3	24	74.5	180	1.94
4	22	75.4	181	1.95
5	19	58.0	173	1.69
Mean	20.6	66.3	176.2	1.81
SD	2.4	9.1	4.7	0.13

methods

The blood flow in the hand, middle finger, foot and middle toe were measured by the Whitney gauge technique (par. 3.1) and skin perfusion by a laser Doppler probe at the ventral side of the distal phalanx of the middle finger and toe (par. 3.2).

Three fine type T thermocouples were used to measure hand or foot skin temperatures (par. 3.3.1). Two thermocouples were positioned within a few mm from two heat flux transducers (HFT) (par. 3.4). A third thermocouple was placed on the ventral / plantar side of the third medial phalange on the hand or the foot.

The rectal temperature of the subjects was measured by a thermolinear probe (YSI 701) inserted 120 mm beyond the rectal sphincter (par. 3.3.3). The average rectal temperature before, during and after immersion was registered in order to investigate if the immersion influenced the rectal temperature.

The heat transfer was determined by calorimetry as described in par. 3.5. In initial experiments, the water flow through the calorimeter dropped to half of the intended flow due to technical problems with the flow meter. The flow was recorded continuously, so that this could be accounted for in the calculation of the total heat transfer of the extremities to the water. The water temperature was kept constant at 25.36°C ± 0.16°C.

All experiments were performed in a climatic chamber at 25°C and 50% relative humidity.

procedure

The subjects reported to the laboratory in the morning on four days within a three-week period. After the fixation of the temperature and heat flux sensors on either the hand or foot, the subject,

lightly dressed (T-shirt and casual trousers), rested under thermoneutral conditions (air temperature of 25°C, relative humidity of 50%) for 1 hour. During the last 30 minutes of that period, heat loss measured by heat flux transducers, skin and rectal temperature, and skin blood flow by the laser Doppler method were recorded continuously. At the end of the resting period, the first series of blood flow measurements using the plethysmograph method was performed. Then, the subject immersed his hand or foot for 1 hour in the well-stirred water calorimeter maintained at 25°C. During the immersion, the heat loss measured by the heat flux transducers and the calorimeter and the skin and rectal temperatures were continuously monitored. At the end of the 1-hour immersion, the subject removed his hand or foot from the calorimeter and a second series of blood flow measurements using the plethysmograph was performed, followed 30 minutes later by a third series of measurements. During the 30 minutes of recovery following the immersion, heat loss measured by heat flux transducers, skin and rectal temperatures, and skin blood flows of the hand and middle finger or the foot and middle toe using the laser Doppler were recorded continuously.
In the morning session, the subject's hand was immersed, followed by the immersion of the foot during the afternoon session. The left as well as the right hand or foot were investigated on separate days. Moreover, the experiments were performed twice to test the reproducibility of the results. This set-up led to a total of eight experiments (hand/foot, left/right, duplication (two sets)) for each subject, and a total of 40 experiments.

statistics
Differences in rectal temperature and heat flux before and after immersion were tested with a t-test for paired comparisons and so were differences in temperature and blood flow between the hand and the foot before immersion. Further statistical analysis was performed with an analysis of variance (SYSTAT package) with one constant and subjects, hand/foot, left/right and replication as fixed factors. Results are presented ± SD and were considered significant if $p < 0.05$.

4.3 Results

Every measured parameter was synchronised on the moment of immersion. The average heat flux and transferred power for all subjects and experiments is shown in Fig. 4.1. The heat flux from the ventral side exceeds the heat flux from the dorsal side. On the average slightly more power was transferred from the hands than from the feet.

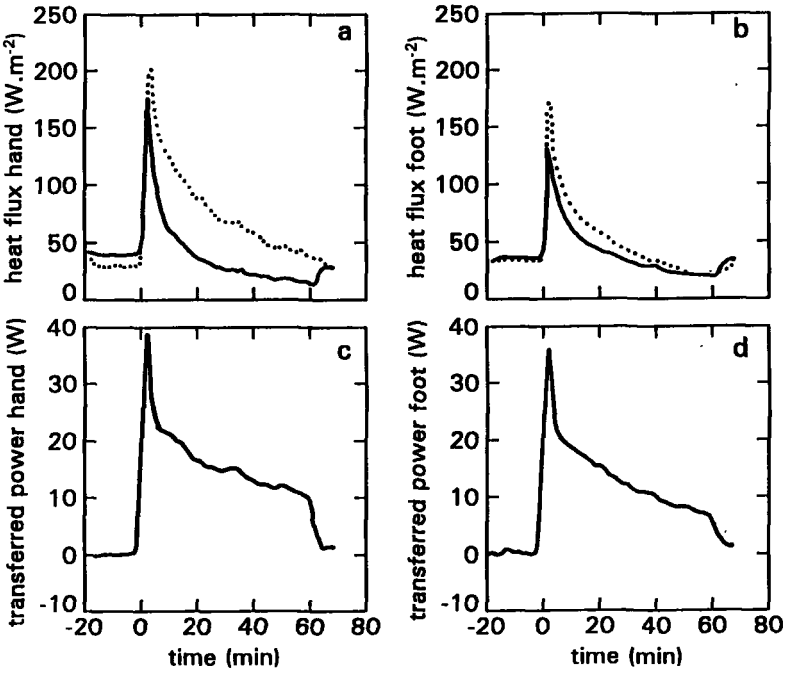

Fig. 4.1 Averaged heat flux from the hand (a) and foot (b) measured by heat flux transducers (HFT's) and averaged transferred power of the hand (c) and foot (d) to the water measured by calorimeter. In a and b dotted lines represent heat flux from the ventral side, while solid lines represent heat flux from the dorsal side. Zero time is the moment of immersion. At minute 60 the hand or foot was removed from the calorimeter bath.

Before immersion the average rectal temperature was 36.75 (± 0.20) °C. About 30 minutes after immersion rectal temperature had decreased to 36.69 (± 0.21) °C. At the beginning of the recovery rectal temperature was 36.64 (± 0.23) °C. These decreases in rectal temperature were small but significant.

The heat flux and local skin temperature for all subjects is shown in Table 4.2 before, during and after immersion, averaged over hands/feet, left/right and the two repeated immersions.

Table 4.2 Average heat flux ($W \cdot m^{-2}$), and local skin temperature (°C) at ten minutes before immersion, at the beginning of the immersion period (minute 0 to 10), at the end of the immersion period (minute 45 to 55) and in the recovery phase (minute 70 to 80) of a 1 hour immersion in water of 25°C (n=40). All averages are indicated with SD.

	before immersion		start of immersion		end of immersion		during recovery	
	mean	SD	mean	SD	mean	SD	mean	SD
HF ventral ($W \cdot m^{-2}$)	32	17	126	57	34	35	27	21
HF dorsal ($W \cdot m^{-2}$)	37	17	94	32	19	15	26	21
T finger or toe (°C)	31.7	3.2	26.6	1.8	25.3	0.3	25.3	2.2
T ventral (°C)	32.1	2.3	26.7	1.0	25.1	0.7	26.0	1.9
T dorsal (°C)	31.7	2.3	26.8	0.8	25.0	0.4	25.2	1.5

The ventral and dorsal heat flux during the first ten minutes of immersion increased as compared to values before immersion. In the recovery phase the heat flux is lower than before immersion (paired t-test, $p < 0.05$). This is in agreement with the reduced skin temperature in the recovery phase. Shortly after removal of the hand from the calorimeter bath a decrease in skin temperature is seen due to evaporation of the water from the skin.

During the last part of the immersion (minute 45 to 55) the fluctuations in skin temperature (SEM: 0.02°C), heat flux (standard error of the mean (SEM): 1.3 $W \cdot m^{-2}$ for ventral and 0.7 $W \cdot m^{-2}$ for dorsal side) and heat transfer (SEM: 0.5 W) were rather low for the hands and feet. The average heat transfer of the hand to the water in this period was only 8.5 W (SD between subjects was 4.7 W).

In Table 4.3 the results related to blood flow are shown.

Table 4.3 Average blood flow (with SD between parenthesis) before immersion, and at the begin and end of the recovery phase (n=20 for the hand and n=20 for the foot). Laser Doppler blood flow is indicated in arbitrary units (a.u.) and blood flow determined by plethysmography in $ml \cdot min^{-1} \cdot 100$ ml $tissue^{-1}$.

	before immersion	begin of recovery	end of recovery
Doppler finger blood flow (a.u.)	10.8 (5.1)	4.1 (2.6)	6.5 (3.9)
pleth. finger blood flow ($ml \cdot min^{-1} \cdot 100$ ml $tissue^{-1}$)	5.1 (4.4)	0.9 (0.6)	1.7 (1.7)
pleth. hand blood flow ($ml \cdot min^{-1} \cdot 100$ ml $tissue^{-1}$)	5.8 (5.2)	1.2 (1.2)	2.1 (2.2)
Doppler toe blood flow (a.u.)	6.7 (5.3)	1.9 (0.7)	3.8 (4.4)
pleth. toe blood flow ($ml \cdot min^{-1} \cdot 100$ ml $tissue^{-1}$)	0.5 (0.5)	0.2 (0.1)	0.3 (0.2)
pleth. foot blood flow ($ml \cdot min^{-1} \cdot 100$ ml $tissue^{-1}$)	0.7 (0.3)	0.4 (0.2)	0.5 (0.4)

In general, blood flow was lower at the begin of recovery than before immersion. During the recovery phase the blood flow increased, but was still lower than before immersion. Blood flow was much higher in the hand and finger than in the foot and toe (paired t-test $p < 0.05$). In the hands the plethysmographic blood flow decreased more than Doppler blood flow. In the foot the reverse was the case.

Maximal heat flux during the water immersion was higher from the ventral side of the hand (225 $W \cdot m^{-2}$) than from the ventral side of the foot (178 $W \cdot m^{-2}$) (Table 4.4). There was no difference in maximal heat flux between the dorsal sides of the hand (186 $W \cdot m^{-2}$) and the foot (160 $W \cdot m^{-2}$). The maximal heat flux tended to be higher from the ventral side of the foot and hand than the dorsal side (difference for the hand: 39 $W \cdot m^{-2}$ ($p = 0.06$), foot: 18 $W \cdot m^{-2}$ ($p < 0.01$)).
There were no significant differences in maximal power transfer between the hand and the foot (Table 4.4).

Table 4.4 Differences between hand and foot for heat flux ($W \cdot m^{-2}$), the maximal transferred power (W), the total amount of heat transferred (kJ), the average power transfer of minute 45 to 55 of the 1 hour immersion period (W) and the average fall in local skin temperature (hand and finger, foot and toe) due to immersion (°C). Differences are tested with analysis of variance. SD is indicated between parentheses..
Significance level: $^{*}= p<0.05$, $^{**}= p<0.01$.

	hand	foot
max. HF ventral ($W \cdot m^{-2}$)	225 (93)	178 (53)*
max. HF dorsal ($W \cdot m^{-2}$)	186 (61)	160 (57)
max. transferred power (W)	37 (14)	34 (15)
total heat transferred (kJ)	47 (21)	36 (18)
power transfer end immersion (W)	8.5 (4.7)	5.8 (3.2)**
local temp. decrease (°C)	7.9 (2.1)	5.5 (2.1)**

The maximal power transferred to the water is shown for each investigated subject in Fig. 4.2, both for the hand and the foot.

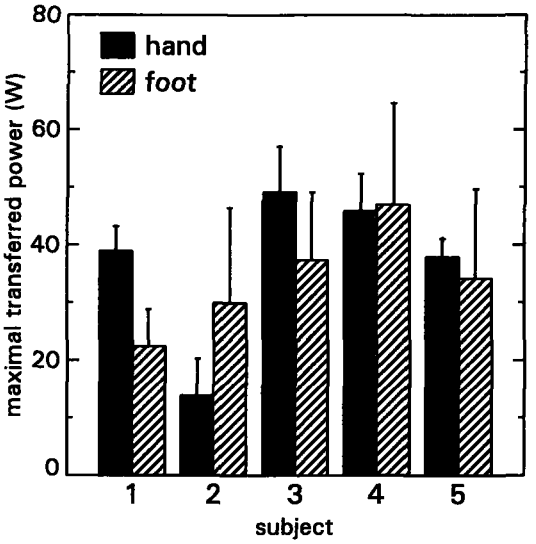

Fig. 4.2 Maximal power (W) transferred to the water by a hand or a foot during 60 minutes of immersion for each subject in the study (standard deviation is shown by vertical bars).

Before immersion in the water, the hand was on the average 2.4°C warmer than the foot (Table 4.5). The dorsal side of the hand was cooler (32.5°C) than the fingers (33.0°C) or the ventral side (33.6°C). The foot was almost uniform in temperature.

Table 4.5 Average temperature of the hand and foot (°C) before immersion in the water. Differences between the hand and the foot were tested with a paired t-test (n=40). Significance level: $^{*}= p<0.05$, $^{**}= p<0.01$.

		hand	foot
dorsal side	(°C)	32.5 (2.0)	30.8 (2.1)*
ventral side	(°C)	33.6 (2.1)	30.5 (1.2)**
finger or toe	(°C)	33.0 (2.6)	30.4 (3.3)**
average temperature	(°C)	33.0 (2.2)	30.6 (2.1)**

Of all the dependent variables, only the maximal heat flux on the ventral side of the hand showed a difference between the right and the left hand (226 versus 177 $W \cdot m^{-2}$). The cause for this difference is unknown.

Analysis of variance revealed differences between subjects for all investigated variables (heat flux, transferred power and heat, rectal- and local skin temperature, Doppler and plethysmographic blood flow).

4.4 Discussion

subject variability
The temperature of the extremities prior to the immersion is dependent on the temperature of the environment, the subject's metabolism prior to the experiment and the peripheral blood flow of the subject. This may explain the high significance of the 'subject'-term in the statistical model, despite the one hour resting period before immersion in the water.

skin temperature
In some experiments the skin temperature dropped slightly below the water temperature. It was shown afterwards that this was due to crosstalk between skin sensors when immersed in chlorided water. Due to the balanced design of the study, this error did not differ between subjects and hand and foot. It thus produced a random error in skin temperature of about 0.5°C, which obscures details. In all other experiments in this thesis, the ends of the thermocouples were sealed with PVC (par. 3.3.1).

heat transfer
In our experiment with water at 25°C the maximal heat loss was about 37 W for the hand and 34 W for the foot. Newman and Breckenridge (1968) estimated the heat loss of a hand in water at 5°C. They used a calorimeter without continuous water circulation and found a maximal heat loss of 40.5 W. Greenfield et al. (1951c) found a maximal heat loss of 55.8 W in water of about 1°C for the hand and 28.3 W for the fore-foot (1951b). It can be concluded that even in water as high as 25°C a considerable amount of heat transfer is present.
Raman and Vanhuyse (1975) measured the rate of heat transfer during steady state immersion of a hand in water at 25°C. They found that the rate of heat transfer was $25 \cdot 10^3$ W per m^3 tissue. Assuming an immersed volume of about $300 \cdot 10^{-6}$ m^3 this means that 7.5 W is being transferred. From occlusion experiments they determined the contribution of blood flow. This accounted for about 6.5 W. The metabolism of the hand was estimated at 0.25 W, so that conduction from the lower arm to the hand accounted for about 0.75 W. In their experiments they defined the start of the steady state period at 45 minutes of immersion. In our experiments the average power transfer from the 45th to the 55th minute was 8.5 W which is close to the 7.5 W of Raman and Vanhuyse (1975)

(Table 4.4). However, no steady state was found in this study after 55 minutes. There still was a small decrease in heat transfer in time.

blood flow

Before immersion, the hand (33.0 ± 2.2°C) was warmer than the foot (30.6 ± 2.1°C) and the blood flow was also higher: respectively 5.8 ± 5.2 versus 0.7 ± 0.3 ml·min^{-1}·100 ml tissue^{-1} as determined by strain gauge plethysmography and 10.8 ± 5.1 versus 6.7 ± 5.3 by the Doppler method. In contrast with this, Allwood and Burry (1954) found that the blood flow at equal ambient temperature was higher in the feet than in the hands; at 32°C ambient temperature, the blood flow in the hand was about 3 ml·min^{-1}·100 ml tissue^{-1} and about 9 ml·min^{-1}·100 ml tissue^{-1} in the foot. Thus, in our experiment, performed at a water temperature of about 25°C, the feet were relatively more vaso-constricted than the hands.

Nagasaka et al. (1987) stated that the penetration depth of the Doppler method is so small that blood flow in the arteriovenous anastomoses (AVA) can hardly be detected. Although this is disputed (see par. 3.2), the fact remains that the plethysmographic method measures the blood flow through the entire hand or foot, including the muscles and the skin with the AVA, while the Doppler method only partially measures AVA blood flow. Therefore, the ratio of the decrease in blood flow determined with the plethysmographic method and the Doppler method may give an indication about the ratio of blood flow decrease through the AVA's and other micro vessels. After withdrawal of the hand, plethysmographic blood flow had decreased by a factor 5.2. The Doppler blood flow only decreased by a factor 2.6. This might mean that AVA blood flow is relatively more reduced by immersion than blood flow in the other micro vessels. In the foot, which was colder at the moment of immersion, the plethysmographic blood flow decreased with a factor 2.1 and Doppler with a factor 3.5. Here possibly AVA blood flow was less reduced than in the hand.

It has to be noted that the plethysmographic changes can be attributed mainly to the circulation of the skin. The hand and foot contain a relatively low percentage of muscles compared to the rest of the human body.

comparison between local and total heat transfer

The average power transfer of the hand determined by the calorimeter 20 to 30 minutes after immersion was 17.4 W. In the same time interval the average heat flux determined by heat flux transducers on the ventral and dorsal side of the hand was 110 W·m^{-2}. If we assume an immersed surface area of about 0.04 m^2 a power of 4.4 W is transferred. The difference between both methods can be (partly) explained by the inhomogeneity of the heat transfer at different sites of the hand. The heat flux in the finger tip can be five times as high as that of the whole hand (Greenfield et al., 1951c).

4.5 Summary

To determine the time course and magnitude of heat loss of the hand and foot in a moderately cold environment, five healthy males immersed their hands and feet twice in a 25°C water calorimeter bath. Prior to the immersion, the foot was relatively vasoconstricted as compared to the hand.
Immersion of hands or feet leads to an initial increase in heat transfer, during which the heat of the extremity is removed. The peak power transfer is 37 W for the hand and 34 W for the foot. After a few minutes the power transfer decreases, probably due to vasoconstriction in the skin. During the 60 minute immersion more heat is transferred to the water from the hand (47 ± 20 kJ) than from the foot (36 ± 18 kJ). Heat flux is higher from the ventral than from the dorsal side of the extremities. Local skin temperature drops to values close to the water temperature and blood flow is strongly reduced at the end of immersion, especially in the foot. In the hand, the reduction in plethysmographic blood flow exceeds the reduction in Doppler blood flow. It is discussed that this disproportional decrease might form an indicator of the involvement of arteriovenous anastomoses.

Chapter 5*

Stability of the esophageal temperature threshold that determines cutaneous vasodilation

5.1 Introduction

It is a common observation that cold hands are inevitable when the human body core is cold, and that a high body core temperature (T_c) is accompanied by warm hands. For every subject there seems to be a rather fixed threshold in T_c above which the blood flow through the hands suddenly increases (Wenger et al., 1975). This sudden increase in blood flow is probably caused by the opening of arteriovenous anastomoses (AVA) due to a decreased sympathetic tone.
This threshold is altered by the average (body) skin temperature ($\bar{T}_{sk}$). When $\bar{T}_{sk}$ is increased, this threshold decreases, in other words the hand becomes warm at a lower T_c when $\bar{T}_{sk}$ is high. In 1975 Wenger et al. quantified the relative contribution of T_c and $\bar{T}_{sk}$ to hand blood flow and found that T_c was 5.9 to 9.4 times more important than $\bar{T}_{sk}$. Wyss et al. (1974, 1975) found comparable values. The absolute values of the thresholds were determined by strain-gauge plethysmography, which yields unreliable results at low blood flows. Also, the temperature of the skin of the hand was kept constant in their investigations, making it impossible to assess the influence of hand skin temperature ($\bar{T}_h$) upon hand blood flow.
Cooper et al. (1949) investigated the relation between blood flow of the hand and hand skin temperature. They found a sharp increase in blood flow when $\bar{T}_h$ was higher than 30°C. This increase was similar for the foot (Allwood and Burry, 1954) and the forearm (Barcroft and Edholm, 1943). However, in their studies T_c and $\bar{T}_{sk}$ was not varied.

In this study the finger blood flow is investigated in relation to T_c, $\bar{T}_{sk}$, and $\bar{T}_h$. The threshold in T_c above which cutaneous vasodilatation occurs is not determined by plethysmographic measurements, but by heat flux measurements of the finger tip. The relative contribution of the averaged temperature to the regulation of hand blood flow is of importance for the development of thermoregulation models of blood flow through the human extremities (see par. 2.5.6).

* This study has been published as TNO report IZF 1991 B-17 and in the proceedings of the fifth int. conf. on Environmental Ergonomics, Maastricht, 1992 (pages 222 - 223).

5.2 Materials and methods

subjects

Four males and two females participated in the study. Their relevant anthropometric data are presented in Table 5.1. The subjects were fully informed of the purpose of the study and of their right to withdraw from experimentation at any time without prejudice. They all gave their written consent.

Table 5.1 Anthropometric characteristics of the participating subjects, with their mean and standard deviation for each variable.

subject	sex	age	weight	stature	body surface area	palmar surface area	hand volume
		years	kg	cm	m^2	cm^2	cm^3
1	F	28	75	180	1.94	154	260
2	F	28	64	167	1.72	147	290
3	M	23	92	194	2.24	187	500
4	M	24	75	180	1.94	179	430
5	M	22	62	178	1.78	157	380
6	M	19	74	185	1.97	179	440
Mean		24.0	73.7	180.7	1.93	167.2	380
SD		3.2	9.7	8.1	0.17	15.0	80

methods

All measurement sites are shown in Fig. 5.1.

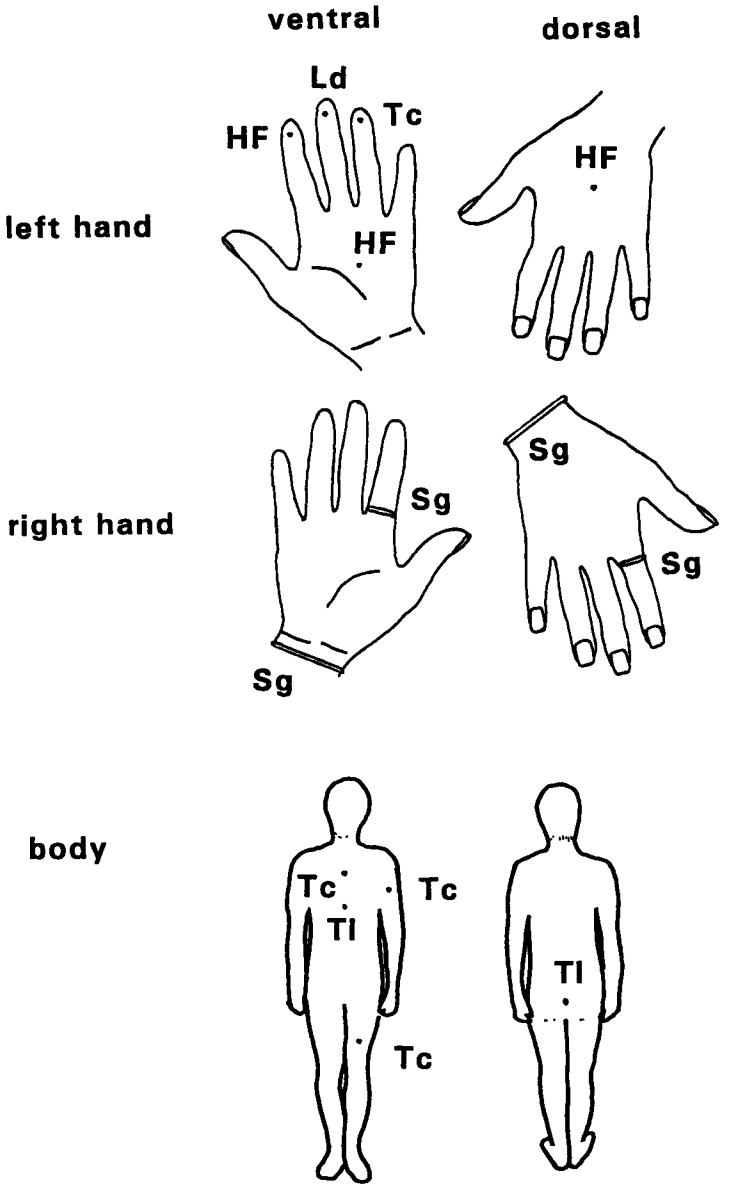

Fig. 5.1 Location of the measurement sites. Tc = Thermocouple, Tl= Thermolineair probe, HF = heat flux sensor with integrated thermocouple, Sg = Strain gauges, Ld = Laser Doppler.

The skin perfusion of the left middle finger was measured by laser Doppler flowmetry (par. 3.2). The blood flow of the right hand and index finger was measured by the Whitney gauge technique (par. 3.1). The pressure cuff was placed on the right upper arm, and inflated to a pressure of 80 mm Hg for 5-10 s.

The mean (body) skin temperature ($\bar{T}_{sk}$) was assessed by thermocouples on the upper arm, chest and thigh (par. 3.3.2). The hand skin temperatures and heat flux (HF) were measured at the index finger, the palm and the back of the left hand (par. 3.3.1 and par. 3.4 respectively). An extra thermocouple was located at the ventral side of the distal phalanx of the ring finger. The mean hand skin temperature ($\bar{T}_h$) was calculated as the average of the index and ring finger skin temperatures and the ventral and dorsal hand skin temperatures.

The subjects were instrumented with thermistors to assess the core temperature. The rectal temperature of the subjects was measured by a thermolinear probe (YSI 701) inserted 120 mm beyond the rectal sphincter. The esophageal probe was inserted through the nasal passage to a point 41.5 cm beyond the external nares.

The heat transfer was determined by calorimetry as described in par. 3.5.

procedure

Subjects reported to the laboratory in the morning of two consecutive days. The experiments were carried out in a climatic chamber. The ambient temperature (T_a) was set at 12, 19 or 26°C. The relative humidity varied from 14 to 36% (mean 20.8 ± 6.4%).

During the experiment each subject was lightly dressed (T-shirt and shorts) and seated on a special chair, which enabled bicycle exercise (Fig. 5.2).

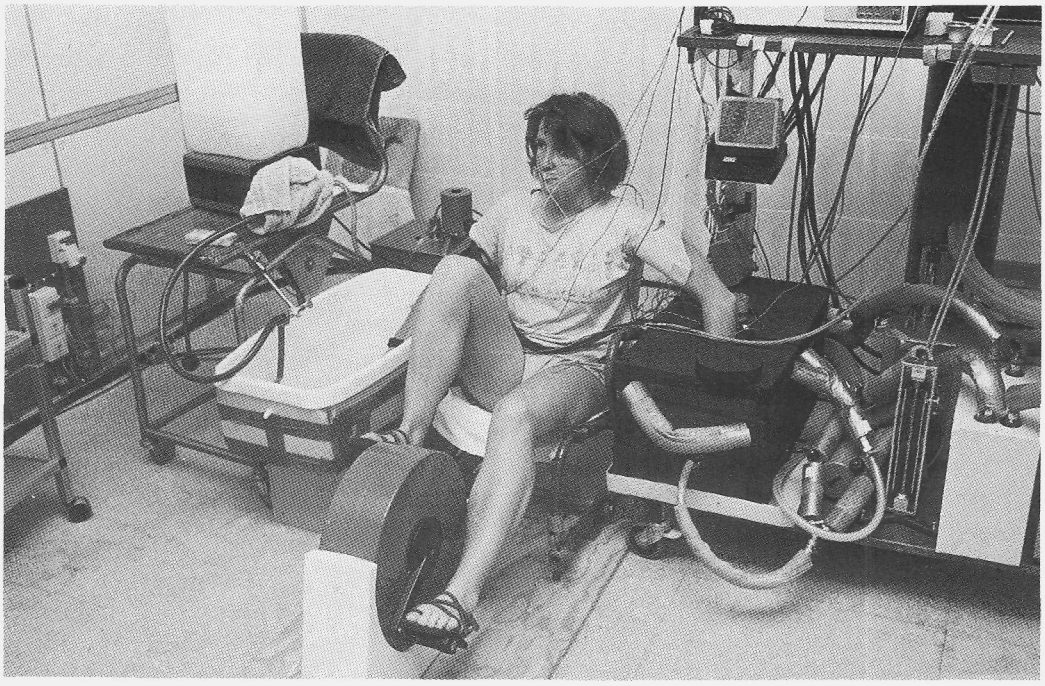

Fig. 5.2 Overview of the measurement set-up.

The hands of the subjects were immersed in water of 15, 20 or 25°C. The left hand was immersed in a calorimeter, the right hand in a water bath with the same temperature. As soon as the heat transfer from the index finger to the water had decreased to zero, the subjects started cycling on an ergometer (Lode Angio) with an external power of 80 W. This power was chosen since in pilot sessions it appeared to be heavy enough to increase the core temperature, and was tolerable for all subjects. About two minutes after the occurrence of a sharp increase of the heat flux from the index finger, the exercise was stopped. The two minute delay was used to be sure that the heat flux continued to increase. Exercise was restarted when the HF from the index finger had decreased to zero. Thus, the subject exercised on command of the experimenter. The maximal immersion time never exceeded two hours.

Every subject was submitted to four experimental conditions (two different ambient and two different water temperatures in the calorimeter) according to Table 5.2. In this design four of the nine possible cells (three water temperatures times three ambient temperatures) are filled for one subject. This is accounted for in the ANOVA process. The total number of experiments thus was 6 (subjects) x 4 (experimental conditions) = 24.

Table 5.2 Experimental setup (F=female, M=male).

time of day (hours)		9.00 - 11.00		11.30 - 13.30	
subject	day	ambient temp. (°C)	water bath temp. (°C)	ambient temp. (°C)	water bath temp.(°C)
1 (F)	1	19	20	19	25
	2	26	20	26	25
2 (F)	1	26	25	26	20
	2	19	25	19	20
3 (M)	1	12	15	12	25
	2	19	15	19	25
4 (M)	1	19	25	19	15
	2	12	25	12	15
5 (M)	1	12	15	12	20
	2	26	15	26	20
6 (M)	1	26	20	26	15
	2	12	20	12	15

data processing

The temperature of the water and the environment, the thermopile signal, the heat flux and the temperature of the skin were scanned continuously during the experiments by a data acquisition system (Fluke 2400 B). The values were sent to a PC every 16 seconds by means of a RS 232 port. Simultaneously, the laser Doppler blood flow, ergometer power and pedalling rate of the ergometer, rectal and esophageal temperature and flow of the water through the calorimeter were digitized by a data-acquisition board (DT2821, Data Translation) every 16 seconds.
The data were presented real-time on a monitor to the subjects and the experimenter.

statistics

A simple computer program was written in order to detect the threshold in esophageal temperature in an objective manner. The algorithm first determined the maximal finger HF of the entire experiment. This maximum was set to 100%. Hereafter, the routine determined the moments at which the finger HF increased above the 1% level in the entire registration of the finger HF. The esophageal temperatures at these moments were named $T_{es\text{-}i}$ in which i denotes the increased finger heat flux. When the finger HF decreased again below the 1% level, the esophageal temperature was

determined again and called T_{es-d} in which d denotes the decreased finger heat flux. The same procedure was also followed for rectal temperatures, yielding T_{re-i} and T_{re-d}, respectively.
In previous testing, the increase in finger HF was marked by a sharp deflection point, which was more reproducible than finger skin temperatures or skin perfusion.
The number of exercise periods a subject could finish within the two hour immersion time limit, varied from 1 to 4. All together 56 exercise periods were measured. T_{es-i}, T_{es-d}, T_{re-i} and T_{re-d} were averaged over the entire experiment. Thus, a total of 24 (6 subjects times 4 experiments) thresholds in T_{es} and T_{re} were calculated, each for increasing and decreasing heat flux of the index finger.
The hypothesis that this 'threshold'-temperature is dependent on $\bar{T}_{sk}$ and $\bar{T}_{h}$ was tested with analysis of variance (SYSTAT, module MGLH). The dependent variables were T_{es-i}, T_{re-i}, T_{es-d} and T_{re-d}. The independent variables were: the three water bath temperatures (T_w) and ambient temperatures (T_a) and their interaction, subjects, day of investigation (first or second appearance) and time of day (early or late morning). Thus, $\bar{T}_{sk}$ is supposed to be varied by T_a and T_h by T_w.
Results are presented as means ± SD and were considered significant if $p < 0.05$. Significant results were elaborated with a post-hoc analysis (SYSTAT, module CONTRAST). For the post-hoc analysis the results were considered significant if $p < 0.01$.

5.3 Results

changes in thermal status of the hand due to exercise
In Fig. 5.3 a typical example is shown of the changes in thermal status of the hand due to exercise.

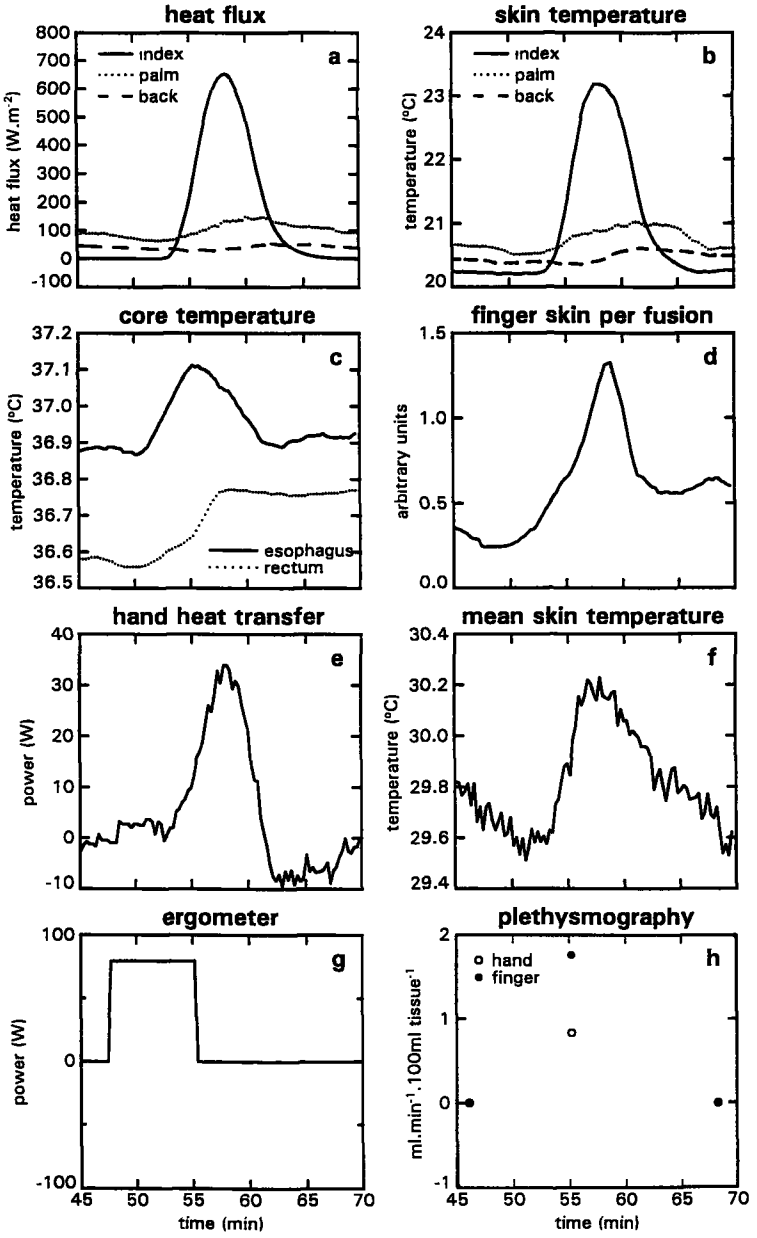

Fig. 5.3 Changes due to exercise in heat flux (window a) and temperature (b) of the index finger, palm and back of the hand, core temperature (c), laser Doppler skin-blood flow (d), transferred power by the entire hand (e), mean body skin temperature (f), exercise (g) and blood flow determined by strain-gauge plethysmography (h). Ambient temperature was 19°C, water bath temperature was 20°C, subject number was 2.

Immediately after the start of the exercise (window g), the temperature of the esophagus drops due to cold peripheral blood coming towards the heart (window c). This initial decrease in temperature is only present the first time the exercise is started. Thereafter, the temperature increases almost linearly with time due to the heat produced by the working muscles and transported by the circulating blood.

The heat flux and temperature of the fingers show a sharp increase several minutes after the exercise has started. The temperature and heat flux of the volar side of the hand increase too, but less abruptly. The temperature and heat flux of the dorsal side of the hand was almost unaffected by exercise (window a and b of Fig. 5.3).

The skin perfusion, as measured by laser Doppler flowmetry, increases exponentially during exercise, indicating an increased blood flow through the skin of the middle finger (window d). After ceasing exercise, skin perfusion and heat flux of the fingers drop simultaneously. Similarly, the blood flow in the finger and hand, as determined by plethysmography (window h), was found to be elevated when measured right after the exercise period.

The mean (body) skin temperature decreases as soon as the exercise is started, due to cooling of the upper leg caused by the movement of cycling (window f). After several minutes of exercise an increase in $\bar{T}_{sk}$ is found, mainly caused by a raised temperature of the chest and upper arm. This moment often coincides with the start of sweating and precedes the increase in heat flux of the index finger.

The heat transfer of the hand to the water, as measured by calorimetry (window e), showed similarity to the HF of the index finger, illustrating the importance of the fingers for the heat transfer of the hand.

threshold core temperature

In Fig. 5.4 the relation between heat flux of the finger and esophageal temperature is shown for an entire session of one subject.

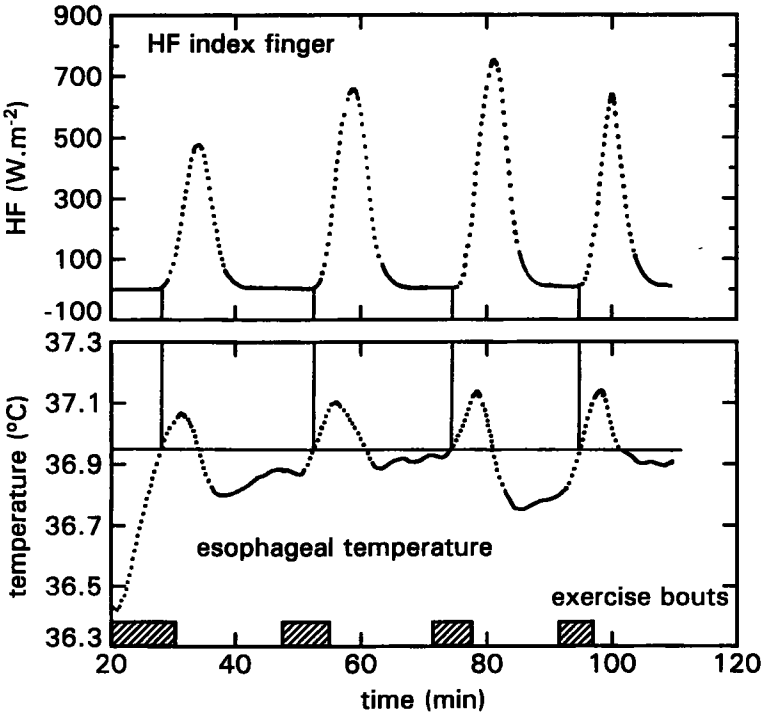

Figure 5.4 Typical registration of heat flux of the finger tips ($W.m^{-2}$) (upper window) and esophageal temperature (°C) (lower window) for an entire session. The computed four esophageal thresholds are almost identical and indicated by the horizontal lines in the lower window.

In the experiment shown in Fig. 5.4 four exercise periods were present. In 12 of the 24 experiments more than two exercise periods were present. For these experiments the mean standard deviation in $T_{es\text{-}i}$ was only 0.07°C, indicating a good reproducibility. This suggests that the threshold value is rather constant during a single experiment.

The $T_{es\text{-}i}$, averaged over all subjects and experimental conditions, was 37.06 ± 0.29°C. The average $T_{es\text{-}d}$ (37.00 ± 0.29°C) was significantly lower (paired t-test). The corresponding thresholds for rectal temperature were 37.16 ± 0.30 and 37.25 ± 0.28°C respectively. The latter threshold was significantly higher (paired t-test). This might be due to the time lag in rectal response to exercise.

threshold dependence on water bath and ambient temperature

The variance in the threshold is larger between experiments (SD is 0.29°C for T_{es-i}) than within experiments (SD is 0.07 in T_{es-i} for 12 experiments). This may be attributed to the different water bath temperatures of 5 and 10°C and the different ambient temperatures of 12, 19 and 26°C, but also to differences between subjects or days. Analysis of variance was used to analyse which factors affected the threshold in esophageal and rectal temperature (Table 5.3).

Table 5.3 Significance levels, as indicated by p-values, for four factors which may influence the threshold in esophageal (T_{es}) or rectal temperature (T_{re}) as determined by analysis of variance. $_i$ Denotes moment of increase of left index finger heat flux and $_d$ denotes decrease. df = degrees of freedom. T_w = water bath temperature. T_a = ambient temperature.

	df	T_{es-i}	T_{re-i}	T_{es-d}	T_{re-d}
subject	5	<0.01	0.02	<0.01	0.01
T_a	2	0.01	0.07	0.01	0.16
T_w	2	0.02	<0.01	0.61	0.01
day	1	0.05	0.09	<0.01	0.07

Time of day and the interaction between T_a and T_w were never significant.

Both thresholds in esophageal temperature differ between subjects, days and ambient temperatures, while T_{es-i} also differs between water temperatures. However, the magnitude of the effect of T_w on T_{es-i} is rather small. An increase of 1°C in water bath temperature is related to a decrease in T_{es-i} of less than 0.01°C. The threshold T_{es-d} was slightly higher on the first day than on the second day. Both thresholds in rectal temperature differ between subjects and water temperatures.

In Fig. 5.5 the thresholds are shown for every subject. The differences are mainly caused by subject 1, who has a relatively high esophageal threshold and subject 2, who has a relatively low rectal threshold.

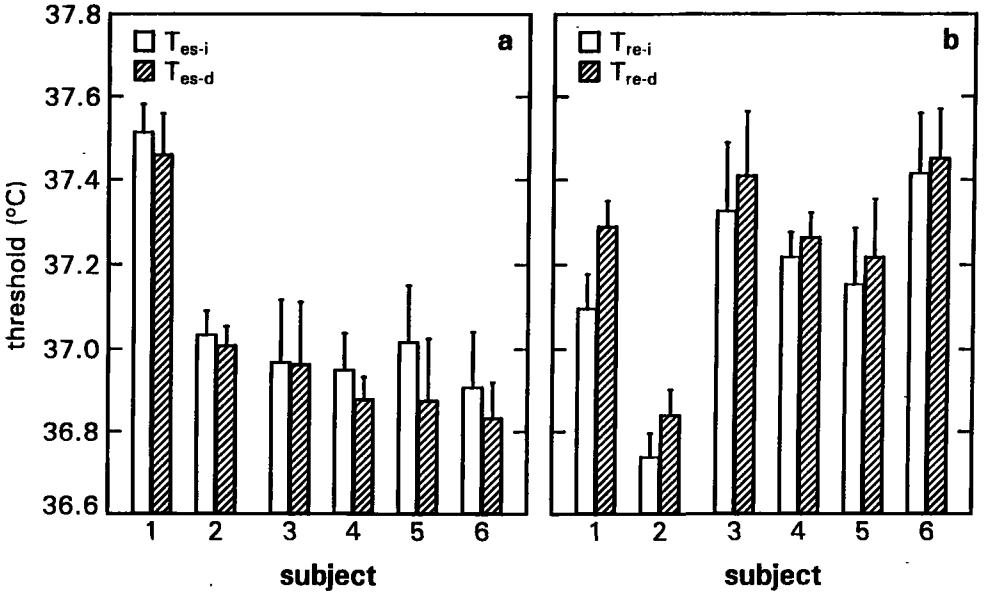

Fig. 5.5 Thresholds in esophageal (T_{es} - window a) and rectal temperature (T_{re} - window b) shown for every subject. The thresholds are determined at the moment that the heat flux of the left index finger shows an increase (i) or decrease (d). Error bars indicate the standard deviation.

In Fig. 5.6 T_{es-i} and T_{es-d}, averaged over all subjects, are shown for different ambient temperatures. T_{es-i} and T_{es-d} were higher at an ambient temperature of 12°C than at 19 or 26°C. There was no significant difference in T_{es} between 19 and 26°C.

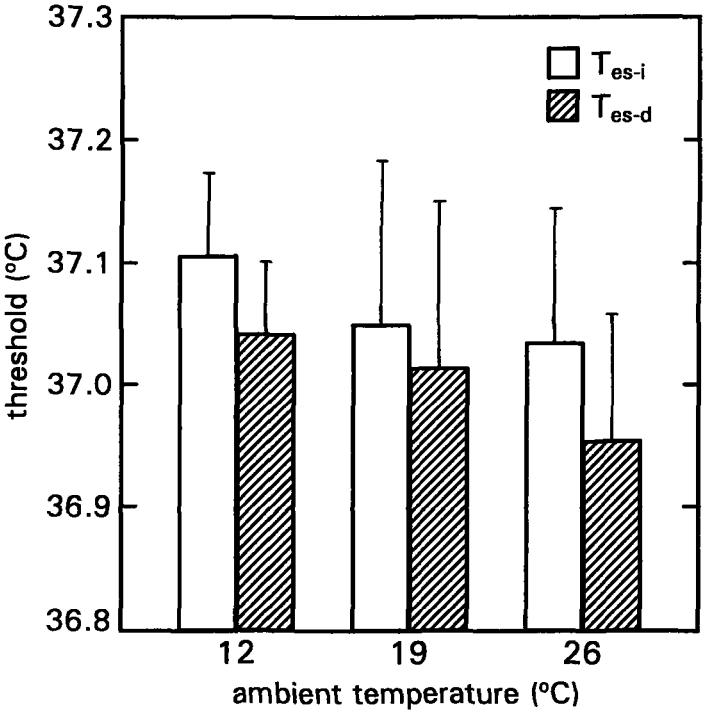

Fig. 5.6 Mean thresholds in esophageal temperature (T_{es}) for different ambient temperatures. The thresholds are determined by the increase and decrease in heat flux of the left index finger. Error bars indicate the standard deviation.

Since T_{re} does not differ between ambient temperatures but only between water temperatures, Fig. 5.7 shows the mean T_{re} for different water temperatures.

T_{re-i} and T_{re-d} were higher at a water bath temperature of 15°C then at 20 or 25°C. There was no significant difference in T_{re} between 20 and 25°C.

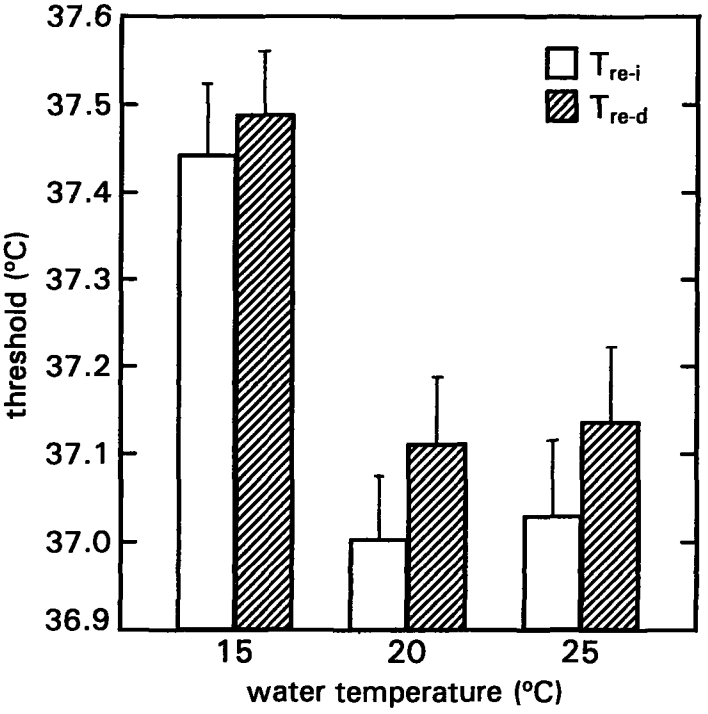

Fig. 5.7 Thresholds in rectal temperature (T_{re}) for different water temperatures in the calorimeter. The thresholds are determined by the increase and decrease in heat flux of the left index finger. Error bars indicate the standard deviation.

At the water bath temperature of 15°C T_{es-i} was higher than at water bath temperatures of 20 or 25°C. No differences were found between water bath temperatures of 20 and 25°C.

relation between ambient temperature and mean body skin temperature ($\bar{T}_{sk}$)

In Table 5.4 the relation between ambient temperature and mean skin temperature is shown at the moment the HF of the finger increases due to exercise ($\bar{T}_{sk-i}$) and at the moment this HF decreases ($\bar{T}_{sk-d}$).

Table 5.4 Relation between ambient and mean body skin temperature. The mean body skin temperature is determined at the moment the heat flux of the index finger increases due to exercise ($\bar{T}_{sk\text{-}i}$) and decreases after exercise ($\bar{T}_{sk\text{-}d}$) and is shown with standard deviation.

Ambient temperature (°C)	$\bar{T}_{sk\text{-}i}$ (°C)	$\bar{T}_{sk\text{-}d}$ (°C)
12	28.4 ± 0.8	28.4 ± 1.0
19	30.2 ± 1.1	30.6 ± 1.1
26	32.6 ± 0.8	32.5 ± 0.9

The skin temperature was significantly different between the ambient temperature settings. There is no difference in skin temperature between the moment of increase and decrease in HF due to exercise.

relation between water temperature and mean hand skin temperature ($\bar{T}_h$)

In Table 5.5 the relation between water bath temperature and $\bar{T}_h$ is shown at the moment the HF of the finger increases due to exercise ($T_{h\text{-}i}$) and at the moment this HF decreases ($T_{h\text{-}d}$).

Table 5.5 Relation between water bath and mean hand temperature.
Mean hand temperature is determined at the moment the heat flux of the index finger increases ($\bar{T}_{h\text{-}i}$) and decreases ($\bar{T}_{h\text{-}d}$) and is shown with standard deviation.

Water bath temperature (°C)	$\bar{T}_{h\text{-}i}$ (°C)	$\bar{T}_{h\text{-}d}$ (°C)
15	15.9 ± 0.4	16.9 ± 1.2
20	20.6 ± 0.2	22.2 ± 0.8
25	25.4 ± 0.1	26.7 ± 0.8

$\bar{T}_h$ is strongly dependent on the water temperature. At the moment of decrease in HF $\bar{T}_h$ is more than 1°C higher than at the moment of increase.

spontaneous increase in heat flux of the finger

Sometimes the HF of the index finger increased without any preceding exercise. This occurred most often at high ambient temperatures and low water bath temperatures. An example is given in Fig. 5.8 where the heat flux of the index finger increased twice spontaneously before any exercise was performed. Note that every spontaneous increase in HF is accompanied by a decrease in esophageal temperature: the hands eliminate heat which comes from the body core. During exercise (minute 63

- 72 i.e. between the vertical bars) this mechanism is overruled by the heat transfer from the working legs to the core.

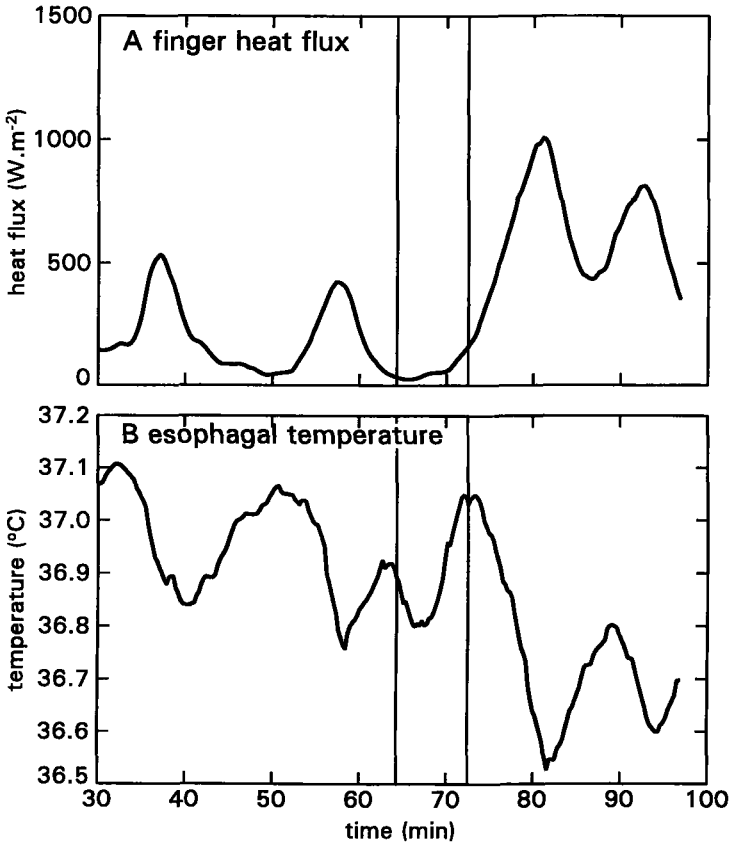

Fig. 5.8 Registration of spontaneous increases in heat flux of the index finger (A) and of corresponding changes in esophageal temperature (B). The two vertical bars border the exercise period. Subject 5, $T_a = 26°C$, $T_w = 15°C$.

If the thresholds of the spontaneous increases in HF are included in the analysis of variance the results remain essentially unchanged.

blood flow

At the moment the HF of the finger started to increase as induced by exercise, the mean laser Doppler blood flow recording was 0.68 ± 0.49 units. This parameter had significantly increased to 0.95 ± 0.63 units at the moment the HF of the finger started to decrease after ceasing the exercise.

The plethysmographic measurements showed a similar pattern as shown in Fig. 5.3, window h. With the plethysmograph, blood flow was often impossible to determine before the exercise period because flow was too low to be detected by this technique, especially in the water bath of 15°C. After the exercise period, the plethysmographic blood flow showed a sharp increase.
The average amount of heat transferred by the hand to the water, as determined by the calorimeter, was only 3.43 ± 3.13 W at the moment of HF increase of the index finger and increased to 24.73 ± 16.22 W at the moment of decrease in finger HF.

5.4 Discussion

contribution of core temperature and mean body skin temperature to finger blood flow
In this study, T_a was used to 'set' the mean body skin temperature ($\bar{T}_{sk}$). An increase of 7°C in T_a led to an increase of about 2°C in $\bar{T}_{sk}$ (Table 5.4). Exercise was used to change the core temperature. The threshold in esophageal temperature (T_{es}) above which the heat flux of the fingers suddenly increased, was dependent upon ambient temperature (T_a) (Table 5.3) and inherently $\bar{T}_{sk}$.
It is well known that $\bar{T}_{sk}$ has an effect on the threshold in T_{es} (e.g., Wenger et al., 1975). In our study, $\bar{T}_{sk-i}$ was 1.8°C higher when T_a was 19°C as compared to 12°C. The threshold in $\bar{T}_{es-i}$ was 0.06°C lower when T_a was 19°C as compared to 12°C. This means that a small change in core temperature has the same effect on finger blood flow than a relatively large change in $\bar{T}_{sk}$. The ratio of the relative importance of $\bar{T}_{sk}$ over $\bar{T}_{es}$ was as low as 0.03. When T_a of 19 and 26°C are compared, the effect of $\bar{T}_{sk}$ on the threshold in $\bar{T}_{es-i}$ was insignificant.
The relative influence of $\bar{T}_{sk}$ on finger blood flow is far less in our study than in the data of Wenger et al. (1975) (ratio of $\bar{T}_{sk}$ over T_c for finger blood flow: 0.11 - 0.17), Wyss et al. (1974) (influence-ratio of $\bar{T}_{sk}$ over T_c for forearm blood flow: 0.12 - 0.18) and Wyss et al. (1975) (ratio of $\bar{T}_{sk}$ over T_c for forearm blood flow: 0.11 - 0.20). The differences may be explained by different measuring techniques and temperature ranges. In our investigation the increased heat flux of the finger was used as the indicator for increases in hand blood flow. Wenger et al. (1975) extrapolated strain gauge plethysmographic measurements of the finger to zero blood flow to determine the threshold in T_c. However, the supposed linearity is doubtful, especially at low finger blood flow, as can be seen in Fig. 5.9.

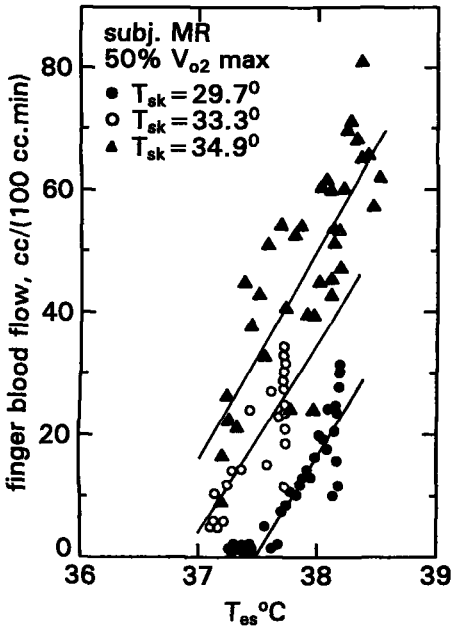

Fig. 5.9 Data from experiments at three different mean body skin temperatures ($\bar{T}_{sk}$) as obtained by Wenger et al. (1975), illustrating the effect of $\bar{T}_{sk}$ on the relation between the threshold in esophageal temperature (T_{es}) and finger blood flow. Note the unreliability of extrapolation to the x-axis, in particular for low mean body skin temperatures.

In our study, the threshold was determined at low finger blood flows, i.e. at the moment the heat flux of the finger to the water increased due to opening of the blood vessels or at the moment the heat flux returned to low values. At low finger blood flows the core temperature was shown to be the main determinant of skin blood flow.

A disadvantage of heat flux measurements as compared to blood flow measurements is that it is an indirect way of assessing the increase and decrease in finger blood flow. In chapter 11 it is shown that the temperature increase at the tip of the finger lags almost two minutes behind on the increase in skin perfusion, as assessed by laser Doppler flowmetry. The time lag between the increase in finger skin temperature and the heat flux of the finger is negligible. Since the increase in finger heat flux is detected about two minutes later than the increase in finger skin blood flow, the core temperature increase will be higher with the heat flux detection technique. This implies that the ratio of $\bar{T}_{sk}$ over T_{es} for finger skin blood flow may be even less than the value of 0.03.

The range in mean body skin temperatures in the investigation of Wenger et al. (1975) was about 30 to 35°C. In our investigation lower $\bar{T}_{sk}$ values were induced: from 28.4 to 32.6°C. Moreover, their $\bar{T}_{sk}$ was based on eight locations, while only three locations were used in this study. The exposure time to the ambient temperature previous to the exercise was not different between this experiment and that of Wenger et al. (1975).

Wyss et al. (1974, 1975) controlled $\bar{T}_{sk}$ and increased it gradually from 34 to 40°C, while measuring T_{es} and the temperature in the right atrium. They measured forearm blood flow by strain gauge plethysmography. Due to differences in receptors in the blood vessel wall, forearm blood flow shows a lower vasoconstrictor response to sympathetic activity than hand blood flow. They found forearm blood flow to be about 5 to 9 times more dependent upon T_{es} than upon $\bar{T}_{sk}$ but 19 times more dependent upon atrial temperature than upon $\bar{T}_{sk}$. In Wyss et al. (1974) one of the three investigated subjects did not show any dependence of forearm blood flow on $\bar{T}_{sk}$ at all. Therefore, the ratio of $\bar{T}_{sk}$ over T_{es} may be lower. In our investigation also large interindividual differences were found for the threshold in esophageal temperature for different ambient temperatures (Fig. 5.6).

Wyss et al. (1975) showed that the ratio of $\bar{T}_{sk}$ over T_{es} is not constant for finger blood flow, but is modified by changes in the thermal conditions. Therefore, they included the rate of change of $\bar{T}_{sk}$ in their regression equations. In our study, $\bar{T}_{sk}$ was not systematically controlled, so that we were unable to include this parameter in the analysis.

Recently, Pérgola et al. (1996) investigated the effect of $\bar{T}_{sk}$ and T_c on the blood flow in the lower arm. In the lower arm both active vasoconstriction and vasodilation control the blood flow in the skin. They found that the esophageal threshold increased from about 37.4 to 37.8°C when the $\bar{T}_{sk}$ was lowered from about 34.5 to 28.5°C.

contribution of core and hand temperature to hand blood flow

The influence of water bath temperature on the threshold in $\bar{T}_{es}$ was limited (Table 5.3). Mean hand temperature ($\bar{T}_h$) was closely related to the water bath temperatures (Table 5.5). The $\bar{T}_h$ was 4.7°C less and $\bar{T}_{es-i}$ was 0.02°C higher at a water bath temperature of 15°C as compared to 20°C. This means that changes in T_c were about 200 times more important for finger blood flow than changes in $\bar{T}_h$. When the water bath temperatures of 20 and 25°C are compared, the effect of $\bar{T}_h$ on the threshold was insignificant. The insignificant influence of the mean hand skin temperature on blood flow through the hands may be explained by the fact that hand blood flow in a water temperature of 15 - 25°C is rather constant. Raman and Vanhuyse (1975) reported average values over ten subjects for water bath temperatures of 15, 20 and 25°C of 4, 4 and $6 \cdot 10^{-4}$ $m^3 \cdot s^{-1} \cdot m^3$ respectively. Above 25°C the hand blood flow starts to increase exponentially. However, it would be difficult to include higher water bath temperatures in the current setup because T_c would have to be lowered instead of increased.

mechanism of local blood flow changes

The mechanism by which the sudden increase and decrease in heat flux of the finger (and also the palm of the hands) is triggered is likely to be associated with the opening and closure of arteriovenous anastomoses.

In our data the importance of the arteriovenous anastomoses can be seen in the enormous increase in blood flow measured by plethysmography in combination with the small increase in blood flow measured with the laser Doppler method. The latter method is more sensible to superficial skin blood flow and shows an increase of only about 40%. This means that the increased blood flow though the hands can not be explained by an increased circulation through the skin, and therefore deeper structures have to be responsible. The only possibility is that the arteriovenous anastomoses are involved.

Heating of the body core reduces the amount of sympathetic innervation (Hales and Iriki, 1977). The blood vessels in the skin of the hand are normally subjected to a high degree of vasoconstrictor tone. The decreased sympathetic tone opens the vessels. The AVA's are extremely susceptible to sympathetic tone because the strong muscular wall of the AVA's is richly innervated by adrenergic sympathetic nerves (Guyton and Hall, 1996), although some cholinergic, possibly vasodilator, innervation may also be present (Nelms, 1963).

The activity of the sympathetic nerves is not only influenced by temperature changes, but also by exercise (Seals and Victor, 1991). The cycling exercise increases sympathetic nerve activity and leads to a temporary peripheral vasoconstriction in the skin blood vessels of the hand, and also of the AVA. The same phenomenon can also be seen as an increased esophageal threshold for skin blood flow as compared to resting conditions (Johnson and Park, 1981).

Kellogg et al. (1991) concluded that reflexes associated with exercise cause an elevated vasodilator threshold by delaying activation of the active vasodilator system, rather than through the adrenergic vasoconstrictor system. They stopped the norepinephrine release by bretylium tosylate and found no differences in threshold between treated and untreated subjects.

Although the mechanism is still subject to debate, the initial fall in skin temperature after the start of exercise favours the detection of the sharp increase in HF of the finger. The sharp increase in HF is probably caused by a sudden drop in central sympathetic activity when the core temperature exceeds a certain threshold.

In Fig. 5.8 it was shown that an increased heat transfer of the hands was sometimes accompanied by a decrease in core temperature. This phenomenon was also described by Kerslake and Cooper (1950). This stresses the importance of the hands as a medium to transfer heat from the body to the surroundings.

In conclusion, it was shown in this study that the esophageal threshold above which the blood flow in the fingers suddenly increases is rather stable. Within an experiment the standard deviation of the

threshold is only 0.07°C. Changes in mean body skin temperature affect the threshold, but far less than was previously found in the literature. Changes in core temperature are about 30 times more important for finger blood flow than changes in mean body skin temperature. The effect of hand temperature is almost negligible in the range of 15 to 25°C.

5.5 Summary

The relative contribution of core temperature (T_c), mean skin temperature ($\bar{T}_{sk}$) and mean skin temperature of the hand ($\bar{T}_h$) to the blood flow of the hand was determined experimentally in six subjects. When the heat flow from the left index finger, immersed in cool water, was almost zero, the subjects increased their core temperature by exercise until a sharp increase of the HF of the finger was found. As soon as the HF increased, they stopped exercise. This procedure was repeated until a maximum of two hours immersion time was reached. The esophageal temperature at which the HF of the finger increased was stable within one experiment (SD = 0.07°C), so that one can speak of an individual threshold in esophageal temperature for hand (finger) blood flow.
Three different ambient and water bath temperatures were chosen which led to $\bar{T}_{sk}$ of 28.4, 30.2 and 32.6°C and $\bar{T}_h$ of 15.9, 20.6 and 25.4°C respectively. For these temperature ranges, changes in T_c were about 30 times more important for finger blood flow than changes in $\bar{T}_{sk}$ and 200 times more important than changes in $\bar{T}_h$. Therefore, a warm body core is essential to keep the hands warm.