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Overview

The main objective of this thesis was to investigate the central and peripheral effects on the vascular reaction of the hands to cold. The **literature review** revealed that quantitative data on the influence of body core and body skin temperature on blood flow in the hands is lacking. The qualitative effects of various variables such as food intake, gender and age on hand blood flow are reasonable well described. Also, it is well documented that arteriovenous anastomoses (AVA's) play a key role in the regulation of peripheral blood flow. However, the estimations on the amount of AVA's in the fingers varies tremendously.

In **chapter 4** the time course and magnitude of heat transfer from hands and feet to a moderately cold environment was quantified. For this purpose, five healthy males immersed their hands and feet twice in a 25°C water calorimeter bath.
Immersion of hands or feet lead to an initial increase in heat transfer, with a peak power transfer of 37 W for the hand and 34 W for the foot. After a few minutes the power transfer decreased, probably due to vasoconstriction in the skin. During the 60 minute immersion more heat was transferred to the water from the hand (47 ± 20 kJ) than from the foot (36 ± 18 kJ). Heat flux was higher from the ventral than from the dorsal side of the extremities. Local skin temperature dropped to values close to the water temperature and blood flow was strongly reduced at the end of immersion, especially in the foot. In the hand, the reduction in plethysmographic blood flow exceeded the reduction in Doppler blood flow. It is discussed that this disproportional decrease might form an indicator for the involvement of arteriovenous anastomoses.

It was well documented in the literature that there is a threshold in core temperature above which the fingers suddenly become warm, identical to the well-know threshold for sweating. The absolute values of this threshold had sofar mainly been determined by plethysmography, which yields unreliable results at low blood flows. In **chapter 5** the finger heat flux (HF) was used as an indicator for finger blood flow and the question was addressed how stable the threshold in core temperature is above which the blood flow in the hands increases. Moreover, the relative contribution of core temperature (T_c), mean body 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 flux from the left index finger, which was 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 rather stable within each 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 temperatures and three different 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.

The mechanism responsible for cold induced vasodilation (CIVD) is still subject to debate. Several theories are based on local mechanisms such as the release of a dilating substance, an axon reflex or local paralysis of smooth muscles in the vessel wall. However, it has also been shown that core temperature has to play a major role, because CIVD decreases in magnitude when the core gets colder. In chapters 6 and 7 the interplay between local and central influences on the hunting reaction was investigated by taking a closer look at the amount of correspondence between the hunting patterns of the fingers tips in one (chapter 6) or two (chapter 7) cold exposed hands. A good correspondence supports a relatively great central influence; a low correspondence is in favour of a prevailing peripheral influence. In **chapter 6**, twelve subjects immersed their left hand in a calorimeter water bath of about 5°C. Pearson Correlation Coefficients (PCC's) were calculated for the temperature fluctuations of all fingers and of the ventral and dorsal side of the left hand. A period of 30 minutes was analysed, starting 10 minutes after immersion. The temperature fluctuations of the fingers had a relatively high amount of correspondence. The amount of correspondence differed between subjects and finger combinations. The PCC was higher for neighbouring fingers (PCC = 0.67) than for fingers separated by other fingers (PCC = 0.48). The temperature fluctuations of the palm and back of the hands were unrelated to the hunting reaction of the finger tips.

In **chapter 7**, eight male subjects immersed both hands simultaneously (S) and five minutes after each other (NS) in water of about 10°C. The similarity between the onset times of CIVD was used as a quantitative value for the amount of synchronization between hunting reactions. The PCC was used as an indicator for the amount of correspondence between two hunting reactions.

In NS immersion, the hunting reaction in the finger tips of the two immersed hands was generally not synchronous (only in 14% of the cases synchronization occurred). In S immersion synchronization between two hands occurred more often (in 20% of the cases), but intersubject differences were large. The amount of correspondence yielded similar results. The PCC between all finger combinations of different hands was only 0.30 in NS. This makes it likely to assume different vasomotor control centres for the left and right hand.

The amount of synchronization between the fingers of one immersed hand was about 21%. The mean PCC within a hand was 0.63, which implied a greater central influence than in the previous chapter, in which the body heat content and water temperature were lower (PCC = 0.55). The higher central influence for one immersed hand was also shown by the variation in heat transfer of the hand to the water, which was 43% of the average fluctuation in finger temperature and only 31% in the previous chapter.

In **chapter 8** the aim was to identify the amount of common vascular control between one cold exposed hand an a non-cold exposed hand. Seven subjects immersed one hand in 6°C water, and exposed the other hand to 31°C air. The finger skin temperatures of the immersed hand showed a hunting reaction, while the finger skin temperatures of the non-immersed hand showed small fluctuations around 35°C. The fluctuations of the finger skin temperatures of the immersed and non-immersed hand were not related. Thus, common control is absent and, again, it is likely that separate vasomotor control centra for the right and left hand exist.

The immersed hand lost on average 44 W when the body was slightly chilled before the hand immersion and 52 W when the core was slightly warmed previously. This heat loss caused a slow decrease in core temperature during immersion. However, the body core temperature did not reflect the changes in finger skin temperature during immersion of the hand, probably due to counter current heat exchange. The small difference in body thermal status caused significant changes in the hunting parameters. In the warm body CIVD onset occurred sooner and minimum and maximum finger skin temperatures were higher. This illustrates the high sensitivity of the hunting reaction for body thermal status.

Chapter 8 clearly showed that the hunting reaction was sensitive for the thermal status of the body. **Chapter 9** investigates the combined effect of body temperature and hand temperature on the hunting reaction. It was suggested previously that an individual with a high threshold in core temperature for finger blood flow (see chpt. 5) may have a reduced hunting reaction. Therefore, in eight subjects the individual esophageal threshold for finger vasodilation was related to the hunting reaction. After determination of the threshold, the subjects immersed their hands four times: in 5 and 8.5°C water with a slightly cooled and also with an elevated body core temperature.

Even when the body heat content was mildly elevated, the characteristics of the hunting reaction showed significant changes. An increased body core temperature was related to higher finger skin temperatures, increased heat transfer of the hands to the water, higher T_{min} and T_{max}, shorter onset times to CIVD, increased CIVD amplitude, less pain and more comfortable temperature sensation.

Immersion of the hands in colder water was related to lower finger skin temperatures, increased heat transfer from the hands to the water, lower T_{min} and T_{max}, increased CIVD amplitude, more pain and less comfortable temperature sensations.

The individual esophageal threshold for finger vasodilation was not related to the hunting parameters. This indicates that, in addition to the thermal status of the body, the local cold stimulus has a strong impact on the CIVD response as well.

In the experiments described in the previous chapters, the combined effect of an increase or decrease in body core temperature and mean (body) skin temperature ($\bar{T}_{sk}$) on the hunting reaction was investigated. The goal of the experiment in **chapter 10** was to investigate the combined and separate effects of core temperature and $\bar{T}_{sk}$ on the hunting reaction. Therefore, nine subjects immersed their right hand in 8°C water. Core and skin temperatures were manipulated by exposing the subjects to different ambient temperatures (30, 22, 15°C), by adjusting their clothing insulation (moderate, light, none), and by drinking beverages at different temperatures (42-44, 37 and 0°C). The middle finger temperature response was recorded (T_{fi}), together with ear canal (T_{ear}), rectal

(T_{re}), and $\bar{T}_{sk}$. The core temperature was mainly determined by the temperature of the beverages; $\bar{T}_{sk}$ mainly by the ambient temperature. The induced mean T_{ear} changes were -0.34 ± 0.08 and +0.29 ± 0.03°C for the cold and hot beverage respectively. $\bar{T}_{sk}$ ranged from 26.7 to 34.5°C during the tests. In the *warm environment* after a hot drink, the initial finger temperature ($T_{fi,base}$) was 35.3 ± 0.4°C, the minimum finger temperature during immersion ($T_{fi,min}$) was 11.3 ± 0.5°C and 2.6 ± 0.4°C hunting waves occurred in the 30 minute immersion period. For the *neutral condition* (thermoneutral room and beverage) $T_{fi,base}$ was 32.1 ± 1.0°C, $T_{fi,min}$ was 9.6 ± 0.3°C and 1.6 ± 0.2 waves occurred. For the *coldest condition* (cool room, cold drink) these values were 19.3 ± 0.9°C, 8.7 ± 0.2°C and 0.8 ± 0.2 waves respectively. A colder body induced a decrease in magnitude and frequency of the hunting reaction. The total heat transferred from the hand to the water was also dependent upon the induced increase or decrease in T_{ear} and $\bar{T}_{sk}$. We conclude that the characteristics of the hunting temperature response curve of the finger are in part determined by core temperature and mean skin temperature. T_{min} and T_{max} were higher when the core temperature was elevated; $\bar{T}_{sk}$ seemed to be an important determinant of the onset time of the cold induced vasodilation response.

Only one reference was found in the literature on reproducibility of the hunting reaction. Therefore, **chapter 11** was dedicated to the determination of the reproducibility of the hunting reaction. Eight subjects immersed their hands three times in 6°C water on different days. Although the experimental conditions of the three immersions were rather similar (SD of water temperature 0.3°C, SD of body heat content within subjects only 48 kJ), the reproducibility of the hunting reaction was rather poor. The standard deviation of the onset time within subjects was almost a minute and the SD of T_{max} was 1.3°C. Also, the correlation between the temperature registrations of the finger tips showed large differences between experiments. The poor reproducibility may partly be explained by the findings in previous chapters that even minor differences in core and mean skin temperature may have a large impact on the hunting reaction. Skin perfusion, as measured by laser Doppler flowmetry, precedes the finger skin temperature response by about 90 to 150 seconds during the hunting reaction. The time shift is dependent on the magnitude of the hunting reaction: a strong response leads to rapid tissue heating and relatively short time delays.

A complete picture on the influence of body thermal status on the CIVD response, and whether an axon reflex might be involved in the onset of CIVD, is still lacking from the current literature. Therefore, an investigation was performed in **chapter 12** on eight subjects who immersed their right hand in 5°C water (and left hand in 35°C water) during hypothermia, thermoneutrality and hyperthermia. High body core and mean skin temperatures appeared to be related to high finger skin temperatures during cold water immersion and shorter onset times to CIVD. To investigate the plausibility of the axon reflex as an explanation for the occurrence of CIVD, axon reflexes were evoked by electrical stimulation during hand immersion. An increase in skin perfusion was seen in the warm hand but absent in the cold hand, which indicates that the axon reflex is not a likely explanation for CIVD. In three subjects the median nerve was completely blocked during hypothermia to investigate the interaction between sympathetic activity and CIVD. The hunting pattern remained unchanged. This indicates that changes in sympathetic activity are not very important for the occurrence of CIVD.

In the **general discussion** it was concluded that the hunting reaction is not an adequate reaction against the occurrence of local cold injuries mainly because the response is of limited magnitude in hypothermia when most cold injuries occur. CIVD still occurs after a complete block of the mixed peripheral nerve. This means that the trigger for CIVD should have a peripheral origin. Some evidence was gathered which was not in favour of the axon reflex hypothesis. Possible other hypothesis are the paralysis of the contractile apparatus in the vessel wall and an adrenergic neurotransmitter blockade due to cold. The experimental support for these hypotheses is conflicting. When one finger has started the hunting reaction, the next one is likely to be a neighbouring finger. This is probably due to local heating of the surrounding tissue, but deserves a closer look. The local tissue temperature seems to be the most important parameter for the timing of CIVD, while the magnitude of CIVD is dependent on the core temperature of the body. No subject related factor could be identified that explained the large interindividual variations in the hunting reaction. For a group, however, the average hunting reaction can be estimated based on body core temperature, mean body skin temperature and water bath temperature. Thus, computer models can predict the average hunting reaction on a group level, but not for a certain individual.

Overzicht

Het doel van dit proefschrift was om na te gaan wat de centrale en perifere invloeden waren op de vasculaire reactie van de handen op kou. Het literatuuroverzicht in **hoofdstuk 2** leerde dat kwantitatieve gegevens over de invloed van kern- en huidtemperatuur op de handdoorbloeding vaak ontbraken. Het kwalitatieve aspect van variabelen als voedsel, geslacht en leeftijd op handdoorbloeding was redelijk goed beschreven. Ook was het redelijk goed gedocumenteerd dat de arterioveneuze anastomosen (AVA's) een sleutelrol speelden in de regulatie van de perifere doorbloeding. Echter, schattingen over de aantallen AVA's in de vingers liepen sterk uiteen.

In **hoofdstuk 4** werd het tijdsverloop en de grootte van de warmteafgifte van handen en voeten naar een gematigd koude omgeving gekwantificeerd. Hiertoe dompelden vijf gezonde mannen hun handen en voeten twee maal in een calorimeter, die gevuld was met water van 25°C.
Onderdompeling van de handen of voeten leidde tot een aanvankelijke toename van de warmteoverdracht, met een piekvermogen van 37 W voor de hand en 34 W voor de voet. Na een aantal minuten nam het vermogen af, waarschijnlijk door vasoconstrictie in de huid. In het uur onderdompeling werd meer warmte door de hand afgegeven (47 ± 20 kJ) dan door de voet (36 ± 18 kJ). De warmtestroom was groter van de binnenzijde van de hand en voet dan van de buitenzijde. De locale huidtemperatuur daalde tot waarden die dicht bij de watertemperatuur lagen. De doorbloeding was sterk afgenomen aan het eind van de onderdompeling, met name in de voet. In de hand nam de doorbloeding gemeten met plethysmografie meer af dan de huiddoorbloeding gemeten met de Doppler methode. In de discussie wordt verondersteld dat deze niet proportionele afname een indicator kan vormen voor de mate van betrokkenheid van AVA's.

Uit de literatuur is bekend dat er een drempel is in kerntemperatuur waarboven de vingers plotseling warm worden, identiek aan de bekende zweetdrempel. De absolute waarden van deze drempel zijn tot nu toe voornamelijk bepaald met plethysmografie, dat onbetrouwbare resultaten geeft bij geringe doorbloeding. In **hoofdstuk 5** wordt de warmtestroom van de vinger (HF) gebruikt als een indicator voor de vingerdoorbloeding en de vraag wordt beantwoord hoe stabiel de drempel in kerntemperatuur is waarboven de doorbloeding in de vinger plotseling toeneemt. Ook werd de relatieve bijdrage van kerntemperatuur (T_c), gemiddelde huidtemperatuur ($\bar{T}_{sk}$) en huidtemperatuur van de hand ($\bar{T}_h$) aan de doorbloeding van de hand experimenteel bepaald bij zes proefpersonen. Als de HF van de linker wijsvinger vrijwel nul was, werd aan de proefpersonen gevraagd te gaan fietsen om zo de kerntemperatuur te verhogen. Als de HF plotseling toenam stopten ze met fietsen. Deze procedure werd twee uur lang herhaald. De drempel in slokdarmtemperatuur waarbij de HF plotseling toenam bleek stabiel te zijn binnen elk experiment (SD = 0,07°C), zodat men kan spreken van een individuele drempel in slokdarmtemperatuur voor vingerdoorbloeding.
Er werden drie verschillende omgevingstemperaturen ingesteld en drie verschillende waterbad temperaturen, die respectievelijk leidden tot een $\bar{T}_{sk}$ van 28,4, 30,2 en 32,6°C en een $\bar{T}_h$ van 15,9,

20,6 and 25,4°C. Voor dit temperatuursbereik waren de veranderingen in T_c ongeveer 30 keer belangrijker voor de vingerdoorbloeding dan veranderingen in $\bar{T}_{sk}$ en 200 keer belangrijker dan veranderingen in $\bar{T}_h$. Het kan daarom worden gesteld dat een warme kern essentieel is om de handen warm te houden.

Over het mechanisme achter door-koude-geïnduceerde-vaatverwijding (CIVD) is men het nog niet eens. Er zijn verschillende theorieën gebaseerd op locale mechanismen, zoals een axon reflex, verlamming van de gladde spieren in de wand van het bloedvat of het vrijkomen van een locale vaatverwijdende substantie. Het is daarnaast aangetoond dat de kerntemperatuur een belangrijke rol moet spelen omdat CIVD minder wordt als de kern kouder wordt. In hoofdstukken 6 en 7 wordt de relatie tussen centrale en perifere invloed op de hunting reactie (telkens terugkerende CIVD) onderzocht door nader in te gaan op de gelijkenis tussen de temperatuurschommelingen van de verschillende vingers in één (hoofdstuk 6) of twee (hoofdstuk 7) ondergedompelde handen. Veel gelijkenis ondersteunt dat er relatief veel centrale invloed is; weinig gelijkenis wijst in de richting van een overheersende perifere invloed. In **hoofdstuk 6** dompelden twaalf personen hun linkerhand in een calorimeter met water van ongeveer 5°C. De Pearson Correlatie Coëfficiënten (PCC's) werden berekend tussen de temperatuurschommelingen van alle vingers, de handpalm en de handrug. De registratie van 30 minuten werd geanalyseerd, beginnend 10 minuten na onderdompeling van de hand. De gelijkenis verschilde tussen personen en vingercombinaties. De PCC was hoger voor aangrenzende vingers (PCC = 0,67) dan voor vinger die niet aan elkaar grensden (PCC = 0,48). De temperatuurschommelingen van de handpalm en handrug waren niet gerelateerd aan de schommelingen in de vingertoppen.

In **hoofdstuk 7** dompelden acht mannelijke proefpersonen beide handen gelijktijdig (S) en vijf minuten na elkaar (NS) in water van ongeveer 10°C. De gelijkenis tussen de starttijden van CIVD werd gebruikt als een kwantitatieve maat voor de hoeveelheid synchronisatie tussen de hunting reacties. De PCC werd opnieuw gebruikt als een maat voor gelijkenis.

Bij NS was de hunting reactie in het algemeen niet synchroon (in slechts 14% van de gevallen werd synchronisatie gevonden). Bij S kwam synchronisatie vaker voor (in 20% van de gevallen). De gelijkenis vertoonde identieke resultaten: de PCC was slechts 0,30 bij NS, hetgeen het aannemelijk maakt dat de linker en rechter hand onder verschillende vasomotore controle staan.

De hoeveelheid synchronisatie tussen vingers in een ondergedompelde hand was ongeveer 21%. De gemiddelde PCC in een hand was 0,63. Dit was meer dan de waarde uit hoofdstuk 6 (0,55), hetgeen aangeeft dat de centrale invloed in hoofdstuk 7 groter is dan in hoofdstuk 6. In hoofdstuk 6 was de watertemperatuur lager en de mensen waren meer afgekoeld. De grotere centrale invloed in hoofdstuk 7 was ook zichtbaar in de grotere schommelingen in warmteafgifte aan het water, hetgeen wijst op meer synchronisatie.

In **hoofdstuk 8** was het doel om de vasculaire controle te onderzoeken in een hand die aan kou werd blootgesteld en een andere hand die niet aan kou werd blootgesteld. Zeven proefpersonen dompelden één hand in water van 6°C terwijl de andere hand in lucht van 31°C werd gehouden. De huidtemperaturen van de vingertoppen van de ondergedompelde hand lieten een hunting reactie zien, terwijl de temperatuur in de controle hand fluctueerde rond 35°C. De schommelingen in vingertemperatuur tussen de ondergedompelde en niet-ondergedompelde hand waren ongerelateerd. Gemeenschappelijke controle is dus niet aanwezig en het is aannemelijk dat verschillende vasomotore centra bestaan voor de linker en rechter hand.

De ondergedompelde hand gaf gemiddeld zo'n 44 W aan vermogen af als de proefpersoon wat was afgekoeld voor de handonderdompeling en 52 W als hij voor de onderdompeling wat was verwarmd. De temperatuur in de slokdarm was niet gerelateerd aan de schommelingen in de temperatuur van de vingertoppen van de ondergedompelde hand. Het tegenstroom-principe is hier waarschijnlijk debet aan. Het kleine verschil in lichaamstemperatuur tussen afgekoelden en opgewarmden veroorzaakte toch significante verschillen in de hunting parameters. In het warme lichaam begon CIVD eerder en de minimale en maximale vingertemperaturen lagen wat hoger. Dit illustreert de gevoeligheid van de hunting reactie voor thermische toestand van het lichaam.

Hoofdstuk 8 liet zien dat de hunting reactie gevoelig is voor de thermische toestand van het lichaam. **Hoofdstuk 9** onderzoekt het gecombineerd effect van lichaamstemperatuur en handtemperatuur op de hunting reactie. Eerder was al gesuggereerd dat een individu met een hoge drempel in kerntemperatuur voor vingerdoorbloeding (zie hoofdstuk 5) een verminderde hunting reactie heeft. Daarom werd bij acht proefpersonen onderzocht of de individuele drempel in slokdarmtemperatuur gerelateerd was aan de hunting reactie. Na bepaling van de drempel dompelden de proefpersonen hun handen vier keer in koud water: in water van 5 en 8,5°C bij een licht verlaagde en licht verhoogde kerntemperatuur.

Zelfs wanneer de warmteinhoud van het lichaam slechts licht verhoogd was, werden significante veranderingen in de hunting parameters gevonden. Een hogere lichaamstemperatuur ging gepaard met een verhoogde warmteafgifte van de hand, hogere minimum en maximum vinger temperaturen, sneller optreden van CIVD, toegenomen amplitude van CIVD, minder pijn en meer comfort. Onderdompeling in kouder water was gerelateerd aan lagere vingertemperaturen, toegenomen warmteafgifte van de hand, toegenomen CIVD amplitude, meer pijn en minder comfort. Dit geeft aan dat de locale koude-stimulus, naast de thermische toestand van het lichaam, een impact heeft op de CIVD-reactie.

In de experimenten die in de vorige hoofdstukken zijn beschreven, is het gecombineerde effect van kerntemperatuur en gemiddelde huidtemperatuur op de hunting reactie onderzocht. Het doel van **hoofdstuk 10** is om de invloed van kern- en huidtemperatuur separaat te onderzoeken. Voor dit doel dompelden negen proefpersonen hun rechterhand in water van 8°C. De kern- en huidtemperatuur werd gemanipuleerd door de proefpersonen aan verschillende omgevingstemperaturen bloot te stellen (30, 22 en 15°C), hun kledingisolatie te wijzigen (redelijke, lichte en geen isolatie) en door ze dranken van verschillende temperaturen te geven (heet - 43°C , neutraal - 37°C en koud - 0°C). De reactie van de huidtemperatuur van de middelvinger werd gemeten (T_{fi}), tezamen met de oorkanaaltemperatuur (T_{ear}), rectale temperatuur (T_{re}) en gemiddelde huidtemperatuur ($\bar{T}_{sk}$). De kerntemperatuur werd voornamelijk bepaald door de temperatuur van de drank; $\bar{T}_{sk}$ voornamelijk door de omgevingstemperatuur. De geïnduceerde gemiddelde veranderingen van T_{ear} waren respectievelijk -0,34 ± 0,08 en +0,29 ± 0,03°C voor de koude en hete drank. Het bereik van $\bar{T}_{sk}$ beliep 26,7 tot 34,5°C tijdens de tests. In de *warme omgeving* na een hete drank was de begintemperatuur van de vinger ($T_{fi,base}$) 35,3 ± 0,4°C en de minimale vingertemperatuur tijdens onderdompeling ($T_{fi,min}$) 11,3 ± 0,5°C, terwijl 2,6 ± 0,4 hunting golven optraden in de onderdompelingsperiode van 30 minuten. Voor de *neutrale conditie* (thermoneutrale kamer en drank) was $T_{fi,base}$ 32,1 ± 1,0°C, $T_{fi,min}$ 9,6 ± 0,3°C en 1,6 ± 0,2 golven kwamen voor. Voor de *koudste conditie* (koude kamer, koude drank) waren de waarden respectievelijk 19,3 ± 0,9°C, 8,7 ± 0,2°C en 0,8 ± 0,2 golven. In een kouder lichaam zijn de grootte en frequentie van de hunting reactie afgenomen. De totale warmteafgifte van de hand was ook afhankelijk van de veranderingen in T_{ear} en $\bar{T}_{sk}$. Er wordt geconcludeerd dat de hunting parameters gedeeltelijk bepaald worden door kern- en huidtemperatuur. De minimale en maximale vingertemperatuur waren verhoogd bij een warme kern; het lijkt er op dat de huidtemperatuur gekoppeld is aan de timing van CIVD.

Er werd maar een referentie gevonden in de literatuur van een onderzoek naar de reproduceerbaarheid van de hunting reactie. Daarom werd **hoofdstuk 11** gewijd op dit onderwerp. Acht personen dompelden hun handen drie keer onder in water van ongeveer 6°C op verschillende dagen. Hoewel de experimentele condities op de drie dagen vergelijkbaar waren (SD van de watertemperatuur 0,3°C, SD van lichaamswarmte binnen proefpersonen slechts 48 kJ), was de reproduceerbaarheid teleurstellend. De SD van de starttijd van CIVD was bijna een minuut en de SD van de maximale vingertemperatuur was 1,3°C. Ook waren er grote verschillen in de correlaties tussen de temperatuursregistraties van de verschillende vingertoppen. De tegenvallende reproduceerbaarheid kan gedeeltelijk verklaard worden door de bevinding in vorige hoofdstukken dat zelfs een kleine verandering in kern- en huidtemperatuur een grote impact op de hunting parameters heeft. De huiddoorbloeding, bepaald met laser Doppler flow-metingen, gaat 90 tot 150 seconden vooraf aan de temperatuurrespons. De tijdverschuiving is afhankelijk van de grootte van de hunting reactie: Een sterke respons leidt tot snelle weefselverwarming en relatief korte vertragingen.

Een compleet beeld ontbreekt nog steeds betreffende de invloed van lichaamstemperatuur op CIVD en de rol van de axonreflex in de start van CIVD. Daarom is in **hoofdstuk 12** een experiment beschreven dat op acht proefpersonen werd uitgevoerd die hun rechterhand dompelden in water van 5°C en hun linkerhand in water van 35°C. Tijdens het experiment waren ze hypotherm, thermoneutraal of hypertherm. Een hoge kerntemperatuur en huidtemperatuur ging gepaard met hoge vingertemperaturen tijdens onderdompeling en met een snellere start van CIVD. De geloofwaardigheid van de axonreflex als het mechanisme achter CIVD werd onderzocht door met electrische stimulatie axonreflexen te genereren. Een toename in huiddoorbloeding werd gevonden in de warme hand, maar niet in de koude hand. Dit wijst er op dat een axonreflex waarschijnlijk niet het mechanisme achter CIVD is. Bij drie vrijwilligers werd bovendien de mediane zenuw in de pols geblokkeerd om de interactie tussen sympathische activiteit en CIVD te onderzoeken. Het hunting patroon bleef ongewijzigd, hetgeen duidelijk maakt dat de invloed van sympathische activiteit op CIVD niet zo groot is.

In de algemene discussie (**hoofdstuk 13**) werd geconcludeerd dat de hunting reactie niet een adekwate reactie is om koudeletsel te voorkomen met name omdat de reactie beperkt is tijdens hypothermie, juist de situatie wanneer de meeste koudeletsels voorkomen. CIVD treedt nog steeds op als de gemengde zenuw is geblokkeerd. Dit betekent dat de trigger voor CIVD van perifere origine moet zijn. Het onderzoek van hoofdstuk 12 gaf aan dat de axonreflex waarschijnlijk niet verantwoordelijk is voor CIVD. Andere hypothesen zijn verlamming van het contractiele apparaat in de wand van de bloedvaten en een adrenerge blokkade door kou. De experimentele ondersteuning van deze hypothesen is niet eenduidig. Als een vinger met de hunting respons is gestart, is de kans groot dat de tweede vinger een aangrenzende vinger is. Waarschijnlijk heeft dit te maken met locale verwarming van het weefsel in de hand, maar dit moet nader onderzocht worden. De locale weefseltemperatuur lijkt de belangrijkste parameter voor de timing van CIVD, terwijl de amplitude van de respons afhankelijk is van de kerntemperatuur. Er kon geen persoonsgebonden factor worden geïdentificeerd die de grote interindividuele verschillen in de hunting reactie kon verklaren. Op groepsniveau echter kon de hunting reactie worden getypeerd met behulp van kerntemperatuur, huidtemperatuur en waterbadtemperatuur. Op deze wijze kunnen computermodellen de gemiddelde respons van een groep voorspellen, maar niet een individuele reactie.

Summary

When human fingers are exposed to cold, the blood vessels in the skin contract. Thus less blood goes to the periphery for heat transfer with the environment. This, however, can lead to problems in the fingers: the cold reduces the mobility and sensitivity of the fingers, thus increasing the risk for cold injuries and decreasing the manual dexterity. Fortunately, the fingers are equipped with arterio-venous anastomoses (AVA). These are shortcuts between the arterial and venous system. The AVA open and close periodically and thus allow warm blood to enter the finger tips. The opening of the vessels in the cold is called Cold Induced Vasodilation (CIVD). A competition exists between mechanisms under central control (closure of blood vessels to retain body heat) and local mechanisms (opening of blood vessels to avoid local cold injuries). This competition is the topic of this thesis.

In a series of experiments the relation between finger blood flow and body temperature is investigated. Heat is easily transferred to the environment by the fingers when the body is relatively warm. A distinction can be made between body core temperature and mean skin temperature of the body in relation to their effect on the CIVD response. A relatively high skin temperature leads to a quick onset of CIVD; a relatively high core temperature leads to a large amplitude of CIVD. CIVD is minimal in a cold body and consequently the risk for local cold injuries is higher than with a warm body. The temperature of the hand also plays a role: CIVD is enhanced when the hand is cold.

The CIVD-reaction of neighbouring fingers shows much similarity in shape and timing. This similarity is probably not related to nerve supply, but more likely to blood supply. No relation was found in CIVD between fingers of different hands. This suggests that finger blood flow is controlled by different mechanisms for the left and right hand.

The mechanism of the CIVD-reaction is not well known. For a long time it was assumed that the cold/pain sensors in the skin trigger nerves that release vasodilating substances (axon-reflex). In an experiment, however, it appeared to be impossible to evoke an axon-reflex in a cold hand. This makes another hypothesis more likely that states that a paralysis of the muscle wall of the AVA occurs in the cold.

Samenvatting

Als de vingers van een mens in een koude omgeving komen, vernauwen vrijwel direct de bloedvaten in de huid. Hierdoor houdt het lichaam meer warmte vast. In de vingers kan deze reactie tot problemen leiden: de kou leidt tot minder beweeglijkheid en gevoel van de vingers, waardoor de handvaardigheid afneemt en de kans op koude-letsel toeneemt. Gelukkig vinden we in de vingertoppen Arterio-Veneuze Anastomozen (AVA). Dit zijn kortsluitingen tussen het slagaderlijke en aderlijke bloedvatstelsel. Deze gaan in de kou ritmisch open en dicht, en laten aldus pulserend bloed en daarmee warmte toe in de vingertoppen. Het opengaan van de bloedvaten in de kou wordt Cold Induced Vasodilation (CIVD) genoemd.
Er ontstaat aldus competitie tussen mechanismen op centraal nivo (bloedvaten dicht om de warmte vast te houden) en lokaal nivo (bloedvaten open om problemen te voorkomen). Deze competitie vormt het onderwerp van dit proefschrift, waarin de onderlinge strijd in kaart wordt gebracht.

In een reeks experimenten is nagegaan wat de relatie is tussen de vingerdoorbloeding en de temperatuur van het lichaam. Als het lichaam warm is, staat het relatief gemakkelijk warmte af door de vingers. Hierbij kan nog een onderscheid gemaakt worden tussen kern- en gemiddelde huidtemperatuur van het lichaam met betrekking tot hun effect op CIVD. Een hoge huidtemperatuur leidt er toe dat CIVD snel optreedt, een hoge kerntemperatuur zorgt ervoor dat de amplitude van CIVD groot is. Bij een koud lichaam is CIVD nauwelijks zichtbaar en de kans op koude-letsel natuurlijk groter dan bij een warm lichaam. Ook de temperatuur van de hand speelt een rol: hoe kouder de hand is geworden, des te krachtiger is de CIVD reactie.

De CIVD-reactie van aangrenzende vingers heeft veel gelijkenis in vorm en tijdsverloop. Deze gelijkenis heeft waarschijnlijk niets te maken met overeenkomstige zenuwvoorziening van de vingers, maar mogelijk wel met gedeelde bloedvoorziening. Er is geen verband gevonden tussen CIVD van de vingers van verschillende handen. Het lijkt er op dat de doorbloeding van de verschillende handen apart wordt geregeld.

Hoe de CIVD-reactie tot stand komt is nog niet goed bekend. Lang is verondersteld dat de koude/pijn-sensoren in de huid een zenuw prikkelen die vervolgens een stof afscheidt die de locale bloedvaten verwijdt (axon-reflex). In een experiment bleek het echter onmogelijk deze axon-reflex op te wekken in een koude hand. Daarmee wordt een andere hypothese aannemelijker die stelt dat er een soort verlamming optreedt van de spierwand van de AVA.

APPENDIX 1 - List of abbreviations

%	Percent
Δt period	Time from first to second minimum
Δt peak	Time between the occurrence of T_{max} and T_{min}
ΔT	Temperature difference
Δt_{onset}	Time from immersion to T_{min}
µm	Micrometer (10^{-6}m)
ρ	Density of water
Φ_v	Flow of the water
A-V	Arteriovenous
ACh	Acetyl Choline
ATP	Adenosine Tri Phosphate
a.u.	Arbitrary Units
AVA	Arteriovenous Anastomosis
CCCF	Cross Correlation Coefficient Function
CCHE	Counter Current Heat Exchange
CGRP	Calcitonin Gene-Related Peptide
Chpt	Chapter
CIVD	Cold Induced Vasodilation
CNS	Central Nervous system
C_p	Specific heat
CV	Coefficient of Variation (standard deviation divided by the mean)
DCIEM	Defence and Civil Institute of Environmental Medicine

exp.	Experiment(s)
F	Female
FBF	Forearm blood flow
$\bar{T}_{fi}$	Mean finger skin temperature during immersion in °C
Fig.	Figure
g	Gram
HE	Heat Exchanger
HF	Heat Flux in W/m^2
HFT	Heat Flux Transducer
Hg	Mercury
HIVC	Heat Induced Vasoconstriction
i.e.	Id est (this is)
imm.	Immersion
IZF	Instituut voor Zintuigfysiologie (former name of TNO Human Factors Research Institute)
J	Joules
kg	Kilogram (10^{3}g)
kJ	Kilojoules (10^{3}J)
l	Liter
Ld	Laser Doppler flowmetry
m	Meter
M	Male
M_b	Mean body mass in kg
MCCC	Maximal Cross Correlation Coefficient

min	Minutes
mm	Millimeter (10^{-3}m)
n	Number of cases, Nerve
NKA	Neurokinin A
NO	Nitrogen oxide
NS	Non-simultaneous immersion
p	Significance level
Par	Paragraph
PC	Personal computer
PCC	Pearson Correlation Coefficient
PVC	Poly Vinyl Chloride
Q_b	Body heat content in kJ
RIF	Resistance Index of Frostbite - an index based on three hunting reaction parameters (onset time, minimal finger temperature and mean finger temperature) developed by Yoshimura and Iida (1950)
S	Simultaneous immersion
SD	Standard Deviation
SEM	Standard Error of the Mean
Sg	Strain gauge
SP	Substance P
Subj.	Subject(s)
t	Time in seconds
T	Temperature in °C
Tc	Thermocouple

Tl	Thermolinear probe
temp.	Temperature in °C
T_{es}	Esophageal temperature in °C
$\bar{T}_{fi}$	Mean finger skin temperature in °C
$\bar{T}_{h}$	Mean hand temperature in °C
T_{max}	First maximum temperature during the hunting reaction in °C
T_{min}	First minimum temperature during the hunting reaction in °C
TNO	Organisatie voor Toegepast Natuurwetenschappelijk Onderzoek (Organisation for Applied Scientific Research)
T_{re}	Rectal temperature in °C
$\bar{T}_{sk}$	Mean (body) skin temperature in °C
T_{w}	Water bath temperature in °C
$T_{x\text{-}d}$	Temperature in °C of body part x at the moment that the heat flux of the finger starts to decrease
$T_{x\text{-}i}$	Temperature in °C of body part x at the moment that the heat flux of the finger starts to increase
V_0	Volume of the water in liters
W	Watt
°C	Degrees centigrade

APPENDIX 2 - Pain and thermal comfort scales

	English	**Dutch**
	TEMPERATURE	
2	Comfortable warm	comfortabel warm
1		
0	Neutral	neutraal
-1		
-2	Comfortable cool	comfortabel koel
-3		
-4	Uncomfortable cool	oncomfortabel koel
-5		
-6	Cold	koud
-7		
-8	Very cold	zeer koud
-9		
-10	Very, very cold	zeer zeer koud
	PAIN	
1	Painless	pijnloos
2		
3	Little painful	beetje pijnlijk
4		
5	Rather painful	tamelijk pijnlijk
6		
7	Very painful	zeer pijnlijk
8		
9	Very, very painful	zeer, zeer pijnlijk
10		
11	Unbearable pain	ondraaglijke pijn

Curriculum vitae

Hein Daanen was born on July 13th 1958 in Mierlo, The Netherlands. He attended high school in Helmond, Carolus Borromeus College (VWO-B). In 1978 he went to the Free University of Amsterdam and studied Human Movement Science. He graduated in 1984. Also in 1984 he acquired a teaching degree in Medical-Biological Sciences. From 1985 to 1990 he was a research scientist at the Orthopaedic Laboratory of State University Leiden and specialised in surface electromyography. This function was combined with teaching exercise, neural and general physiology on several locations. From 1990 onwards he was a research scientist at the department of Thermal Physiology and later Work Environment of the TNO Human Factors Research Institute, where he specialized in cold physiology. In 1992 he was appointed as program manager of the workplace ergonomics group. In 1995 and 1996 he spent six months for collaborate research in cold physiology at the DCIEM in Canada with Dr. M.B. Ducharme. In 1996 he spent six months at Wright Patterson Air Force base for collaborate research in anthropometry at the CARD-lab.

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Daanen is the first author of about 25 TNO-Reports, which can be supplied on request.

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Cover: Infrared photographs of cold induced vasodilation in the fingers of the author (courtacy of Dr. M.B. Ducharme, DCIEM, Toronto). Note that CIVD starts in the finger tips and that one finger after another warms up.

Omslag: Infrarood opname van vasodilatatie in de vingers van de auteur gedurende blootstelling aan koude (met dank aan Dr. M.B. Ducharme, DCIEM, Toronto). De vaatverwijding start in de vingertoppen en achtereenvolgens worden alle vingers warm.

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