Appendix

Overview of core temperature measurement methods
A.1 ELECTRICAL RESISTANCE

The electrical resistance of a metal or semi-conductor changes with temperature. With the right calibration, both can be used to measure temperature. Most digital thermometers make use of a semi-conductor resistance, like a thermistor, which is a temperature sensor made of a heavy metal oxide. In general it is accurate, reliable and can be made very small. A disadvantage may be that the direct contact with body tissue poses the risk of inconvenience, injury and infection. Further, reliability can become lower when metal resistance increases over time, which makes frequent calibration necessary (1). An extensive report on these and other biosensors can be found in Wise (2). This chapter will list the locations at which this type of core temperature measurement has been applied.

Pulmonary artery temperature ($T_{pa}$)

As discussed previously, $T_{pa}$ is considered as a gold standard for core temperature (3-6), but only usable during specific clinical interventions.

Comparative analysis. When properly measured, pulmonary arterial temperature is per definition a reliable value for the core temperature of the trunk. Whether it is also a reliable measure for brain temperature is not clear. Camboni et al. (7) found that brain temperature better correlated with $T_{pl}$ and $T_{ty}$ than with $T_{pa}$. However, these measurements were done in hypothermic circulatory arrest during cardiac surgery.

Contraindications. Tricuspid or pulmonary valve mechanical prosthesis, tricuspid or pulmonary valve endocarditis, right heart mass (thrombus and/or tumour).

Esophageal temperature ($T_{es}$)

$T_{es}$ is a reliable alternative for $T_{pa}$. Therefore, it is frequently used as a reference temperature in scientific research (8-15). An esophageal probe is introduced through the nose, swallowed with water and placed at the required position in the thermally stable lower third of the esophagus. The optimal location is the region at the level of the 8th and 9th thoracic vertebrae. At this level, the esophagus is close to the lower border of the left atrium and the upper border of the left ventricle (16). This is sufficiently beyond the tracheal bifurcation to exclude ventilatory influence and the cold spots of the corniculate
cartilage. Mekjavic et al. (16) developed a standardized probe length (L) for esophageal measurements. Sitting height is the preferred parameter to calculate the optimal L for a subject: L = (0.479 x sitting height) – 4.44 ($r^2=0.86$).

$T_{es}$ is a reliable indicator of core temperature, which responds almost instantly to central blood temperature changes. However, insertion of the probe is often experienced as difficult and uncomfortable and can even be dangerous (nasal trauma, esophageal perforation). Some subjects have a strong rejection reflex and do not tolerate the esophageal probe. Therefore, $T_{es}$ is not suitable to use at home and regularly not preferred in clinic or laboratory. Further disadvantages are the fact that ingestion of food and drinks, as well as breathing cold air may confound the measurement and the fact that swallowing saliva causes temporary relapses that have to be filtered out (17).

**Comparative analysis.** Robinson et al. (5) report that $T_{es}$ is more accurate than $T_{ty}$, $T_{re}$, $T_{ax}$ and $T_{bl}$ over a wide range of temperatures in anesthetized patients. Lefrant et al. (4) compared several measurement sites to $T_{pa}$ as gold standard in critically ill patients. The esophagus and bladder appeared the most reliable locations, better than the rectum, axilla and inguinal region. Based on theoretical considerations and empirical results, $T_{es}$ is in the scientific world considered as a reliable gold standard for core temperature.

**Contraindications.** $T_{es}$ should not be used in case of esophageal disorders, a cold, strong gagging reflexes and when undergoing procedures on the face, airways or esophagus.

**Nasopharyngeal temperature ($T_{np}$)**

$T_{np}$ is a more superficial surrogate for $T_{es}$, in which the esophageal probe has to be placed above the palate, in contact with the mucosa. It is suited for subjects that have difficulty swallowing the esophageal probe and its proximity to the brain suggests a reliable reflection of core temperature. However, research results are scarce. Besides, measurements can be disturbed by displacement of the probe and nose bleedings.

**Oral temperature ($T_{or}$)**

In 1776, John Hunter was the first known clinician to measure body temperature with a mercury-in-glass thermometer under his patients’ tongue (1). And still it is the standard method in US hospitals and widely used in other medical settings. A sensor is placed
under the tongue in the posterior sublingual cavity, which is supposed to reflect the temperature of the lingual arteries. The mouth should be held closed for minimal 4 min (18), ISO/CD 9886 (19) even recommends 8 min at ambient temperatures between 18 and 30°C. They also recommend not to use Tor under 18°C ambient temperature.

Tor is easy to use, convenient for the subject and has a small delay of about 2 min (20; 21). However, it is difficult to measure Tor properly. Measurements can be severely affected by probe positioning, (hyper)ventilation, food, drinks and external conditions (22; 23). Face and head temperature, saliva and local infection might also confound results. Therefore it is an error prone method, which cannot be used during exercise above 35% VO₂max, eating/drinking and talking (21). Further, it is unsuited for young children and shivering subjects who may bite and break the thermometer.

Comparative analysis. Compared to Tes, negative offsets of 0.1°C (24), 0.16°C (25), 0.1-0.4°C (26) have been found, although Erickson and Kirklin (27) report a positive offset of 0.1°C. Giuliano et al. (3) compared Tor to Tpa and measured a positive offset of 0.15 ± 0.36°C. However, mostly Tor is considered to be 0.4°C below central blood temperature (21; 28). Methodological differences might explain the varying offset, but overall these studies show an acceptable agreement. So under strict conditions and when properly measured, Tor may be a useful temperature measure in a clinical setting (29).

Contraindications. Tor should not be measured in patients following oral surgery, children under five years of age, uncooperative or unconscious children and in patients receiving oxygen therapy.

Exhaled breath temperature (Tx)
Because airway temperature appears to be reflect mucosal and bronchial blood flow (30), exhaled breath was recently explored as a way to estimate core temperature (31). Tx was measured in the one-way valve of a mask and put into a linear regression model to predict Tre. During a protocol in which subjects were heated and cooled in a dynamic sequence, Tx significantly correlated with Tre and model predictions were within acceptable levels of agreement. However, temperature fluctuations during the trial were limited and the protocol was performed under controlled conditions. Therefore, the
usability of a single $T_x$ based model for individual core temperature prediction across a large temperature range and in various conditions remains to be tested.

**Tympanic temperature – direct contact ($T_{ty}$)**

The tympanum is potentially a good location for temperature measurement. It is protected from the external environment, but still easily accessible. Due to a partly common blood supply, the tympanic membrane is said to have a temperature similar to the hypothalamus, the main human thermoregulatory node (32; 33). As this suggests tympanic temperature ($T_{ty}$) is a reliable, fast responding and practical measure of core temperature, it is a regularly used parameter. $T_{ty}$ can be measured directly and indirectly. This paragraph will discuss the direct contact method, paragraph A.2.1 describes the indirect (infrared) method.

Direct $T_{ty}$ measurements can be obtained by holding a thermocouple against the tympanic membrane. If contact is maintained at the lower anterior quarter of the membrane and the sensor is insulated from outside conditions by cotton and earmuffs or rubber pads (34), a reliable measurement can be obtained. Repositioning of the sensor might be necessary during multiple measurements (14).

The major disadvantage of this method is the risk of pain or damage. Making contact between sensor and tympanum may damage the membrane. A slight touch of the inner ear canal causes severe pain because of the many pain sensors on that location. So the method is only suitable for use during research and even then not preferable because of the inconveniences. In addition, $T_{ty}$ measurement can be confounded easily by insufficient isolation of the probe (14) and slight displacement of the probe from the tympanum. Further, $T_{ty}$ itself might be affected by external conditions, which cause local cooling or warming of superficial blood vessels of the head (35-37).

**Comparative analysis.** Because of its location close to the hypothalamus, $T_{ty}$ has been thought to reflect brain temperature. However, brain temperature cannot yet be studied in healthy subjects. Some studies compared $T_{ty}$ to brain temperature and $T_{es}$ during surgery (7; 9; 33; 38; 39) but results were inconclusive, possibly due to the extraordinary measurement conditions. In addition, in any attempt to estimate brain temperature, the gradient within the brain is a factor to account for (40-42). Superficial layers may display
more ‘tympanic like’ behaviour than deeper locations and may not give a good indication about the average or deep brain temperature. So measurement location may affect research results on the agreement of $T_{ty}$ and brain temperature.

More often, studies have investigated the agreement of $T_{ty-c}$ with $T_{es}$. If properly measured in stable conditions, $T_{ty-c}$ is equal or slightly higher than $T_{es}$ at rest (8; 14; 34; 38; 43; 44). However, in studies applying manipulations like heat stress and/or face fanning $T_{ty-c}$ has been regularly reported to deviate from $T_{es}$, showing a stronger cooling or suppressed temperature increase (10; 12; 13; 40; 44-46). Again, the occurrence and extent of the deviation is inconclusive. The varying results may be caused by methodological differences in protocol, ambient conditions, measurement technique etc. But even if $T_{ty-c}$ and $T_{es}$ physiologically differ in certain conditions, it is still debatable whether this is a local tympanic phenomenon or a demonstration of selective brain cooling across (part of) the brain.

**Aural canal temperature ($T_{ac}$)**

The temperature of the external aural canal ($T_{ac}$) is a socially acceptable and occasionally used surrogate for $T_{ty}$. A small temperature sensor has to be placed against the wall of the aural canal, preferably close to the tympanum.

*Comparative analysis.* The correlation between $T_{ac}$ and core temperature is disputable (47). Daanen and Wammes (48) measured $T_{ac}$ at several locations in the ear. Even at room temperature, they measured a temperature difference of >1°C between two points that were 9 mm apart. Thus thorough insulation by cotton and earmuffs or rubber pads is required to prevent the ear canal wall and sensor from being affected by environmental conditions (49). Some promising results have been achieved with $T_{ac}$ measurement, at least in warm and stable conditions (50; 51), but individual monitoring and application in colder conditions do not seem reliable (18; 52). Chapter 4 elaborates more on this subject.

**Forehead temperature ($T_{fh}$)**

Skin temperature of the forehead is sometimes used as an estimate of brain temperature. Cutaneous liquid-crystal thermometers, thermistors or thermosensitive materials are available as measurement devices. However, simply touching the forehead
is still used as a quick assessment method as well, especially providing a rough first approximation in fever situations.

Comparative analysis. Research results indicate that $T_{fh}$ is not a very reliable method. Ikeda et al. (53) used LCD thermometers to test core-to-forehead and core-to-neck temperature differences. They concluded that core-to-forehead temperature difference was smaller than the core-to-neck difference, which frequently exceeded 1.0°C. However, the core-to-forehead temperature difference was still $>0.5°C$ during approximately 35% of the measurements. Rasch et al. (13) measured $T_{fh}$ values that deviated 1.5-3.0°C from $T_{es}$ and $T_{ty}$ in rest. During moderate exercise, the difference increased even more, because $T_{fh}$ slightly decreased. Head cooling experiments indicate that during wind or cold, $T_{fh}$ deviates enormously from core temperature (14; 15). For hypothermia $T_{nh}$ is not a suited indicator of core temperature at all. In a study of Singh et al. (54), mothers touched the forehead, abdomen and feet of their babies. Only abdomen and feet gave a good estimation of hypothermia.

Axillary temperature ($T_{ax}$)
A thermometer in the axilla theoretically gives an estimate of the temperature in the subclavian artery and thus indirectly core temperature. It is an easy and convenient method that might give some approximation in vasodilated subjects with the arm held tightly against the body. However, the subclavian artery is not a major vessel and external influences (ambient temperatures, changes in skin perfusion, sweat, hair density) are considerable. So the method is very error prone, especially in cold conditions (27; 55).

Comparative analysis. $T_{ax}$ is known to be about 1-2°C lower than other core temperatures (56) and highly variable (27; 57; 58). Several studies showed a poor sensitivity of 27-33% (59; 60). In a study on nearly 1000 small children, a false negative rate for fever of 75% at home and 27% in hospital was measured (61). Robinson et al. (5) reported that their axillary probe showed a mean difference of 1.3°C ± 1.3°C with $T_{pa}$ in anesthetized children. In comparative studies, $T_{es}$, $T_{re}$, $T_{ty}$, $T_{bl}$ and $T_{fh}$ all appeared more reliable than $T_{ax}$ (4; 5; 62). It can be concluded that $T_{ax}$ is one of the least reliable of all well-known measurement methods and should only be used as a last resort.
Rectal temperature ($T_{re}$)

The rectum is one of the most often used methods for core temperature determination, as well in hospital as in laboratories as at home. Currently, electronic devices have replaced the mercury devices on the home market, laboratories mostly use a flexible catheter. Usually a minimum insertion depth of about 8 cm is accepted. ISO/CD 9886 (19) recommends an insertion depth of >10 cm for scientific studies, as insertion depth may affect the temperature readings by 0.1-0.2°C (63).

The rectum provides a stable temperature measurement, because it consists of a large mass of deep body tissue and is not affected by environmental conditions (64-66). For some people it is an acceptable measurement, but others find it uncomfortable, dislike the concept or consider it unhygienic. For children it may be traumatic. An important issue regarding $T_{re}$ is the considerable delay time of up to 10-20 min in response to changes in central blood temperature, which makes the method unsuited for monitoring rapidly changing body temperatures (7; 65; 67). Rectal temperature has a slow response, because blood flow to the rectum is low and the mass of organs in the body cavity is large, requiring a greater amount of energy to change temperature (64; 65; 68; 69). Further, $T_{re}$ may be confounded by cold blood from vasoconstricted legs, warm blood from exercising legs, insulation by feces or heat-producing bowel organisms (55).

**Comparative analysis.** In a stable situation, $T_{re}$ has been found to be about 0.2°C higher than $T_{es}$ (25; 32) and provides a reliable indication of the thermal situation of the body. When body heat content changes rapidly, it should be recognized that $T_{re}$ can differ substantially from faster responding measures like $T_{pa}$, $T_{es}$ and $T_{ty}$ (7; 25). Proulx et al. (69) showed for example marked $T_{re}$-$T_{es}$ differences during their warming/cooling protocol. They concluded that $T_{re}$ did not provide a timely thermal status of the vital organs. This may have dangerous consequences, for example during treatment of hyper/hypothermia (65; 69). For the same reason, using $T_{re}$ as a reference for other measurement methods (70-73) may be hazardous. Hansen et al. (71) and Roth et al. (73) measured $T_{re}$ and $T_{ty}$ in heat-suffering marathon runners. They found $T_{ty}$ to be significantly lower and therefore discouraged the use of $T_{ty}$. However, the 10-20 min time delay of $T_{re}$, possibly explaining the difference, was ignored.
So in a stable situation with well controlled insertion depth, $T_{re}$ is suited as a general reference for core temperature (25). In rapidly changing thermal conditions, $T_{re}$ does not provide an appropriate indication of central blood temperature, but still reliably indicates the temperature in the thermally vulnerable abdominal cavity. This might still be valuable information.

*Contraindications.* $T_{re}$ measurement is contraindicated for the following conditions: gastrointestinal/rectal bleeding, following rectal surgery, bleeding tendency (e.g. leukemia, thrombocytopenia), prolapsed rectum, imperforate anus, severe diarrhea, local infections, immuno-compromised state, heart condition (the thermometer probe could stimulate the vagus nerve in the rectum and cause cardiac arrhythmias), severe haemorrhoids (when a thermometer would damage a haemorrhoid this could result in bleeding and pain). For children who are premature, under one year of age or have an oncology diagnosis, $T_{re}$ measurement is also contraindicated.

*Bladder temperature ($T_{bl}$)*

Urine temperature is representative of body core temperature, as urine is a filtrate of blood plasma (18). One way of measuring urine temperature is directly in the bladder. This is only possible in clinic in patients who require urinary catheters and in that case, it causes little additional discomfort. Although response time is slightly faster than $T_{re}$, there is a significant delay when body heat content fluctuates (20; 55).

*Comparative analysis.* Most studies show good agreement between $T_{bl}$ and other core temperature measures. Patient studies found differences with $T_{pa}$ of $0.03 \pm 0.23°C$ and $0.21 \pm 0.20°C$ (4; 27). They concluded that $T_{bl}$ and $T_{es}$ are more reliable for estimating core temperature in critically ill patients than $T_{re}$ and $T_{ax}$. Nimah et al. (62) also reports good correlation of $T_{bl}$ and $T_{pa}$ in their study with febrile children. Fallis (20) reviewed several studies to $T_{bl}$ measurements and states that these studies support the use of $T_{bl}$ as an index of core temperature during times of thermal stability. So it appears that under steady state conditions, $T_{bl}$ is a reliable method to measure core temperature in patients requiring a urinary catheter. Under thermally unstable conditions, other methods are preferable.
Urine temperature ($T_{ur}$)

Besides measuring inside the bladder, urine temperature can also be measured outside the body, placing a sensor with short response time directly in the flow of urine (67). The ambient temperature is recommended to be between 15 and 25°C (19). The non-contact nature of this method is an advantage, but it is has some practical limitations like the fact that it can only be used during urination. Further, just like $T_{re}$, the time constant is quite long (67). $T_{ur}$ appears to be systematically lower than $T_{re}$ by 0.2-0.5°C and is not highly reliable (18; 67). It might be used for comparative or supportive purposes, or when other methods are unacceptable (18), but is not a preferable method.

Vaginal temperature ($T_{va}$)

Vaginal temperature is an alternative for rectal temperature in females. However it is not generally acceptable and has no advantage over rectal temperature (18).

A.2 INFRARED (IR)

IR thermometry determines the temperature of an object by measuring the IR radiation from its surface. The wavelength of IR radiation corresponding to body temperatures between 36 and 40°C is 9.38-9.26 μm (15). It is a non-invasive, convenient and safe measurement technique with little delay (73). But it is a disadvantage that measurement results can be affected by the position towards the measurement surface, heating of the detector and use of a probe cover (74). Further Pusnik and Drnovsek (74) showed that many commercially available IR devices do not meet the calibration standard (ASTM, 1998 and CEN12470-5, 2003). An IR thermometer has to be calibrated at regular intervals using a black body radiator and reference thermometer.

Tympanic temperature – IR ($T_{ty-ir}$)

Next to direct contact, $T_{ty}$ can also be determined indirectly by an IR thermometer. The IR tympanic thermometer measures the IR radiation emitted by the tympanic membrane. Using IR sensors increases safety, speed and comfort of tympanic measurements. Because of the high acceptability for subjects (75) it is a very popular method for clinical and private use.
However, there is a major risk of underestimating the real $T_{ty}$ and thus incorrectly estimating core temperature. The ear canal is shaped irregularly and a measurement is easily taken too superficial or aiming in the wrong direction (25; 36). As a result, the view at the tympanum is compromised and the relative contribution of the temperature of the ear canal wall increases. External conditions affect this temperature increasingly as one gets further from the tympanum (36; 37; 48). Other blockades that affect the visibility of the tympanum, like cerumen and to a minor extent hair, may cause an underestimation as well (25).

*Comparative analysis.* The methodological issues of $T_{ty}$ measurement might well explain the fact that studies to commercial IR devices have shown very divers research results in comparison to other temperature measures, with often a high variability. Compared to a standard reference, the 95% limits of agreement (LoA) exceed in many studies ±1.0°C (3; 5; 7; 25; 27; 62; 76; 77), which is an unacceptable level (70). Daanen et al. (25) found that ear canal circumference is the most reliable parameter in explaining differences of $T_{es}$ with $T_{ty}$. Currently, $T_{ty}$-ir does not seem to be a reliable measurement method for core temperature determination (78), although it may be usable for monitoring rough changes in core temperature during exercise (72).

*Contraindications:* An infected or draining ear, a lesion/incision adjacent to the ear, otitis media or sinusitis, premature infants with a small ear canal.

**Temporal radiation temperature (T_r)**

Measuring the radiant skin temperature at the region of the superficial temporal artery is a quite recent way of determining core temperature. This major artery of the head has a constant blood flow because it lacks arteriovenous anastomoses. Further it is fast responding to temperature changes. The reliable blood flow theoretically allows for an accurate calculation of the arterial temperature, taking into account the heat losses to the environment (79). The thermometer measures the emitted IR heat and ambient temperature at the measurement site and synthesizes these into the body temperature (55).
This contact free IR measurement is simple, convenient and safe. Besides the fast response time, the costs are low and it can be used in sleeping subjects. So the method seems very suitable for measuring patients, babies and children. However, few validation trials have been carried out so far and reliability is questionable.

**Comparative analysis.** Two studies found that the temporal radiation thermometer performs well in stable periods, but does not agree to $T_{re}$ and $T_{es}$ during periods of increasing body temperature (80; 81). In a study on adults and children with mild fever, $T_{tr}$ differed $>0.5^\circ C$ in more than 89% of the measurements (82). In studies with infants only, sensitivity and specificity for detecting rectal fever $<39^\circ C$ was rather poor as well (83; 84). More recently, Rubbens (85) compared $T_{tr}$ with $T_{re}$ and $T_{ty}$ in 48 child patients at rest and found values that were $0.63 \pm 0.43$ and $0.94 \pm 0.89^\circ C$ lower respectively. The distance between $T_{tr}$ device and temporal skin may have been a cause for these large offsets. The head-thermometer distance should be 1-2 cm, because $T_{tr}$ decreased when at greater distances. Further research has to prove whether the $T_{tr}$ method with a corrected offset and a short head-thermometer distance is clinically useful for infants and/or adults.

**Infrared thermography**

IR thermography involves the composition of a thermal image of the body, reflecting emitted radiation. This is largely determined by superficial temperature and is usually applied for diagnostic purposes or neonatal monitoring (86-88). However, the method has also been used for mass screening of fever (88; 89), predicting core temperature from the thermal image of the entire face (90) or more specific the ear (91) or the inner canthus of the eye (92). The latter is supplied by the internal carotid artery, which is thought to provide a better estimation of core temperature than the external carotid which supplies most of the face. However, reliability of IR thermography for core temperature estimation is questionable (93). Chapter 3 is focused on this subject.

**Near infrared spectroscopy (NIRS)**

The spectral change of near infrared light returned from biological tissue is temperature dependent. Penetrating a few centimetres into the body, it can provide an estimation of core temperature, but in vivo research is scarce.
A.3 RADIO WAVES

Radio waves are a type of electromagnetic radiation with a frequency from about 300 GHz to 300 Hz, containing temperature dependent information. This could allow for convenient non-invasive temperature measurement. However, apart from the temperature pill, most methods are only at the initial stage of development.

**Intestinal temperature measured by a temperature pill (T\text{pill})**

The temperature in the abdominal cavity can be measured by a temperature pill, which is swallowed and passes gradually through the gastro-intestinal tract. These temperature pills contain a quartz crystal, which vibrates at a frequency relative to its surrounding temperature. The low frequency FM signal of the crystal is received outside the body (radio telemetry) and converted into a temperature value. As such, it is a convenient and wireless alternative for the traditional measurement methods, especially suitable for operational settings and/or long-term recordings.

Gastrointestinal temperature is not influenced by environmental conditions and is reported to respond slightly faster than rectal temperature (94). However, food, drinks and saliva might affect temperature measurements as long as the pill is located in the stomach. Therefore, the pill is recommended to be swallowed 6 h before the start of measurement in order to reach the intestinal tract (95). As transit time varies from eight hours to five days, the exact measurement location is unknown and there is a risk that the sensor is expelled before finishing the measurement. Further disadvantages are that the pills are quite expensive, may be difficult to swallow and its measurement might be disturbed by gastrointestinal motility and electromagnetic interference (94; 96; 97).

**Comparative analysis.** In a recent review, Byrne and Lim (94) showed that there is an acceptable level of agreement between T\text{pill} and T\text{es} (systematic bias <0.1°C and 95% LoA within ±0.4°C). The 95% LoA of T\text{pill} with T\text{re} were also acceptable, though there was a systematic bias of >0.1°C. Response time of T\text{pill} was slower than T\text{es}, but faster than T\text{re}. Byrne and Lim (94) conclude in their review that T\text{pill} is a valid index for core temperature in ambulatory field-based applications, though they state that care should be taken to
control sensor calibration and ingestion time. Chapter 5 discusses the use of \( T_{\text{pill}} \) during high intensity exercise.

**Contraindications.** \( T_{\text{pill}} \) should not be used in patients who weigh less than 36 kg, have a known or suspected obstructive disease of the GI tract, exhibit or have a history of exhibiting gag reflex impairment, have undergone GI surgery, have felinization of the esophagus, have a hypomotility disorder of the GI tract, have a cardiac pacemaker or other implanted electromedical device or might undergo magnetic resonance imaging while the sensor is still in the body.

**Magnetic resonance imagery (MRI)**

The last decade, MRI is emerging as a tool to measure deep body temperatures non-invasively. Nuclear magnetic resonance measures proton motion, which is dependent on temperature. This magnetic resonance signal can be translated into a picture of the human body by MRI. Several MRI based methods have been studied for this purpose and some of them are already being applied during thermotherapy of tumours. Recent literature indicates that some MRI based methods, particularly proton MR spectroscopy, may also be suited to determine human brain temperature (98).

A great disadvantage is the fact that MRI devices are bulky and expensive. Miniaturisation of the technique might give it potential for success in practice (67). Further, the procedure takes at least 30 min, although new techniques claim to reduce measurement time to about 3 min (99). Finally, the technique is unsuited for people with conductive implants.

**Comparative analysis.** Comparative temperature studies with MRI are scarce. Comparisons in gel phantoms resulted in acceptable deviations within 0.3°C of reference temperature (100-103). However, some exploratory papers on the measurement of brain temperatures in vivo report more variable data (101; 102; 104; 105). Repeated measurements on individual voxels showed a standard deviation of 1.2°C (102) and an average difference with \( T_{\text{re}} \) of 1.3 ± 0.4°C was found (104). A complication in these studies is that a reliable reference for brain temperature is unavailable. Currently, measurement precision may be sufficient for pathophysiological studies to brain.
disorders (102) or for monitoring long term temperature changes (105), but further improvements are required for usable absolute temperature measurements.

**Microwave radiometry**

Microwaves are radio waves with lengths of a metre to a millimetre. The microwave spectrum is temperature dependent and has been explored for temperature measurement of subcutaneous tissue and the neonatal brain (106; 107). Although the method is more practical than MRI and penetrates deeper than IR thermography, it suffers from electrical interference and a poor spatial and temporal resolution (108).

**Ultrasound**

The time and frequency spectrum of ultrasound reflection is temperature dependent and might be used for core temperature estimation. Ultrasound is cheaper and easier to measure than MRI. So far, this method has shown potential for monitoring tissue temperature change during thermotherapy (109; 110).

### A.4 HEAT FLOW

In 1973, Fox et al. (111) were the first to develop a zero heat flux (ZHF) sensor in order to conveniently measure core temperature at the skin. ZHF sensors locally insulate the skin, ensuring the particular patch of skin is warmed by the natural heat flow from the body core to the skin. When the core and skin come into thermal equilibrium, a situation of zero heat flux has been reached and core temperature can be measured at the skin.

The probe of a ZHF thermometer consists of two thermistors, of which the lower one is in contact with the skin. The thermistors are separated by a thermal insulator and a heating element is mounted on top of the probe. The heater is set to drive the heat flux between the thermistors to zero in order to eliminate heat loss from the skin. The probe has to function as an ideal insulator, since it has to prevent heat loss from the skin surface beneath the probe (112-114).

ZHF sensors are acceptable for subjects and quickly respond to temperature changes (18). They require a very good insulation of the used skin from external influence.
disadvantage is the long start-up time and the requirement of power supply. Further, it is not entirely known to what extent a ZHF sensor really reflects the core temperature beneath it and which body site is most suitable for measurements. A suitable body location has low skinfold thickness and few large veins (112). The deeper the sensor has to measure, the larger the required sensor, measurement time and power supply, which is not desirable. Typical body locations for ZHF sensors are the sternum, forehead and occipital region of the head.

Gunga et al. (70) developed an innovative heat flux device. Their ‘Double Sensor’ does not contain a heating element, which brings the heat flux down to zero. Instead, it predicts core temperature mathematically by analysing skin temperature, heat flux through the sensors and heat losses through the exterior surface. This improves the start-up time and decreases power supply.

Comparative analysis. Research on heat flux sensors is scarce, but some promising results have been achieved, especially for clinical use (70; 114-116). Compared to $T_{es}$, 95% levels of agreement of $-0.59$ to $0.36^\circ\text{C}$ have been reported during hypothermic therapy (114), while differences of $0.2 \pm 0.3^\circ\text{C}$ have been observed during gynaecological surgery (116). The Double Sensor achieved 95% limits of agreement of $-0.72$ and $+0.55^\circ\text{C}$ (115). Future research should investigate the optimal location, improve its performance under different conditions and reduce delay time. In chapter 2 ZHF measurement is discussed more extensively, including the results of newly developed sensor.

Contraindications. Wounded or inflamed skin at the measurement location.

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