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Enhanced brain protection during passive hyperthermia in humans

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Summary. Selective brain cooling during hyperthermia by emissary venous pathways from the skin of the head to the brain has been reported both in animals and humans. Heat protection of the brain extends tolerance to high deep body temperature in animals, and may be enhanced in humans if the head is cooled. In order to quantify to what extent brain protection could be obtained by face fanning, 9 non-anesthetized human volunteers were placed in ambient conditions as close as possible to those of passive therapeutic hyperthermia. Face-fanning maintained tympanic temperature 0.57° C lower than esophageal temperature, and improved comfort. External head cooling techniques enhancing physiological brain cooling can therefore be useful for the protection of the human brain during heat stress or passive therapeutic hyperthermia.

Key words: Brain cooling — Heat stress — Whole-body hyperthermia — Tympanic temperature — Thermoregulation

Introduction

During systemic hyperthermia such as heat stress or whole-body hyperthermia for the treatment of disseminated cancer (WBH) (Storm 1983; Bull 1984), danger to life occurs at a core temperature above 42° C because of the intolerance of liver and brain (Bull 1980; Ostrow et al. 1981) and excessive cardiovascular challenge (Pettigrew et al. 1974; Faithfull et al. 1984). Some of the harmfull effects (toxicity) of WBH have been found to be related to the methodology used, and may be minimized by the use of adequate induction techniques (Milligan 1984), careful patient selection (Lange et al. 1983; Gerad et al. 1984) and close cardiovascular monitoring (Bull 1980; Faithfull et al. 1984). However, many disorders are due to a direct toxicity of heat on tissues and, in this respect, the brain is the organ most susceptible to thermal damage (Hartman 1937; Malamud et al. 1946; Mehta and Baker 1970; Caputa 1980; Lind 1983; Jessen 1984; Narebski 1985). Heat-induced neurological disorders during systemic hyperthermia such as clinical seizures (Barlogie et al. 1979; Larking 1979; Gerad et al. 1984) or recurrent non-infectious fever (Barlogie et al. 1979; Bull et al. 1980; Lange et al. 1983), and lesions of the brain at intracranial temperatures above 40.5–41° C (Hartman 1937; Lind 1983) have been reported and remain a limiting factor of therapeutic WBH (Bull 1980; Noguchi et al. 1984). The CNS toxicity of hyperthermia may lead to persistant central disorders of temperature regulation (Morgan and Vonderhe 1939; Cabanac and Brinnel 1987). Recent reports on the physiopathology of heat stroke have shown that high temperature rather than dehydration seems to be its main toxic agent (Lind 1983; Khogali et al. 1983). Data from EEG analysis of patients undergoing WBH provide further evidence in favor of this hypothesis: Core temperature beyond 41.0–41.5° C gives rise to specific heat-induced EEG slow waves independently of anesthesia alone in correctly hydrated patients (Reilly et al. 1980; Dubois et al. 1980; Noguchi et al. 1984).

Selective brain-cooling during hyperthermia by blood flowing through venous pathways from the surface of the head through the bone to the intracranial space ("emissary veins" is the generic name given by anatomists to these veins) has been reported both in animals (Baker and Hayward

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1967; Magilton and Swift 1968; Baker and Chapman 1977) and humans (Caputa et al. 1978; Cabanac and Caputa 1979a; Cabanac and Brinnel 1985) (see review in Baker 1982 and in Narebski 1985). According to the thermal state of the subject, venous blood draining the skin of the face or the nasal mucosa can either enter the cavernous sinus through the angularis oculi and ophthalmic veins during hyperthermia, or bypass the cavernous sinus, flowing into the external or internal jugular veins via the facial veins during hypothermia (Caputa et al. 1978). A similar temperature-dependent reversal of blood flow occurs in the emissary veins of the mastoid and parietal bone, and probably also in the numerous diploic veins of the calvaria (Cabanac and Brinnel 1985). Inhaling air through the nose and exhaling it through the mouth lowers the tympanic temperature in exercising subjects (Hirata et al. 1978). Furthermore, counter-current thermal exchange may occur in the human neck between veins draining the head and the common and internal carotid arteries (McCaffrey et al. 1975a).

The efficacy of such vascular mechanisms can be estimated by intracranial temperature recordings. At thermal neutrality, the temperature of the mammalian brain is slightly higher than trunk temperature because of the high rate of heat production by brain cells (MCaffrey et al. 1975b; Caputa 1980; Baker 1982; Fuller and Baker 1983). During hyperthermia, the important heat exchange between hot arterial and surface-cooled venous blood within the intracranial venous spaces lowers the temperature of the brain, which falls below core temperature (Narebski 1985). The temperature gradient (ΔT) between the brain and the rest of the thermal core is thus inversed during hyperthermia (Baker 1982).

The subsequent heat protection of the brain during hyperthermia extends tolerance to high deep-body temperature in animals (Carithers and Seagrave 1976; Baker and Chapman 1977; Baker 1982) and exercise performance in humans (Shvartz 1970; Kissen et al. 1971; Williams and Shitzer 1974; Greenleaf et al. 1980). Heat tolerance may be enhanced in humans, especially during exercise, if the head is cooled (Cabanac and Caputa 1979b; Caputa and Cabanac 1980; Greenleaf et al. 1980; Brown and Williams 1982; Cabanac 1983; Hirata et al. 1987).

In this experiment, we placed healthy human volunteers under ambient conditions as close as possible to those of passive therapeutic hyperthermia, in order to explore the extent of brain protection that could be obtained by face-fanning. The extent of hyperthermia was, of course, much lower in the non-anesthetized volunteers than that achieved during therapeutic WBH.

Methods

The subjects were 9 healthy adult male volunteers (mean age ±SE: 33.7±4.5 years, weight: 70.2±1.5 kg, height: 1.76±0.01 m). Each subject underwent two sessions, one with face-faning, the other without (control). Hyperthermia was produced by heat exposure in 1×1×1 m plastic (PVC) boxes heated by hot air saturated with water vapor. Only the subject's head protruded from the box, which was airtight. Outside the box, ambient temperature was 27.5±0.2° C, humidity 48–54% (range) and natural convection 0.05 $m \cdot s^{-1}$. A centrifugal ventilator, producing a 10 $m \cdot s^{-1}$ wind on the tip of the nose and 6 $m \cdot s^{-1}$ on the cheeks and forehead, was placed 10 cm in front of the subject's head when face-fanning was being carried out. Temperatures, circulatory variables, and comfort votes were recorded every second minute. Temperatures were measured by copper-constantan thermocouples and computed by an EXACON multiunit thermometer; intracranial temperature on the tympanic membrane (T_{ty}) (Baker et al. 1972; Narebski 1985) through a hermetically-closed Perspex hearing prothesis; core temperature in the esophagus (T_{es}) at a distance of 42 cm from the nostril, and skin temperature in the box on the left forearm. Oesophageal temperature was chosen rather than rectal temperature because the latter is known to lag behind blood temperature during rapid thermal changes (Fuller and Baker 1983). The thermocouples were calibrated with a mercury thermometer to an accuracy of 0.1° C. Blood pressure and heart rate were recorded by a programmable monitor of vital parameters, model 845 XT by DINAMAP. Thermal comfort (positive values) or discomfort (negative values) were evaluated by the subjects on a magnitude estimation scale anchored at zero (indifferent). The subject left the box when discomfort became unbearable. The comfort rating of the subject's last recording was reduced to −10 and his other ratings were then computed with the same multiplication factor. Ambient temperature in the box rose to 40.5° C within 10 min and then remained between 40.5 and 41.2° C under face-fanned and control conditions (Fig. 1). There was no statistical difference in the ambient temperatures in sessions with face-fanned and controls subjects; the same held good in the box temperatures. Mean evaporative water loss, calculated from total body-weight loss throughout the sessions, was identical in both face-fanned and control series, 14.0±2.4 $g \cdot min^{-1}$. Statistical analysis was carried out with Student's *t*-test (paired when appropriate). Mean values are given with their standard error (±SE).

Results

The subjects remained in the sweating boxes for 48.2±4.5 min under face-fanned, and 27.6±2.2 min under control conditions. The two longest sessions under face-fanned conditions (54 and 78 min) were interrupted by the experimenters because the subjects started to feel cold and began shivering while their T_{es} was at 38.8 and 39.4° C. As recurrent fever after therapeutic WBH

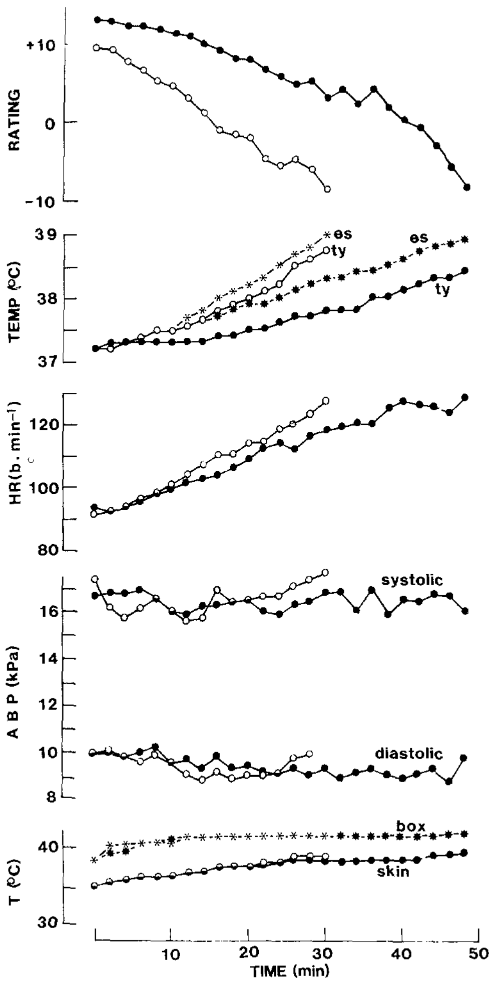

Fig. 1. Changes in the means of comfort rating, deep-body temperature, heart-rate *(HR)*, arterial blood pressure *(ABP)*, and temperatures in the box and on the skin of the subjects. Open dots and light stars, control session (up to min 30). Closed dots and heavy stars, face-fanned sessions. The number of subjects decreased from 9 at time 0 until 16 min (control), and min 30 *(fanned)*, to 7 at min 24 (control) and to 6 at min 46 *(fanned)* until the end of the sessions

(Lange et al. 1983; Gerad et al. 1984) and paradoxical resetting of the deep body temperature set-point to higher values during decompensated heat stroke have been reported (Attia et al. 1983), we were afraid of triggering heat stroke and so interrupted the session on both occasions.

Figure 1 shows the changes in mean temperature, blood pressure, heart rate and comfort ratings plotted with time, under face-fanned and control conditions. Computation for this figure was stopped when fewer than 6 subjects remained. Under both conditions, systolic and diastolic blood pressure underwent a slight decrease throughout the session, while heart rate rose. T_{es} rose steadily to 38.42 ± 0.1 °C at min 48 in face-fanned subjects and to 38.48 °C ± 0.1 °C at min 30 in controls.

The influence of face-fanning on comfort is represented in Fig. 2. This figure shows the mean comfort rating at each session and its linear regression line, plotted against T_{ty} and against T_{es}, of the face-fanned group and the controls. It shows that comfort neutrality (comfort vote = 0) was obtained with a 0.5 °C higher T_{es} in face-fan-

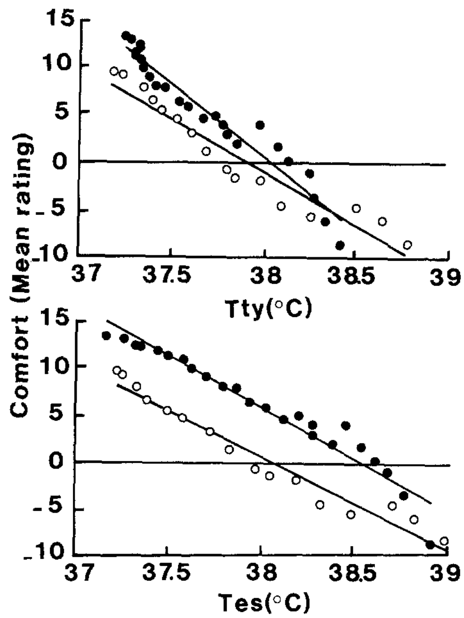

Fig. 2. Mean comfort vote plotted against tympanic temperature (T_{ty}) and oesophageal temperature (T_{es}) and their linear regression lines in face-fanned subjects (closed circles) and controls *(open circles)*

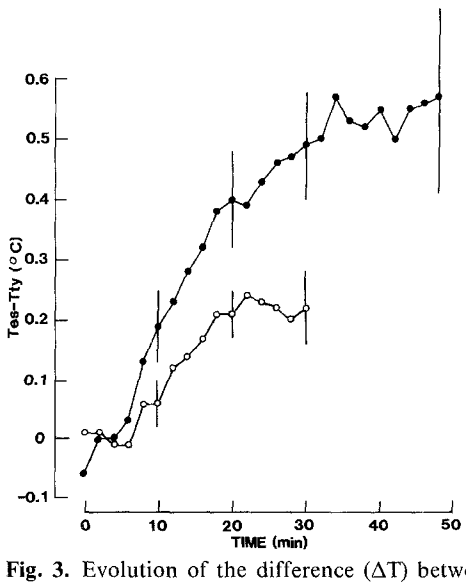

Fig. 3. Evolution of the difference (ΔT) between esophageal temperature (T_{es}) and tympanic temperature (T_{ty}). Mean difference ±S.E. in control sessions (open dots) and face-fanned sessions (closed dots). Number of subjects as in Fig. 1

ned subjects than in controls. In contract, the relationship between comfort/discomfort and T_{ty} was poorly influenced by face-fanning.

The influence of face-fanning on T_{ty} is represented in Fig. 3, which shows the evolution of the mean difference between T_{es} and $T_{ty}(\Delta T)$ under face-fanned and control conditions plotted against time. Until min 6, whether the face was fanned or not did not change ΔT. Under control conditions, from min 12 until the end of the sessions, T_{ty} was significantly lower than T_{es} and ΔT was maximal (0.23 ± 0.06 °C) at min 24 ($n=7$, $t=4.0423$, $p<0.01$). Under face-fanned conditions, ΔT was significant from min 8 until the end, and ΔT reached its maximal value (0.57 ± 0.16 °C, $n=6$, $t=3.5145$, $p<0.01$) at min 48, the last computable time. ΔT was significantly higher in face-fanned subjects than in controls from min 14 to the end ($2.0228 < t < 3.7395$, $0.001 < p < 0.05$).

Discussion

These results give further evidence and quantification of selective brain cooling during general passive hyperthermia, since the thermal gradient between body core and tympanic temperature was enhanced 2.5 times by face-fanning for nearly identical esophageal temperatures.

One main argument in favor of selective brain cooling is the lower T_{ty} recorded. Head cooling is known to lower both tympanic membrane and oral temperatures (McCaffrey et al. 1975b). This effect is unlikely to be due to direct conduction from the surface, since the external auditory canal was totally occluded by the hearing prothesis. Furthermore, local heating or cooling of different areas of the head located at various distances from the tympanic membrane had similar effects on T_{ty} (McCaffrey et al. 1975b), and hemiface cooling has been shown to lower T_{ty} on the opposite side although the latter was thermally insulated (Cabanac et al. 1987), suggesting a vascular mechanism for cooling the intracranium. Direct recordings of intracranial temperature in various species have shown similar values for tympanic and brain temperature (Rawson and Hammel 1963; Baker et al. 1972; Fuller and Baker 1983), and a study in pigs clearly demonstrated that T_{ty} remains within a narrow range (± 0.2 °C) of brain temperature during WBH (Dickson et al. 1979). Face-fanning in monkeys has shown the effectiveness of head cooling on deep cerebral regions such as the hypothalamus (Fuller and Baker 1983). In all those patients who have undergone conductive therapeutic WBH, continuous EEG recordings showed major pathological change at a core temperature of 40—41 °C and above. However during the cooling period this did not hold good. During this period EEG returned to normal even at high T_{es} (41—41.5 °C), thus suggesting that "esophageal temperature may not reflect brain temperature" (Dubois et al. 1980). In the light of the present results, WBH induction techniques, which do not heat the surface of the head by conduction, should be less dangerous for the brain during hyperthermia sessions than conductive whole-body heating. A recent study in three patients undergoind systemic therapeutic WBH with pulmonary arterial temperatures of 41.3 °C has shown a mean esophageal-tympanic temperature difference of 0.31 °C (Shiraki et al. 1986). Taking into account the higher level of core temperature and the absence of head cooling, this temperature difference is comparable to that of the present study under control conditions (0.23 ± 0.06 °C).

In the present work, the comfort votes obtained under fanned and control conditions (Fig. 2) were better correlated with T_{ty} than with T_{es}. In previous studies, head cooling has been found to increase comfort during active exercise-induced hyperthermia (Shvartz 1970; Cabanac and Caputa 1979b; Caputa and Cabanac 1980) or passive hyperthermia (Kissen et al. 1971; Williams and Shitzer 1974; Cabanac 1983; Brinnel et al. 1986) and to lower the temperature of the external auditory canal (Brown and Williams 1982) and T_{ty} (Brinnel et al. 1986). However, forehead skin temperature is reduced significantly during a session of passive heat exposure with face-fanning (Brinnel et al. 1986). It may be argued that the improved comfort during face-fanning was due to a skin input from the face (Crawshaw et al. 1975). However, the influence of cutaneous receptors from the skin of the face can be ruled out since it is already taken care of in the comfort vote, which shows a better correlation with T_{ty} (Fig. 2). Comfort incorporates all the thermal sensory inputs from the subject's body including the face, whether fanned or not.

With face-fanning, heat was tolerated for 18 minutes longer (i.e. 60%) than in the control group while T_{es} was identical at the end of both sessions. Figure 1 shows that the rise in T_{es} was delayed by face cooling. One could argue from this delay against the existence of selective brain cooling. Alternatively, this can be taken as an indication of the great cooling power of the human head only, since, of course, the blood of the head returns to the right atrium. It should be recalled that T_{es} was lower during face-fanning than in controls; in the case of T_{ty} this difference was significantly greater at any time from min 14 to the end (Fig. 3). Moreover, comfort correlated better with T_{ty} (Fig. 2). Further studies should confirm whether high-power brain cooling devices counter the systemic danger of the longer duration of therapeutic WBH. Head-cooling techniques engaging complementary emissary venous pathways are also known to reduce heat stress or to increase exercise tolerance (Shvartz 1970; Kissen et al. 1971; Williams and Shitzer 1974; Caputa et al. 1978; Cabanac and Caputa 1979a). It is likely that complementary or more powerful cooling techniques (Shvartz 1970; Kissen et al. 1971) could further enhance selective brain cooling. Cooling of the upper part of the neck and the chin, however, may be less efficacious for selective brain cooling (Cabanac et al. 1984) and act more upon T_{es} than on T_{ty}. Considering that the moderate power of the head-cooling technique of this experiment was able to reduce T_{ty} by nearly 0.6° C, one may speculate that more powerful techniques would increase this ΔT. Higher ΔT, up to 2° C, has been reported during exercise-induced hyperthermia (MacDougall 1974; Cabanac and Caputa 1979b). In addition, rectal temperatures recorded in humans after prolonged heavy exercise reached 42° C (Maron et al. 1977), which is beyond the temperature that damages the brain (Malamud et al. 1946; Mehta and Baker 1970; Lind 1983). Such a finding therefore implies strong natural selective brain cooling (Jessen 1984). In any case, a gradient of 0.6° C may already be beneficial for the protection of the brain in heat-stressed subjects or patients in whom WBH brings their temperature to the border of lethal values.

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