Head and Neck Cooling Decreases Tympanic and Skin Temperature, But Significantly Increases Blood Pressure

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Background and Purpose—Localized head and neck cooling might be suited to induce therapeutic hypothermia in acute brain injury such as stroke. Safety issues of head and neck cooling are undetermined and may include cardiovascular autonomic side effects that were identified in this study.

Methods—Ten healthy men (age 35 ± 13 years) underwent 120 minutes of combined head and neck cooling (Sovika, HVM Medical). Before and after onset of cooling, after 60 and 120 minutes, we determined rectal, tympanic, and forehead skin temperatures, RR intervals, systolic and diastolic blood pressures (BP), laser-Doppler skin blood flow at the index finger and cheek, and spectral powers of mainly sympathetic low-frequency (0.04–0.15 Hz) and parasympathetic high-frequency (0.15–0.5 Hz) RR interval oscillations and sympathetic low-frequency oscillations of BP. We compared values before and during cooling using analysis of variance with post hoc analysis; (significance, \( P < 0.05 \)).

Results—Forehead skin temperature dropped by 5.5 ± 2.2°C with cooling onset and by 12.4 ± 3.2°C after 20 minutes. Tympanic temperature decreased by 4.7 ± 0.7°C within 40 minutes, and rectal temperature by only 0.3 ± 0.3°C after 120 minutes. Systolic and diastolic BP increased immediately on cooling onset and rose by 15.3 ± 20.8 mm Hg and 16.5 ± 13.4 mm Hg \((P=0.004)\) after 120 minutes, whereas skin blood flow fell significantly during cooling. RR intervals and parasympathetic RR interval high-frequency powers increased with cooling onset and were significantly higher after 60 and 120 minutes than they were before cooling.

Conclusions—Head and neck cooling prominently reduced tympanic temperature and thus might also induce intracerebral hypothermia; however, it did not significantly lower body core temperature. Profound skin temperature decrease induced sympathetically mediated peripheral vasoconstriction and prominent BP increases that are not offset by simultaneous parasympathetic heart rate slowing. Prominent peripheral vasoconstriction and BP increase must be considered as possibly harmful during head and neck cooling. (\textit{Stroke}. 2012;43:2142-2148.)

Key Words: head cooling ■ hypothermia ■ sympathetic activation ■ blood pressure increase ■ peripheral vasoconstriction

Therapeutic hypothermia is neuroprotective after cardiac arrest or hypoxic ischemic encephalopathy, and after traumatic brain injury, and seems to be promising in acute stroke treatment. Ongoing clinical phase 3 trials such as EuroHYP-1 and ICTUS 2/3 evaluate therapeutic benefits of hypothermia for acute ischemic stroke.

Even mild hypothermia might be beneficial, but neuroprotective effects most likely depend on early induction of hypothermia. Induction by endovascular or surface-cooling devices is complex, invasive, and often requires sedation and an intensive care setting. In contrast, localized head and neck cooling is an easily applicable method that might be suited for immediate hypothermia induction already in the prehospital setting. However, hypothermia also influences the autonomic nervous system. Even local cold stimulation, eg, by immersion of a limb into ice water—known as the cold pressor test—activates sympathetic cardiac and peripheral vasomotor outflow and may increase heart rate (HR) and blood pressure (BP); whereas, cold stimulation of the facial area—known as the cold face test—induces cardiovascular outflow with HR slowing and peripheral sympathetic activation with vasoconstriction and BP increase.

Kallmünzer et al recently showed that local head and neck cooling may slightly reduce body core temperature. Therefore, the method might be suited for noninvasive hypothermia induction. However, cardiovascular autonomic effects of

Received January 30, 2012; accepted April 26, 2012.
Costantino Iadecola, MD, was the Guest Editor for this article.
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Costantino Iadecola, MD, was the Guest Editor for this paper.
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\textit{Stroke} is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.112.652248

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localized head and neck cooling are still unknown and might be similar to effects of cold pressor or cold face testing with changes in BP and HR that might limit benefits of cooling.

In this study, we therefore evaluated changes of cardiovascular parameters and autonomic modulation during local head cooling.

Patients and Methods

Ten healthy men (mean age, 35 ± 13 years) with a mean body weight of 78.4 ± 12.0 kg and a mean body mass index of 24.2 ± 3.2 kg/m² participated in the study. None of the participants had any known disease or was taking medication known to affect the cardiovascular or autonomic system. Before testing, all participants refrained from nicotine, caffeine, or alcohol for at least 18 hours. The Institutional Ethics Committee of the University of Erlangen-Nuremberg had approved the study, and written informed consent had been obtained from all study participants according to the Declaration of Helsinki.

Measurement of RR Intervals, Blood Pressure, Respiration, Skin Blood Flow and Temperatures

We continuously recorded electrocardiographic RR intervals (RRI) using a standard 3-lead electrocardiogram, and noninvasively monitored beat-to-beat systolic (BPsys) and diastolic blood pressures (BPDia) by means of radial artery applanation-tonometry at the wrist (Colin Pilot, Colin Medical), with oscillometric BP calibration at the brachial artery.10

We recorded respiratory frequency using calibrated 2-belt chest-abdomen inductance plethysmography (Respitrace, Ambulatory Monitoring, Inc) with 1 belt at the level of maximal thoracic and abdomen inductance plethysmography (Respitrace Calibrator, Ambulatory Monitoring, Inc). Temperature was measured continuously with 1 skin probe at-
Results

Data are presented as Mean±SD. Perception of frostiness (Figure 1) significantly increased from baseline visual analog scale scores of 0.1±0.3, to highest visual analog scale scores immediately after onset of cooling (3.4±1.6; *P*=0.005). After 20 minutes cooling, perception of frostiness constantly improved until the end of cooling (2.1±1.7 after 60 minutes; 1.6±1.8 after 120 minutes). Three participants rated their maximum frostiness at a score of 5, and 2 participants even rated their maximum frostiness at 6.

Perception of discomfort (Figure 1) also increased significantly during cooling, from baseline visual analog scale scores of 0.3±0.7 to scores of 1.9±1.4 immediately after cooling onset, similar scores after 60 minutes cooling (1.9±1.9), and highest scores after 120 minutes cooling (2.2±1.8; *P*=0.018). Two participants rated their maximum discomfort at a score of 4, 1 participant rated his maximum discomfort at 5, and 1 participant rated his maximum discomfort at 6.

Head cooling significantly decreased forehead skin, tympanic, and rectal temperatures (Figure 1). Forehead skin temperature decreased from 37.3±0.3°C at baseline to 31.8±2.4°C immediately after cooling onset, and to lowest values of 24.9±3.2°C (*P*<0.001) after 20 minutes cooling; then, forehead skin temperature slowly increased again until the cooling device was removed (28.5±3.5°C after 60 minutes, 34.1±2.4°C after 120 minutes).

Tympanic temperature decreased from 36.6±0.7°C at baseline to 34.9±1.2°C immediately after cooling onset, to lowest values of 31.8±1.2°C after 40 minutes cooling (*P*<0.001), and then slowly increased again until the end of cooling (32.1±1.1°C after 60 minutes, 33.3±1.0°C after 120 minutes).

Rectal temperature slowly decreased from 36.7±0.4°C at baseline to 36.5±0.3°C after 60 minutes, and to 36.4±0.3°C after 120 minutes (*P*=0.021) of head cooling.

HR slowed significantly during head cooling, measured as RRI increase from 983.4±192.0 ms at baseline, to 1006.5±178.0 ms on cooling onset (*P*<0.05), and to highest RRIs (1101.5±231.2 ms; *P*=0.005) after 60 minutes cooling. Then, RRIs slightly decreased again to 1099.3±215.5 ms after 120 minutes, values that were still higher than at baseline (*P*=0.011; Figure 2; Table).

BPsys increased steadily during head cooling, from 116.8±7.0 mm Hg at baseline to 123.0±9.0 mm Hg after cooling onset, to 125.9±9.1 mm Hg after 60 minutes and 132.1±16.5 mm Hg after 120 minutes. However, differences compared with baseline values were not significant (*P*>0.05; Figure 2; Table).

BPdia increased steadily and significantly from 64.8±5.0 mm Hg at baseline to 69.3±7.0 mm Hg after cooling onset, to 72.9±6.0 mm Hg after 60 minutes, and to maximum values of 81.3±13.7 mm Hg after 120 minutes of cooling (*P*=0.004; Figure 2; Table).

SBF decreased significantly during cold stimulation, with SBF at the right index finger decreasing from 189.7±84.9 PU at baseline to 94.8±45.2 PU immediately after cooling onset, and to a minimum of 33.8±20.8 PU after 60 minutes cooling (*P*=0.001). Then, index finger SBF slightly increased again to 35.3±30.2 PU after 120 minutes (Table).

SBF at the left cheek decreased from 77.5±46.0 PU at baseline to 55.8±31.9 PU after cooling onset, to 37.3±24.2 PU after 60 minutes, and reached a minimum value of 34.2±22.5 PU after 120 minutes cooling (*P*=0.013; Table).

Respiratory frequency remained unchanged during head cooling (*P*<0.05). Parasympathetically mediated RRI-HF powers increased immediately after cooling onset from 464.9±289.1 ms² at baseline to 1446.3±1019.6 ms² (*P*=0.014). RRI-HF powers after 60 minutes (1271.6±1071.9 ms²) and after 120 minutes cooling (1230.2±1644.9 ms²) were still significantly higher than at baseline, but no longer as high as after cooling onset (Figure 2; Table).

RRI-LF powers, RRI-LF/HF ratios, and spectral powers of BPsys and BPdia did not change significantly during cold stimulation (*P*>0.05; Table).
Discussion

In all our participants, head and neck cooling significantly decreased forehead skin, tympanic, and to some extent, even rectal temperatures.

Although mean scores of frostiness and discomfort did not exceed 3.4 and 2.2 on the 0 to 10 scales, 5 of the 10 participants indicated their maximum frostiness at 5 and 6, and 40% scored their maximum discomfort between 4 and 6. These rather high values most likely contributed to the sympathetic activation and BP increase during head and neck cooling given that stimuli perceived as noxious, cold, or painful cause A-δ- and C-nerve-fiber activation and elicit cold pressor responses with surges in sympathetic outflow.

Despite frostiness, head and neck cooling had a rather slow and limited effect on rectal temperature, with a decrease from 36.7±0.4°C at baseline to only 36.5±0.3°C after 60 minutes and 36.4±0.3°C after 120 minutes.

In individual participants, rectal temperature decreased by more than the average 0.3°C after 120 minutes cooling and even dropped by 0.6°C, showing that there is some effect of local head and neck cooling on body core temperature. Yet, the effect still seems rather small.

Using the same head and neck cooling device in 10 healthy volunteers, Kallmünzer et al observed a maximum decrease in rectal temperature by 0.65°C after 60 minutes cooling. The more prominent effect on body core temperature might be caused by the fact that the authors included 4 women in their study. Although their and our participants had similar body weight, body mass index, and ages, body mass index very likely differed between women and men of the group reported by Kallmünzer et al; this might have accounted for a more prominent effect of head and neck cooling in individual, slender participants.

Although head and neck cooling has some effect on body core temperature, this effect might vary with the body stature and composition; therefore, this still needs to be validated in a large cohort comprising participants with a wide range in age, weight, and body mass index before effects of local head and neck cooling on body-core temperature can be determined to be clinically efficient.
In contrast to rectal temperature, tympanic temperature rapidly decreased from 36.6±0.7°C at baseline to 34.9±1.2°C immediately after cooling onset, and dropped further to 31.8±1.2°C within 40 minutes of cooling.

The therapeutic goal of head cooling is a significant decrease in intracranial temperature.\textsuperscript{5,19} Unfortunately, we were limited to monitoring tympanic temperature instead of the actual intracerebral temperature, as we had to avoid invasive procedures in our volunteers. Therefore, we could not assess temperatures more closely related to actual brain temperatures. Measurement of intraventricular temperature via external ventricular drains may be an option in intensive care unit patients to assess closer correlations with intracerebral temperatures; however, we first had to evaluate cardiovascular effects of head and neck cooling in young, healthy volunteers before considering the method in intensive care unit patients. As most of our volunteers also rejected the placement of an internal jugular vein catheter, we could not measure the temperature of blood returning from the brain, which could be a better parameter of brain-cooling effects than would the decrease in tympanic temperature.

Thus, we cannot rule out that the decrease in tympanic temperature was largely because of local effects on superficial tissue cooling and cooling of blood in the external carotid artery. However, we assume that the decrease in tympanic temperature of more than 4.5°C, ie, from 36.6±0.7°C at baseline to 31.8±1.2°C after 40 minutes, also induced thermal conduction through the skull and cerebrospinal fluid into brain tissue, and thus it had some intracerebral cooling effect. Thoresen et al applied selective head cooling to newborn piglets and were able to lower brain temperatures more effectively than rectal temperatures.\textsuperscript{20} Haaland et al induced hypothermia also in newborn piglets and showed closer correlations of cooling-induced intracerebral temperature decreases with tympanic than with rectal temperature decreases.\textsuperscript{21} However, the findings in newborn piglets do not necessarily imply similarly close correlations between tympanic and cerebral temperatures in human adults; this is because thermal convection differs significantly between the small animals and our adult humans because of different surface-area-to-mass ratios.

Thus, we can only assume that head and neck cooling not only effectively reduces tympanic temperature, but might also lower intracranial temperature. Yet, only more invasive measurements will verify the actual extent of head-and-neck-cooling-induced intracerebral hypothermia.

Forehead skin temperature decreased more quickly and more prominently than did the tympanic temperature. The cooling of skin temperature by, on average, as much as 5.5°C more prominently than did the tympanic temperature. The therapeutic goal of head cooling is a significant decrease in intracranial temperature.\textsuperscript{5,19} Unfortunately, we were limited to monitoring tympanic temperature instead of the actual intracerebral temperature, as we had to avoid invasive procedures in our volunteers. Therefore, we could not assess temperatures more closely related to actual brain temperatures. Measurement of intraventricular temperature via external ventricular drains may be an option in intensive care unit patients to assess closer correlations with intracerebral temperatures; however, we first had to evaluate cardiovascular effects of head and neck cooling in young, healthy volunteers before considering the method in intensive care unit patients. As most of our volunteers also rejected the placement of an internal jugular vein catheter, we could not measure the temperature of blood returning from the brain, which could be a better parameter of brain-cooling effects than would the decrease in tympanic temperature.

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The onset of head cooling resulted in a rapid reduction of superficial SBF, ie, peripheral vasoconstriction, and in an increase in BP, particularly BPD\textsubscript{ia}; whereas HR slowed, ie, RRI\textsubscript{s} increased, because of the activation of parasympathetically mediated HF powers of RRI modulation immediately on and during head cooling.

For all parameters, cooling-induced changes became more prominent during the first 60 minutes and even longer for cheek SBF and for systolic and diastolic BP until the end of cold stimulation, when discomfort also was highest. Cardiovascular changes are similar to those observed during the cold face test that increases BP because of augmented peripheral sympathetic vasomotor tone and lowers HR via enhanced parasympathetic outflow.\textsuperscript{9,11,16}

In contrast to our young and healthy study participants, the sympathetic responses with vasoconstriction and BP increase
are very likely even more prominent in most stroke patients who are usually older than are our volunteers. In older persons, and particularly in patients after stroke, autonomic modulation is shifted toward more prominent sympathetic and less parasympathetic activity.22–25 Thus, we assume that head and neck cooling in older persons, and particularly in stroke patients, might result in at least similar, but most likely more pronounced, peripheral vasoconstriction and BP elevation than in our healthy participants. In contrast, limited cardiovascular modulation of stroke patients23–25 most likely yields less cardiovagal activation with head cooling, and thus less buffering of HR than was observed in our young participants. Consequently, head and neck cooling might further more disadvantageous cardiovascular effects in older persons and after stroke than in our participants.

The cooling-induced cardiovagal activation with slowing of HR may have beneficial effects in patients with cerebral lesions caused by stroke, traumatic brain injury, or epilepsy, ie, in patients with the abovementioned shifts of autonomic balance toward predominant sympathetic outflow.23,25–28 This increase in cardiovagal outflow with subsequent HR slowing may be mediated by direct, cold-induced stimulation of the trigeminal brain stem reflex and of parasympathetic efferent pathways, as described with cold face stimulation;16,17 or, it might be secondary to the cold-evoked increase in sympathetic activity and BP elevation,16 ie, to baroreflex activation.

On cooling onset, BPsys increased immediately and prominently, by an average of 6.2±10.5 mm Hg, and continued to rise to values that were more than 15 mm Hg higher after 120 minutes cooling than at baseline. Because of high interindividual differences, the increase was not statistically significant. Yet, the high SD indicates an even more pronounced sympathetic vasoconstriction and BP elevation in individual participants; this implies a risk of harmful cardiovascular and cerebrovascular side effects of head cooling. Very likely, the concomitant parasympathetic activation and HR slowing prevented the rise of BPsys to even higher values.29

Similar to BPsys, BPdia also increased immediately, and significantly, by an average of 4.5±5.9 mm Hg on cooling onset, and continued to rise to values that were 8.1±7.2 mm Hg and 16.5±13.4 mm Hg higher after 60 and 120 minutes cooling, respectively, than at baseline. The prominent rise in diastolic pressure reflects an increase in peripheral resistance29 caused by peripheral vasoconstriction. Evidently, the rapid decrease in forehead skin temperature by more than 12°C after only 20 minutes cooling and the high level of frostiness trigger a strong sympathetic response,16,17 with drop in peripheral SBF and critical increase in BPs.

Particularly in acute stroke patients, potential benefits of head-and-neck-cooling-induced cerebral hypothermia, which still need to be proven by more direct measures of intracranial temperature, may be offset by such prominent increases in systolic and diastolic BPs.

There is evidence that acute hypertension increases the risk and severity of hemorrhagic transformation in acute stroke.30 In rabbits with experimental ischemic stroke, Bowes et al showed that acute hypertension is associated with an increased risk and severity of hemorrhagic transformation.30 In a follow-up study, Fagan et al showed that acute hypertension is not only a marker related to increased risk of hemorrhagic transformation, but is causative for hemorrhagic transformations.31 In 793 acute ischemic stroke patients of the ECASS-II trial, Yong and Kaste demonstrated that increased variation in BP profiles, including the within-patient BPsys maximum, is associated with an increased hazard ratio of parenchymal hemorrhages.32 The relevance of BPdia elevation, which was particularly prominent in our participants with head and neck cooling, is underlined by the findings of Ko et al.33 The authors monitored BP variability in 792 acute ischemic stroke patients during the first 72 hours after hospital admission and showed that increased variability, particularly of BPdia, is associated with the development of hemorrhagic transformation.33

As mentioned above, older persons,22 and especially acute stroke patients, show even more pronounced sympathetic responses to activating stimuli.23–25,28 Therefore, head and neck cooling might not be indicated in stroke patients unless there is stringent pharmacological BP control or buffering of sympathetic stimulation by pain-relieving and sedating medication. Yet, sedating medication negatively reduces the ability to judge the patient’s clinical status and to monitor any disease deterioration.

Moreover, the significant vasoconstriction with a decrease in cheek SBF by 21.5%±39.0% and in finger-pulp SBF by 43.3%±29.8% on cooling onset may compromise or delay the attempt to lower body core temperature.34 Vasoconstriction of superficial skin vessels and the subsequent decrease in SBF is a powerful defense against cooling16 and delays the decrease in core temperature by slowing temperature exchange between body core and skin surface by reducing cutaneous heat loss.34,35 Consequently, superficial skin cooling with activation of sympathetic outflow and vasoconstriction might result in a delayed induction of central hypothermia unless there is sedation or analgesia.35,36

Moreover, prominent peripheral vasoconstriction, as observed in our volunteers, lowers the ratio between blood flow velocity and arterial BP, ie, the vascular conductance; this occurs not only in superficial cutaneous, but also in deeper peripheral, as well as visceral arteries, and thus contributes importantly to the BP increases seen in our study.37 Thus, pronounced peripheral vasoconstriction may be potentially harmful in fragile patients such as acute stroke patients.35

Only patients with low baseline BP might possibly benefit from blood pooling toward the central circulation and brain caused by cold-induced increases in peripheral resistance and BP.

Summary

The prominent decrease in tympanic temperature by 4.7±0.7°C within 40 minutes suggests that head and neck cooling might also lower cerebral temperature. However, more direct measurements of intracerebral temperature are needed to confirm this assumption. In contrast, head cooling had no relevant effects on body core temperature as shown by the only marginal, 0.3±0.3°C decrease in rectal temperature despite 120 minutes cooling.
However, the pronounced decrease in forehead skin temperature by more than 12°C within 20 minutes and the significant increase in frostiness triggered prominent sympathetic responses with peripheral vasoconstriction9,16,17 and steadily increasing systolic and diastolic BPs by more than 15 mm Hg within 120 minutes head cooling. The concomitant cardiovagal activation and HR slowing could not adequately buffer the sympathetic activation. Thus, BP increased to levels that might compromise brain tissue of patients, eg, after stroke or traumatic brain injury.23,26–28,38 Perhaps, the cooling-induced BP increase might have beneficial effects in patients with critically low BP. Yet, head cooling should not be generally applied in all patients requiring hypothermia without specifically considering the individual cerebral or cardiovascular condition and the possible risks of cooling-induced arterial hypertension.

Sources of Funding
This study was partially funded by the International Brain Research Foundation, Flanders, NJ, and by the Rolf- and Hubertine-Schiffbauer-Foundation, Hof, Germany.

Disclosures
R.K. receives speaker’s fees and project funding from Zoll medical, ELAN, EMCools, and HV Filtramed. In addition, R.K. is principal investigator of the Eurohyp-1 trial and receives funding within the Schiffbauer-Foundation, Hof, Germany. R.K. receives speaker’s fees and project funding from Zoll medical, Schiffbauer-Foundation, Flanders, NJ, and by the Rolf- and Hubertine-Schiffbauer-Foundation, Hof, Germany.

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Stroke. 2012;43:2142-2148; originally published online May 24, 2012; doi: 10.1161/STROKEAHA.112.652248
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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