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Trans Nasal Evaporative Cooling in Healthy Awake Persons

Nordberg P[1], Hermansson T[1], Backman A[1], Svensson L[1], Jonsson M[1], Hollenberg J[1], Ringh M[1], Dillenbeck E[2], Forsberg S[2]

1 Department of Medicine, Karolinska Institutet, Solna, Stockholm, Sweden
2 Department of Clinical Science and Education, Karolinska Institutet, Section of Cardiology, Sodersjukhuset Stockholm, Sweden

Corresponding Author: Per Nordberg

per.nordberg@sodersjukhuset.se

Department of Cardiology, Sodersjukhuset, Sjukhusbacken 11883, Stockholm, Sweden

Tel: 4686163583
Fax: 4686165069

Abstract

Background: Experimental and clinical data indicate that mild hypothermia is neuroprotective after a period of global cerebral hypoxia-ischemia. Trans nasal evaporative cooling (RhinoChill™) is safe and effective in unconscious patients but it has never been properly tested on patients who are conscious and awake (waking patients). The aim of this study is to study if trans nasal evaporative cooling is safe, tolerable and effective in healthy, awake volunteers without providing any sedative medication.

Methods: This was a prospective, single centre study where nine healthy volunteers underwent trans nasal evaporative cooling for up to 60 minutes. Cooling began with a low flow of oxygen at a rate of 10-20 litres/min and was gradually increased to 40 litres/min. Continuous hemodynamic monitoring was performed and temperatures (forehead, tympanic, esophageal and rectal) were assessed every 10 minutes. Visual analogue scales (VAS) were used to evaluate pain and discomfort during cooling.

Results: During cooling there was a significant increase in median heart rate (70 to 81 beats /minutes, p=0.009), median systolic-(140 to 163 mmHg, p=0.001) and diastolic blood pressure (77 to 93, p=0.01) and respiratory rate (14 to 18 breaths/minute, p=0.04) as compared to before cooling.

The volunteers cooled for more than 45 minutes (n=6), experienced a significant decrease in tympanic (37.1 to 36.2, p=0.04) and forehead temperature (36.5 to 35.0, p=0.04), but not in rectal and esophageal temperatures.

All of the nine participants experienced discomfort (VAS 7/10) and pain (VAS 6/10) during cooling. In one case cooling was interrupted due to mild periorbital emphysema.

Conclusion: Trans nasal evaporative cooling in awake and healthy volunteers is safe and may be tolerable. Cooling was associated with modest but significant lowering of tympanic- and forehead temperatures. The volunteers experienced pain and discomfort, and a significant increase in heart rate, blood pressure and respiratory rate was seen.

Keywords: Trans nasal evaporative cooling, Heart rate, Blood pressure

Introduction

Hypothermia decreases the cerebral metabolic rate for oxygen by about 6-7% per 1°C reduction in core body temperature [1]. Both experimental and clinical data indicate that mild hypothermia by several different mechanisms is neuroprotective and improves outcome after a period of global cerebral hypoxia-ischemia [2,3].

Therapeutic hypothermia may improve neurologic outcome in out-of-hospital cardiac arrest patients [4-6]. However the cooling method, optimal target temperature, duration of cooling and time of induction are still uncertain.

Experimental data suggest that hypothermia is beneficial in myocardial infarction (i.e. reduced ischemic area and improved left systolic function) and in ischemic stroke (i.e. limited infarct size

and functional outcome) [7-9]. However despite some promising results from smaller trials [10] the potential benefit of clinical use of therapeutic hypothermia in acute myocardial infarction has not yet been demonstrated [11]. In acute ischemic stroke, low temperature on admission has been associated with improved outcome [12]. Hypothermia in addition to thrombolysis has shown to be safe and feasible in small studies [13], but at present there is no evidence from larger randomised controlled trials that therapeutic hypothermia is beneficial in these patients [14,15]. In general, initiating hypothermia requires a high level of care and monitoring. The patient needs to be sedated or unconscious and therefore requires airway protection. There are several methods that have been shown effective in cooling unconscious patients [16,17]. It has also been demonstrated that the temperature can be lowered to <35 ºC in waking patients when sedative drugs are given [13]. However sedation of patients with ischemic stroke may be problematic as it complicates continuous neurological assessment.

trans nasal evaporative cooling is a safe and effective cooling method after cardiac arrest when patients are unconscious [18]. The method is appealing in ischemic stroke as it is designed primarily to cool the brain and subsequently the rest of the body. However, it has never been properly tested in waking individuals, such as patients with ischemic stroke and myocardial infarction.

The aim of this study is to study if trans nasal evaporative cooling is safe, tolerable and effective in inducing hypothermia in healthy awake volunteers without giving any sedative medication.

Methods

Study setting and population

The study was performed between February 1st and March 30th, 2012. The study has ethical approval from the ethical committee in Stockholm, Sweden (registration number 2012/1594-31/4). All volunteers received oral and written information before participation in the study. The volunteers completed a written medical history and underwent medical examination prior to study start including physical status and 12-lead ECG. The study population consisted of 9 medical students and one person from the armed forces. Written informed consent was received from all volunteers.

The study was performed at the Medical Intensive Care Unit (MICU) at Sodersjukhuset, which is one of the major hospitals in Stockholm, Sweden. All necessary equipment for advanced care and resuscitation was available at the MICU.

The method of trans nasal evaporative cooling

The method of trans nasal evaporative cooling with Rhinochill™ (Benechill, USA) consists of a control unit, a nasal catheter and cooling fluid **(Figure 1)**. The control unit is electric and controls the flow of cooling liquid and oxygen. The liquid is perfluorohexane, a volatile, inert liquid. The cooling liquid is sprayed into the nasal cavity by either air or oxygen at a rate of 40 or 20 litres/min via the nasal catheter. The 10 cm long nasal catheters are inserted fully into the nostrils. The catheters have spray ports on the dorsal side to distribute the coolant in the nasal cavity. The coolant is nebulised by close contact with oxygen at the spray ports. Evaporation of the coolant absorbs heat from the tissue and rapidly cools the nasal cavity to approximately 2°C. The air or oxygen is only used as a transporter for the liquid and has no medical purpose. The air/oxygen flow may be increased from 10 litres/min to 40 litres/min. The coolant comes in 1-litre bottles that last for 30 minutes. The method has been described previously [19].

Study protocol

This prospective, non-randomized, single centre study had the following endpoints:

Efficacy

- Cool the volunteers by -1.5°C from baseline temperature (tympanic or esophageal) or
- Cool the volunteers for 60 minutes, whichever was reached first.

Safety and tolerability

- Adverse events during cooling
- To tolerate cooling for 60 minutes without sedative drugs.

The volunteers received monitoring in the following areas: non-invasive blood pressure (NIBP), oxygen saturation SaO_2, electrocardiogram (ECG), pulse rate, respiratory rate and temperature. Temperature was measured using four different methods: tympanic, esophageal, rectal and forehead thermometers. The tympanic thermometer was a Braun™ (Melsungen, Germany) thermometer. The esophageal and rectal temperatures were continuously measured via probe attached to a Philips monitoring system. The forehead temperature was measured with a crystal line™-moving line™ sensor (Sharn anaesthesia inc Florida, USA) that has previously been used to detect temperature trends [20]. The measurements were documented every tenth minute and when any special deviations were observed. If the volunteer experienced anything adverse, additional measurements were performed. The trial was monitored by at least two nurse anaesthetists and one intensive care specialist.

Visual analogue scales (VAS) were used to evaluate pain and discomfort during cooling, and volunteers were instructed to point on a scale from 0-10 where 10 indicated the worst possible pain and 0 indicated no pain at all. On the discomfort scale, 10 indicated the worst possible discomfort and 0 indicated no discomfort at all. No pharmacological treatment was used in this trial except for local anaesthetics (Lidocain spray 10 mg/ml) that were administered into the nostrils and throat before applying the nasal catheters and the esophageal temperature probe. All volunteers received intravenous lines prior to start of cooling.

Cooling began with a low flow of oxygen at a rate of 10-20 litres/min, which then was increased to 40 litres/min for a total period of 60 minutes of cooling.

After the cooling period, the volunteers were monitored until they were normothermic without any associated symptoms and could eat and drink without problems swallowing. After 1-2 weeks the volunteers were instructed to give summaries of their experiences.

Statistical analysis

Continuous variables are reported as median and ranges. Categorical variables are reported as counts and percentages.

Primary analyses for the efficacy end points (i.e. temperature change) were conducted with Pearson _2 tests for comparison of binomial proportions. Other analyses were performed with 2-group t tests or Wilcoxon signed rank sum tests for continuous variables and Pearson _2 tests for categorical variables. All probability values were 2-sided, with values less than 0.05 regarded as statistically significant. Statistical analyses were performed with IBM SPSS version 20.0.

Results

Among the ten healthy volunteers that were assessed in the previous medical examination, nine could participate in the study. The volunteer that was excluded had undergone nasal surgery due to a fracture, so the nasal catheter could not be placed at the time for the intervention. In the nine persons where cooling was initiated, five of them underwent the entire cooling period of 60 minutes.

Baseline characteristics

The volunteers had a median age of 27 years. **Table 1** shows the baseline characteristics of the 9 participating volunteers before cooling was initiated.

Parameters during cooling

During cooling there was a significant increase in mean heart rate compared to before cooling was started. It increased from 70 to 81 beats /minutes (p=0.009), **Table 2**. There was a significant increase in mean systolic (140 to 163 mmHg, p=0.001) and diastolic blood pressure (77 to 93, p=0.01) during cooling compared to before cooling started. A significant difference in respiratory rate (14 to 18 breaths/ minute, p=0.04) was also observed. The oxygen saturation was not significantly changed during cooling.

Cooling efficacy

As presented in **Table 3** and Figure 1a-d, there was a significant decrease in tympanic temperature (37.1 to 36.2, p=0.04) and forehead temperature (36.5 to 35.0, p=0.04) in the six volunteers that were cooled for more than 45 minutes. No significant changes were seen in rectal and esophageal temperatures.

Physical experience, tolerability and safety

All of the nine participants experienced some discomfort and pain during cooling **(Table 4)**. The pain experienced was somewhat less pronounced. Other registered side effects were headache, shivering, deep voice and hearing sensations.

In one volunteer cooling was interrupted by the investigators after 24 minutes due to an instance of mild periorbital emphysema. This spontaneously resolved within 12 hours without any sequel. In three persons the cooling was terminated due to discomfort.

One person had a short period of dizziness and bradycardia to 40 beats/minutes after 60 minutes of cooling. The same person had a few sequences of ventricular extrasystoles in bigeminy for less than 10 seconds. These symptoms occurred after the cooling had been stopped.

Table 1 Baseline characteristics.

Baseline characteristics prior to cooling,(n=9)	Median (range)
Age (years)	27 (23-32)
Sex, female, n (%)	5 (44)
Heart rate $^{-1}$	74 (57-100)
Blood pressure, systolic (mmHg)	126 (95-150)
Blood pressure, diastolic, mmHg	68 (45-80)
Respiratory rate^{-1}	15 (12-20)
Peripheral oxygen saturation (%)	99,9 (99-100)
Tympanic temperature (°C)	37.1 (36.7-37.5)
Esophageal temperature (°C)	37.0 (36.7-37.2)
Rectal temperature (°C)	37.2 (37,1-37.5)
Forehead temperature (°C)	36.4 (35,9-37.0)

Discussion

Hypothermia is an effective neuroprotectant, and hyperthermia in certain conditions is associated with worsening of neurological outcomes [21]. The emphasis of clinical studies has been on the potential reduction of the injuries associated with global cerebral ischemia/reperfusion response in comatose patients.

There might be other conditions-such as ischemic stroke and myocardial infarction-where mild hypothermia could perhaps be beneficial. A compelling approach would be to find a method that is easy to apply and that is accepted by waking patients without any sedation. Trans nasal evaporative cooling is a potential method to induce cooling among these patients. It cools effectively without giving the patients any volume load such as cold fluids that have proven to be unfavourable in cardiac arrest patients [22].

This study evaluates trans nasal evaporative cooling in waking patients without sedation. Our main finding was that despite discomfort the cooling was tolerated by the majority of those studied. Significant but modest temperature reductions were seen in tympanic and forehead measurements but not in rectal and esophageal temperatures.

One of the obstacles with cooling waking patients is the mechanism to resist temperature reduction, such as shivering. In other trials sedation with synthetic drugs, opioids and anxiolytics have been given to enhance cooling [23,24]. However in patients with ischemic stroke where continuous neurologic evaluation is important it is preferable to avoid sedative drugs that may hide neurological symptoms. In this study, only one person experienced intermittent shivering which might have been a limitation for lowering temperature.

The aim was to cool the healthy volunteers by -1.5°C (tympanic or esophageal) or to continue cooling for 60 minutes. None of the patients reached the temperature goal. This differs from the cooling efficacy seen in unconscious patients with trans nasal evaporative cooling where continuous cooling has shown to lower the tympanic temperature by 2.2 °C per hour and invasive

Table 2 Physiological parameters (median) during cooling among patients cooled >45 minutes, n=6.

	Baseline	Cooling	p-value
Heart rate, minute^{-1}	70	81	0,009
MMR*	57-100	65-100	
Peripheral oxygen saturation %	100	100	Ns
MMR*	99-100	97-100	
Respiratory rate, minute^{-1}	14	18	0,04
MMR*	12-20	12-20	
Systolic blood pressure, mmHg	140	163	0,001
MMR*	115-150	128-179	
Diastolic blood pressure, mmHg	77	93	0,01
MMR*	60-80	75-107	
*Minimum-maximum range			

Table 3 Median temperature change during cooling among patients cooled >45 minutes, n=6.

	Baseline	Cooling**	p-value
Tympanic temperature (°C)	37.1	36,2	0,04
MMR*	36.1-37.5	36.0-37.0	
Esophageal temperature (°C)	37.0	36.6	ns
MMR*	36.7-37.2	35.5-39.9	
Rectal temperature (°C)	37.3	36.9	ns
MMR*	37.1-37.5	36.6-37.3	
Forehead temperature	36.5	35.0	0,043
MMR*	36.0-37.0	34.5-35.3	
*Minimum-maximum range			

Table 4 Physical experience/adverse events among all patients that received cooling (n=9).

Physical experience/adverse events	Median (range)
Pain (VAS)	6(3-8)
Discomfort (VAS) Coolant not fully evaporated, n	7(6-9) 9
Headache, n	4
Deep voice/vocal changes, n	2
ECG changes*, n Periorbital emphysema	2 1
Shivering**, n	1
Hearing affection, n Dizziness, n	1 1

* One pat asymptomatic bradycardia and one patient with ventricular extrasystoles in bigeminy for <10 seconds
**Intermittent, not-continuous shivering.

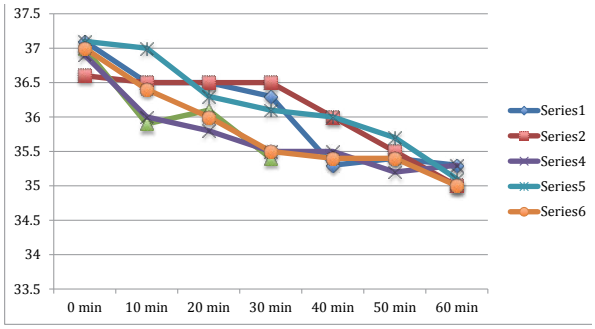

Figure 1a Forehead temperature curve for patients cooled more than 45 minutes.

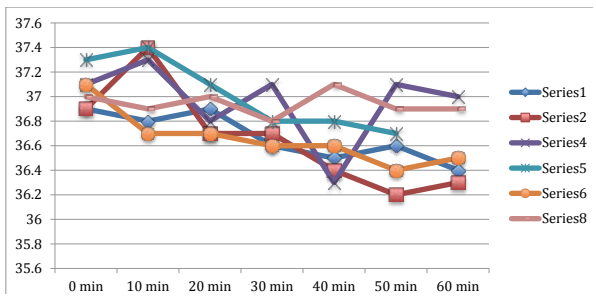

Figure 1b Tympanic temperature curve for patients cooled more than 45 minutes.

brain temperature by 1.4 °C per hour [25]. Most likely, some type of sedative agent is needed to limit the associated defence mechanisms to resist hypothermia [23].

Besides temperature reduction this study investigated the tolerability and safety of trans nasal evaporative cooling in healthy awake volunteers. Although the majority of the participants could tolerate 60 minutes of cooling, they all experienced discomfort by the method. The most obvious problems were residual liquid

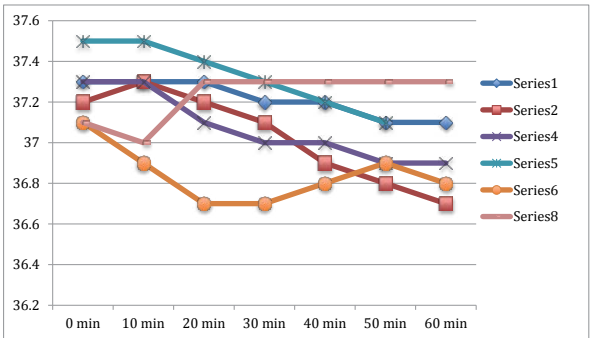

Figure 1c Rectal temperature curve for patients cooled more than 45 minutes.

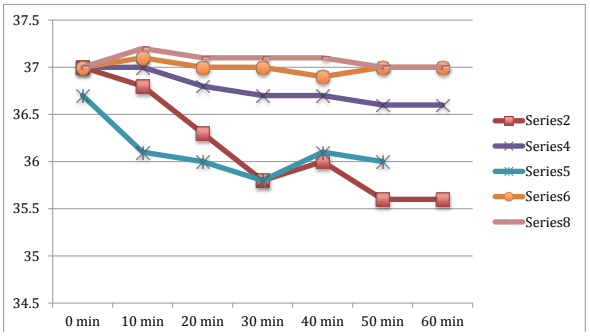

Figure 1d Esophageal temperature curve for patients cooled more than 45 minutes.

in the nasopharynx. Some experienced voice changes. Although local anaesthetics were given, the participants experienced pain to various extents. The combination of pain and discomfort was the main reason for interruption of cooling. We also believe that this combination of pain and discomfort was the main reason for the significant rise in heart rate, respiratory rate, and systolic and diastolic blood pressure. These effects could probably have negative impact on patients with acute ischemic stroke. An increase in blood pressure has also been noted in previous studies in both waking and sedated patients [26,27].

One subject of the study had a local adverse event with discrete periorbital emphysema, which resolved spontaneously within 24 hours. No further investigation regarding this finding was done. This is known as a side effect from a previous clinical study in cardiac arrest patients [18]. One person had a short period of sinus bradycardia and ventricular extrasystoles. We do not know the mechanisms behind these findings. One common side effect to trans nasal hypothermia is epistaxis, but in this study there were no cases of that.

Limitations

In this study we used healthy volunteers that may not be comparable in terms of age and co-morbidity to the target patient population with acute ischemic events.

A small number of subjects were studied.

A probable limitation to achieve temperature reduction was that subjects were not given sedatives or analgesics.

Conclusions

Trans nasal evaporative cooling in waking, healthy volunteers without sedatives is safe and may be tolerated. Cooling was associated with a modest but significant lowering of tympanic and forehead temperatures but not in rectal and esophageal temperatures. The volunteers experienced pain and discomfort and a significant increase in heart rate, blood pressure and respiratory rate was observed.

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