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Resuscitation

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Clinical paper

Effect of high flow transnasal dry air on core body temperature in intubated human subjects

Raghuram Chava[a], *Menekhem Zviman*[a], *Fabrizio R. Assis*[a], *Madhavan Srinivas Raghavan*[a], *Henry Halperin*[a], *Farhan Maqbool*[a], *Romergryko Geocadin*[b], *Alfredo Quinones-Hinojosa*[b], *Aravindan Kolandaivelu*[a], *Benjamin A. Rosen*[a], *Harikrishna Tandri*[a,*]

[a] *Division of Cardiology, The Johns Hopkins University School of Medicine, Baltimore, MD, USA*
[b] *Department of Neuroanesthesia and Department of Neurosurgery, The Johns Hopkins University School of Medicine, Baltimore, MD, USA*

Abstract

Purpose: Early initiation of hypothermia is recommended in the setting of cardiac arrest. Current hypothermia methods are invasive and expensive and not applicable in ambulatory settings. We investigated the evaporative cooling effect of high flow transnasal dry air on core esophageal temperature in human volunteers.

Methods & results: A total of 32 subjects (mean age 53.2 ± 9.3 yrs., mean weight 90 ± 17 kg) presenting for elective electrophysiological procedures were enrolled for the study. Half of the subjects were men. Following general anesthesia induction, high flow (30 LPM) medical grade ambient dry air with a relative humidity ~20% was administered through a nasal mask for 60 min. Core temperature was monitored at the distal esophagus. Half of the subjects (16/32) were subject to high flow air and the remainder served as controls. Over a 1-h period, mean esophageal temperature decreased from 36.1 ± 0.3 °C to 35.5 ± 0.1 °C in the test subjects ($p < 0.05$). No significant change in temperature was observed in the control subjects (36.3 ± 0.3 °C to 36.2 ± 0.2 °C, p = NS). No adverse events occurred.

Conclusion: Transnasal high flow dry air through the nasopharynx reduces core body temperature. This mechanism can be harnessed to induce hypothermia in patients where clinically indicated without any deleteriouseffects in a short time exposure.

Keywords: Therapeutic hypothermia, Core body temperature, Transnasal high flow air, Evaporative cooling, Neurogenic fever

Introduction

Targeted temperature management (TTM) is desirable in patients with threatened neurologic injury and in the setting of neurogenic fevers.[1–3] Reduction of core body temperature to lower than normal temperature, termed therapeutic hypothermia, is thought to prevent reperfusion injury in the setting of ischemic neurologic injuries[4,5] and in post-cardiac arrest patients.[1,2] American Heart Association recommends therapeutic hypothermia to comatose survivors of cardiac arrest as a class I recommendation.[2,4,6] Currently, several in-hospital methods and devices are available for TTM with their own advantages and disadvantages.[7–9] Surface cooling techniques are frequently used in the intensive care setting, however, carry the risk of

* Corresponding author at: Division of Cardiology, The Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA.
E-mail address: htandri1@jhmi.edu (H. Tandri).

https://doi.org/10.1016/j.resuscitation.2018.10.020
Received 2 June 2018; Received in revised form 8 October 2018; Accepted 15 October 2018

skin break down and require paralytic agents to prevent shivering response.[7] Intravascular cooling systems are expensive, require central venous access, and has a risk of infection from the access site.[10,11] A novel device that uses transnasal perfluorocarbon spray to induce evaporative cooling is currently being used in Europe for induction of hypothermia.[12] This device called "Rhinochill" induces mild hypothermia but is expensive and carries a risk of cold induced injury to the nasal turbinates.[13,14] We have previously shown that transnasal high flow dry air causes evaporation of nasal mucosal water and thereby results in selective brain cooling and core body cooling in a porcine model.[15] Human nasal turbinate is a highly evolved heat exchanger capable of heating and humidifying several hundreds of liters of inspired air per day. This process of heating and humidifying the air results in thermal energy loss to the human body.[16] High airflows are associated with an increase in nasal blood flow and mucus production to enhance humidification and water loss from the respiratory tract.[16] Over time, the energy required to evaporate that water is drawn from the person as heat energy,[5] with subsequent reduction in the core temperature. We hypothesized that this heat exchange mechanism can be exploited to induce hypothermia in volunteers.

Methods

Consecutive patients between the ages of 18–80 yrs. presenting for elective electrophysiological procedures under general anesthesia were randomly screened for this study and invited to participate. Exclusion criteria included pregnancy, deviated nasal septum, history of epistaxis, nasal surgery, currently taking oral anticoagulants, and inability to provide informed consent. A 12-lead ECG was obtained routinely prior to the procedure and patients with frequent ventricular or atrial arrhythmias noted on the ECG were excluded. The study protocol was approved by our institutional review board.

Following informed consent, a complete blood count, biochemical profile and a pregnancy test when appropriate was obtained for every patient. All patients were subject to general anesthesia with intravenous Propofol and maintenance of anesthesia with Isoflurane anesthesia. The level of anesthesia was maintained as per the anesthesiologist protocol without any significant changes during the study period. No paralytics were used for the duration of the study. Care was taken not to use blanket warmers or any other warming devices used in the operating rooms. Arterial pressure was monitored through a radial arterial line. An esophageal temperature probe ER 400 (Smith Medical, USA) was advanced through the oropharynx under fluoroscopic guidance to the gastroesophageal junction after calibration. Following this, a nasal CPAP mask was placed on the patient and comfortably secured. The patient was then draped completely to avoid cutaneous heat loss. Baseline recording of the esophageal temperature was performed for 30 min. Medical grade air from the wall air source (relative humidity $\sim$ 20% at room temperature) was delivered through the pneumatic ventilator, set to the continuous positive airway pressure (CPAP) mode (pNeuton, Airon Corp, USA). The CPAP pressure was limited to 10 cm of H2O to deliver a flow of approximately 30 LPM. This pressure was chosen for safety reasons in this pilot study of anesthetized volunteers. The mouth of the patient was kept open with a soft plastic airway to promote unidirectional airflow from nasopharynx to oral cavity. The flow was maintained for 1 h or until the core esophageal temperature was $<35.0\,^{\circ}C$, whichever was earlier. All patients were continuously monitored throughout the experiment. The ambient air temperature, inlet humidity, airflow, and outlet temperature and humidity were monitored during the test experiments. A board-certified cardiologist (ACLS certified) was available during the entire experiment. A change in esophageal temperature of $>2\,^{\circ}C$ from baseline, or a reduction of esophageal temperature to $<35.0\,^{\circ}C$ were considered as early termination endpoints. Sixteen subjects who met the inclusion/ exclusion criteria were randomly enrolled in the control arm where all study procedures were kept the same except for delivery of high flow transnasal air.

Following the completion of the 1-h study period, heating blankets were used to restore normal temperature as needed. The patients underwent electrophysiological testing per standard of care. All patients were observed overnight and had a nasal exam performed by a qualified nurse practitioner. All symptoms were recorded the following morning. Any new nasal redness, bleeding, ulceration, or discharge was recorded.

Statistical analysis

The primary outcome of this study was change in body temperature from baseline values. Data are reported as mean and SD. Safety of trans-nasal airflow was a secondary outcome. The mean baseline temperatures of the patients were compared with the mean temperature at 60 min to assess for significance. Esophageal temperature data following anesthesia and intubation from 16 consecutive patients who served as controls and underwent similar procedures was also used for secondary comparison using student *t*-test.

Results

A total of 40 subjects were screened for the protocol. Four subjects who refused consent, and 4 additional subjects with exclusion criteria (3 on anticoagulation and 1 had atrial fibrillation with rapid ventricular response) were excluded. A total of 32 patients completed the study protocol. Sixteen patients were enrolled in the study arm and 16 subjects served as controls. Controls were not subject to trans-nasal flow but underwent all other aspects of the protocol including arterial blood pressure monitoring, general anesthesia and continuous esophageal temperature monitoring. All subjects completed the study protocol and no patient had the study terminated prematurely.

For the patients who underwent trans-nasal cooling, the inlet air temperature was $21.7 \pm 1.1\,^{\circ}C$ and inlet air relative humidity was $\sim 20 \pm 6\%$. Outlet temperature and humidity could not be reliably measured in all the subjects. Difficulties in positioning the probe close to the mouth of the subject due to concerns of sterility precluded measurement in all subjects and so it was abandoned.

Mean age of the study population who underwent trans-nasal cooling was 53.2 ± 9.3 yrs. and the mean weight was 90 ± 17 kg. No significant differences were found between the study patients and the controls (51 ± 11 yrs. and 85 ± 16 kg for age and weight respectively). Of the 32 study patients, 30 patients presented for elective ablation of paroxysmal atrial fibrillation and 2 patients presented for supraventricular tachycardia ablation. All the patients were in normal sinus rhythm. Half of the study population were men. Mean arterial pressure, pulse rate and oxygen saturation remained stable during the study period for the entire group (72 ± 11 mmHg vs 68 ± 14 mmHg, 64 ± 13

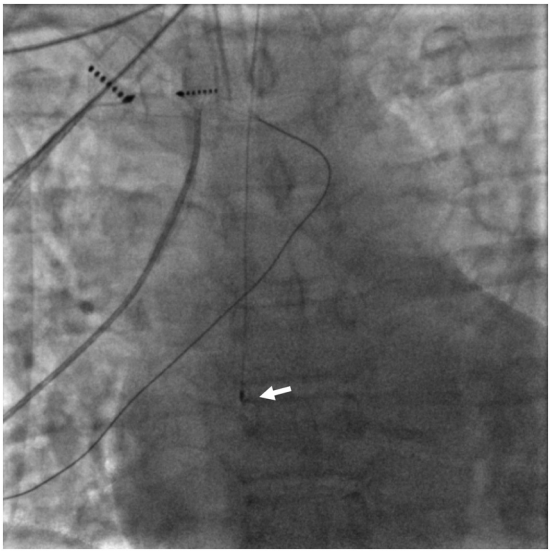

Fig. 1 – Fluoroscopic image in a volunteer showing the location of the tip of the esophageal temperature probe (white arrow).

bpm vs 70 ± 10 bpm, 98 ± 2% vs 99 ± 1% respectively, p = NS). The average delivered pressure through the CPAP was 8 cm of H2O (range 7–10 cm of H20).

Mean air flow rate for the entire study population was 33 ± 18 LPM with a median flow of 24 LPM. Nasal airflow rates remained constant at the CPAP pressure throughout the study. In 3 patients flow rates of > 40LPM was observed even at CPAP of 5–7 cm of H2O and in 5 patients even at the upper limit of pressure at 10 cm of H2O the transnasal airflow was less than 20 LPM.

Change in esophageal temperature

Esophageal temperature was recorded in all 32 patients. The location of the esophageal temperature probe is shown in Fig. 1. Mean baseline esophageal temperature was 36.1 ± 0.3 °C in study patients and 36.3 ± 0. 3 °C in controls (p = ns) and remained stable during the 30-min baseline period. The mean esophageal temperature decreased from 36.1 ± 0. 3 °C to 35.5 ± 0.1 °C ($P < 0.05$) over 60 min of exposure to dry air flow in the patient's subject to transnasal dry air (Fig. 2). No significant change in temperature was observed in the control subjects during the same 60 min of observation (36.3 ± 0. 3 °C to 36.1 ± 0.2 °C, p = NS).

Individual data for the change in temperature from baseline in all the 16 test subjects is shown in Fig. 3. Gradual decline in core esophageal temperature was observed in all test subjects. The range of change in temperature from baseline over the 60-min period was −0.2 °C to −1.0 °C in the test group. One subject (wt. 103 kg) in the test group had no change in the core temperature over 60-min period for unclear reasons (patient 5 in Fig. 3). Air flow rate in this patient was approximately 28 LPM at a CPAP pressure of 10 cm of H2O. No specific association was observed between body weight and rate of cooling.

Safety end points

No minor or major adverse events occurred during the study. All patients were observed overnight as a part of their routine clinical care after electrophysiological procedures and had no unanticipated events over the next 24 h. A thorough clinical exam was performed by a nurse practitioner prior to discharge and confirmed no apparent signs of nasopharyngeal injury. No patient had new nasal symptoms such as dryness, nasal irritation or nasal discharge.

Discussion

Unidirectional transnasal high flow dry air resulted in lowering of core body temperature in intubated human volunteers under general anesthesia. Over a 60-min exposure, at a flow of ~30 LPM which is approximately 4–5 times the minute ventilation, core temperature was reduced by 0.6 °C. We have previously demonstrated the effect of high flow transnasal dry air on brain and core vascular temperature in porcine animals. High flow dry air induced a flow dependent reduction in brain and core body temperature in porcine animals.[16] This effect was independent of air temperature and abolished by humidifying the air suggesting evaporative cooling as the main mechanism. We exploited a similar mechanism of cooling in our human subjects. Rate of cooling in porcine subjects (wt. 35 kg) was much higher (up to 0.3 °C/10 min) probably due to smaller body mass and large turbinate area to facilitate cooling, when compared to cooling in human subjects.

Induction of core cooling has therapeutic applications in neurogenic fever and in comatose survivors of cardiac arrest, and in animal models has been shown to reduce neurologic injury.[17] Anoxic encephalopathy is the consequence of ischemic neurologic damage and is associated with significant morbidity and mortality. Therapeutic hypothermia (TH) after return of spontaneous circulation through systemic cooling has been endorsed by major American and European societies, after resuscitation from cardiac arrest in an unresponsive patient, and should be initiated as soon as possible with a target temperature of 32 °C–34 °C. Nevertheless, the benefits have not yet been realized in human clinical trials. Recent randomized trials have also raised the question on depth of hypothermia needed for clinical benefit,[18,19] however, the need to lower core temperature remains and the current methods like ice-cold saline IV, ice packs, cooling blankets, and cooling helmets for TH are suboptimal. Surface cooling causes shivering and cutaneous vasoconstriction that counteracts the cooling effects. Intravascular cooling is expensive and requires expertise and as such is sparing used in tertiary centers. The novel method of temperature lowering using transnasal dry air has the advantage of being inexpensive and easy to use, thereby potentially increasing the utilization of TH.

Prior studies using the transnasal method have demonstrated brain cooling but not core cooling, because the mechanism behind cooling was not properly exploited. Einer-Jensen et al used high flow oxygen through the upper airways of 11 intubated rats and demonstrated flow dependent decrease in brain temperatures.[16] Mellegard used humidified high flow oxygen (5–10 L/min) through Foley catheter in one nostril in intubated adult patients and observed 0.2 °C drop in brain temperature measured in lateral ventricle.[20] Harris et al used bilateral nasal cannula to deliver air equivalent to minute ventilation in 15 patients and observed no change in brain parenchymal or subdural temperatures.[14] In our animal studies the major determinants of cooling were airflow rate and the air humidity.[15] In all the above studies, the flow rate was sub-optimal and the delivered air was not dehumidified and hence the physiology of evaporative cooling was not harnessed.

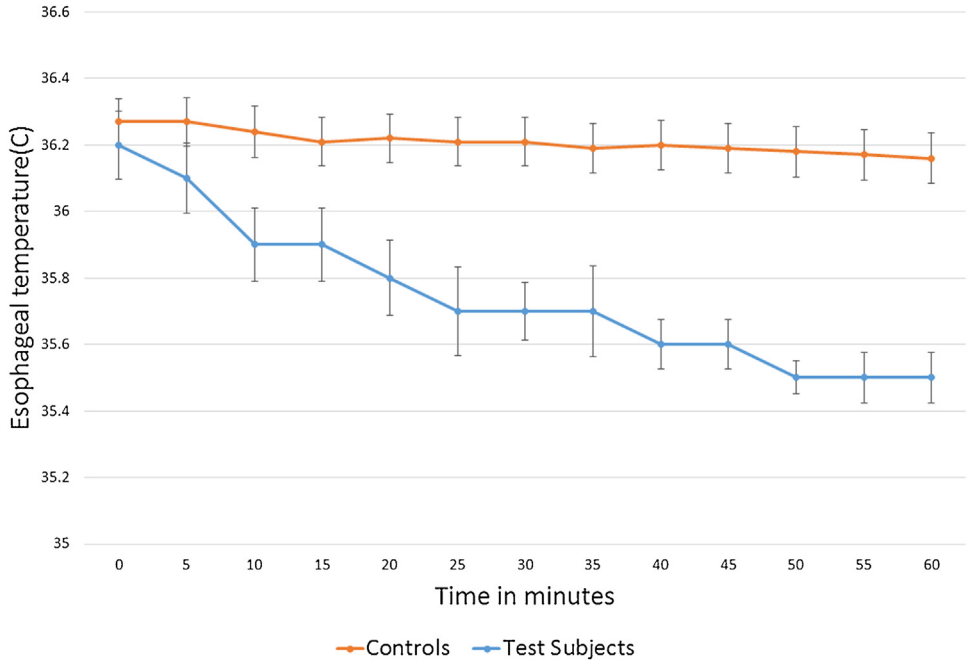

Fig. 2 – Change in core esophageal temperature in test subjects (blue line) and controls (red line) over the 60-min period is shown. Gradual and significant change in core temperature is seen in the test subjects (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

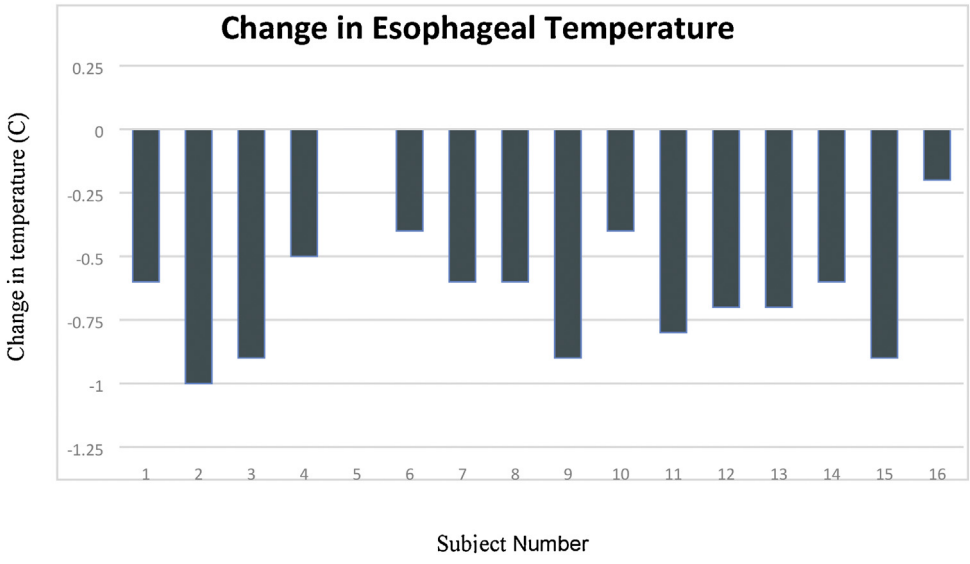

Fig. 3 – Individual change in temperature from baseline temperature is shown in all 16 study subjects. The range of temperature change was −0.2 °C to −1.0 °C with an average change of 0.6 °C in 60 min.

Transnasal evaporative cooling (TEC) using perfluorocarbon nasal spray along with high flow oxygen has been exploited by other investigators for induction of hypothermia. During the TEC process, liquid coolant along with oxygen was sprayed in to the upper airways and evaporated with the high flow oxygen.[13] In animal studies, early intra-arrest initiation on of TEC resulted in high probability of return of spontaneous circulation.[21] In PRINCE (Pre-ROSC Intranasal Cooling Effectiveness) trial TEC was initiated in cardiac arrest patients immediately following arrest before ROSC (return of spontaneous circulation).[13] Intra-arrest trans-nasal cooling improved survival by 27% (56% vs 29.4%) and chances of neurologically intact survival by 26% compared to the group who had in-hospital cooling alone.[22] Rate of cooling in our study is comparable to the rate of cooling in PRINCE[2] study (0.6 °C over 60 min), but without the perfluorocarbons.

As the benefits of systemic (whole-body) hypothermia are consolidated into clinical practice, selective brain cooling seems to emerge as a safe strategy in focal brain injury with promising results in pre-clinical and clinical studies.[23,24] Although selective cooling was not specifically addressed in this study, pre-clinical data support TEC as an effective strategy to induce preferential cerebral hypothermia.[15] Whether these results translate to human studies is yet to be determined.

Limitations

The intranasal pressure was intentionally kept low (<10 mmHg) to avoid complications in otherwise healthy participants. Adequate air flow could not be achieved in all subjects probably due to differences in airway resistance and nasopharyngeal anatomy. We were also unable to measure the humidity of the expired air in all patients. The humidity probe had to be mounted close to the patient's mouth. Sterility concerns in the operating room and cross contamination from the room air prevented accurate and reliable measurement. Core temperature decrease in humans was only 0.6 °C compared to the rate of cooling in porcine subjects (0.3 °C/10 min). This is mainly due to the relative size of the nasopharynx to the body mass which is significantly higher in porcine subjects.

One of the subjects with a very high BMI (49.6 kg/m^2) had no change in core temperature during 1-h cooling therapy. As previously described,[25] patients with a high BMI (>35 kg/m^2) tend to present a slower rate of cooling and we believe that the duration of the therapy was not long enough to reduce the core temperature in this specific case. Additionally, other possible reasons, including medication use such as anticholinergic agents which might influence mucus production, were not systematically tracked in this study.

In our study, the well-controlled environment under which the patients were evaluated (EP laboratory under general anesthesia) may not accurately reproduce the real-world post-ROSC care settings. Therefore, further assessment remains necessary to validate its clinical use in comatose cardiac arrest survivors.

Conclusion

In conclusion, we have demonstrated that high flow of air through the nasopharynx in a unidirectional fashion results in lowering of core body temperature in otherwise healthy subjects. This is devoid of any serious side effects during a short-term exposure. This mechanism can be harnessed to induce hypothermia in patients where clinically indicated.

Grant numbers and funding information

None.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Financial support

None.

Conflict of interest disclosures related to this manuscript

None.

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