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NEUROCRITICAL CARE SOCIETY

ORIGINAL WORK

Feasibility and Safety of Transnasal High Flow Air to Reduce Core Body Temperature in Febrile Neurocritical Care Patients: A Pilot Study

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Abstract

Background: Fever is an important determinant of prognosis following acute brain injury. Current non-pharmacologic techniques to reduce fever are limited and induce a shivering response. We investigated the safety and efficacy of a novel transnasal unidirectional high flow air device in reducing core body temperature in the neurocritical care unit (NCCU) setting.

Methods: This pilot study included seven consecutive patients in the NCCU who were febrile (> 37.5 °C) for > 24 h despite standard non-pharmacologic and first-line antipyretic agents. Medical grade high flow air was delivered transnasally using a standard continuous positive airway pressure machine with a positive pressure of 20 cmH_2O for 2 h. Core esophageal and tympanic temperature were continuously monitored.

Results: Mean age was 40 ± 14 yo, and 72% (5/7 patients) were men. Five patients had intracerebral or intraventricular hemorrhage, one subject had transverse myelitis, and the remaining patient had anoxic brain injury due to a cardiac arrest. After 2 h of cooling, core temperature was significantly lower than the baseline pre-cooling temperature (37.3 ± 0.5 °C vs. 38.4 ± 0.6 °C; $p < 0.002$). Mean transnasal airflow rate was 57.5 ± 6.5 liters per minute. Five of the seven subjects were normothermic at the end of the 2-h period. One subject with severe hyperthermia (39.7 °C) and the other with multiple interruptions to therapy due to technical reasons did not cool. The core temperature within 30 min of cessation of airflow increased and was similar to the pre-cooling baseline temperature (38.3 ± 0.4 °C vs. 38.4 ± 0.6 °C, p = NS). Rate of core cooling was 0.6 ± 0.15 °C per hour at this flow rate. No shivering response was observed. No protocol-related adverse events occurred.

Conclusions: High flow transnasal air in a unidirectional fashion lowers core body temperature in febrile patients in the NCCU setting. No adverse events were seen, and the process showed no signs of shivering or any other serious side effects during short-term exposure. This pilot study should inform further investigation.

Keywords: Fever, Neurocritical Care, Normothermia, Neuroprotection, Transnasal evaporative cooling

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Introduction

Fever is common in the acute stages of brain injury and is frequently encountered in patients after neurologic injury [1, 2]. Several studies have shown the detrimental effects of fever on patient outcomes in this setting, in particular for ischemic stroke, traumatic brain injury and intracranial hemorrhage patients [2–4]. Maintenance of normothermia in the neurocritical care patient population is associated with improved neurologic outcomes, including less cerebral edema [5, 6]. First-line methods include antipyretic agents, ice packs and cooling blankets [7]. Patients who continue to be febrile often need aggressive surface cooling or intravascular temperature management systems for restoring normothermia [8]. Cutaneous cooling often evokes a brisk shivering response needing anti-shivering agents and paralytics [9–11]. Intravascular cooling is associated with the risk of vascular injury and infection, both of which are undesirable in this high-risk cohort [12, 13]. We have previously shown that unidirectional high flow of transnasal dry air results in brain and core temperature reduction in a porcine model [14]. This novel noninvasive method harnesses an evaporative energy exchange process in the nasal turbinates to extract energy by evaporating nasal mucosal water. Over time, as the energy required to evaporate the water is drawn from the surface of the turbinates, this results in a progressive reduction in core body temperature. High airflows also trigger an increase in nasal blood flow, which further enhances the cooling effect. The purpose of our pilot study was to evaluate the safety and efficacy of transnasal high flow air in reducing core body temperature in febrile human subjects in the neurocritical care unit setting.

Methods

We enrolled consecutive patients in the neurocritical care unit (NCCU) who were febrile (core temperature > 37.5 °C) despite standard of care fever management which included antipyretic treatment with Tylenol® (acetaminophen) with or without a surface cooling blanket (Cincinnati Sub-Zero Products, LLC). Patients could have temporary control of fever after standard management, but could not be enrolled until 24 h from the start of fever to ensure that the standard of care was practiced and patients were enrolled only if they failed the standard of care. Patients were identified by the intensive care physician and included in the study after meeting the study criteria. The detailed inclusion and exclusion criteria are shown in Table 1. Briefly, febrile patients with an indication for normothermia and no history of facial trauma or contraindications for hypothermia were included in the study. An esophageal temperature probe (400 Series, Smiths Medical, OH, USA) was placed by an experienced intensive care physician to monitor the core temperature. The position of the esophageal temperature probe was determined to be appropriate by visual inspection of the oropharynx to avoid coiling of the probe. Informed consent was obtained from all patients or their legal representative prior to enrollment in the study. All patients had a detailed physical examination prior to inclusion in the study. Prior to the study, an experienced ear, nose and throat (ENT) physician examined all patients for possible nasal trauma or anatomic abnormalities of the nasal tract, including deviated nasal septum. All study procedures were approved by the university institutional review board.

Table 1 Study inclusion/exclusion criteria

Inclusion criteria	Exclusion criteria
Admitted to NCCU	Skull base or facial fracture
Core temperature > 37.5 °C for > 24 h despite antipyretic agents	Deviated nasal septum
Age between 18 and 80 years	Cryoglobulinemia
	Sickle cell disease
	Serum cold agglutinins
	Coagulopathy or on anticoagulation therapy
	Pregnant
	Participating in another clinical study

NCCU neurocritical care unit

Experimental Procedures

The sequence of study procedures is shown in Fig. 1. No antipyretics or surface cooling was allowed during the study period. Patients received their last dose of acetaminophen 4 h or more prior to onset of the study. Prior to commencement of the nasal airflow, a tympanic temperature probe (400 Series, Smiths Medical, OH, USA) was placed in one ear and a commercial continuous positive airway pressure (CPAP) nasal mask was applied and fitted securely to avoid any air leaks. Medical grade wall air was delivered through a pneumatic CPAP machine (Airon, pNeuton, FL, USA) through the nasal mask to maintain an airflow of ~ 50 to 60 liters per minute (LPM). Airflow rate was recorded using an inline air flow meter (Omega Medical, NY, USA) in series with the setup. The positive airway pressure was kept below 20 cmH_2O to avoid excessive pressure in the nasopharynx. With the airflow turned off, baseline recordings of the vital data and esophageal and tympanic temperature were performed for 30-min temperature. After the baseline data collection was complete, medical grade air was delivered at ambient room temperature through the pneumatic CPAP machine via the nasal mask. Airflow was gradually increased by increasing the CPAP pressure in increments

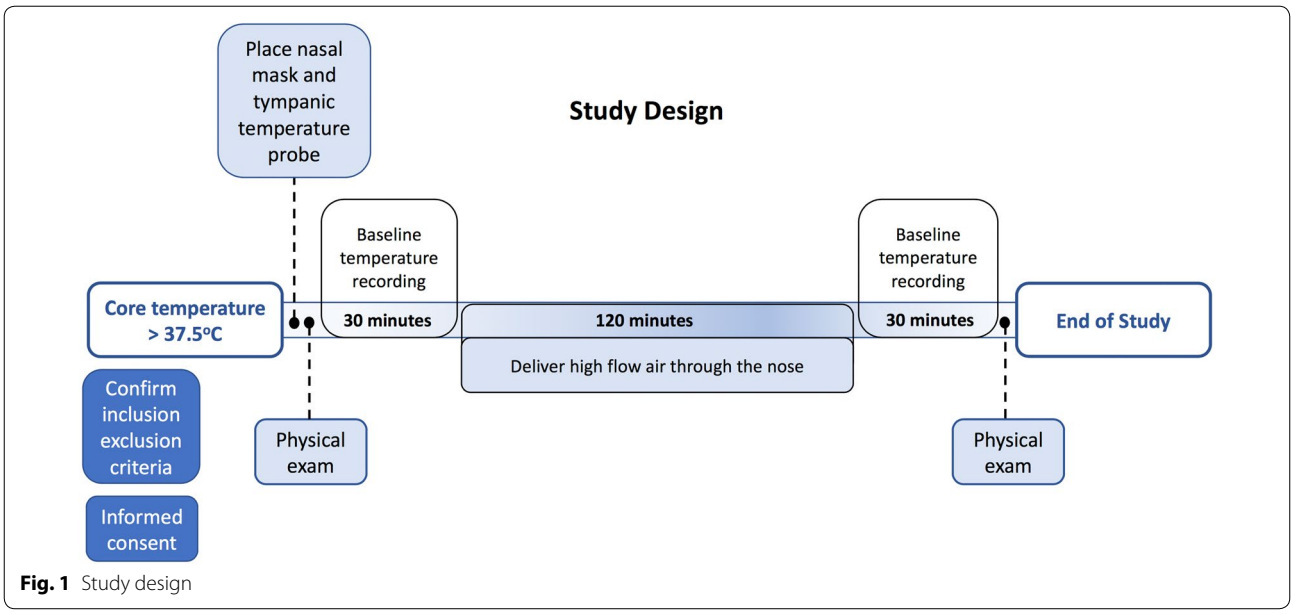

Fig. 1 Study design

of 5 cmH_2O every 5 min, up to a maximum of 20 cmH_2O or to a flow of 60 LPM, whichever came first. The intervention was continued for 2 h or until the core temperature was less than 36.5 °C, whichever came first. At this point, the airflow through the pneumatic CPAP machine was discontinued and 30 min of follow-up monitoring was conducted (while the nasal mask remained in place). At the end of the monitoring period, the tympanic temperature probe and the nasal mask were removed. All study patients were then examined by an ENT physician after the completion of the study. The exam included a detailed anterior nasal and oropharyngeal examination to determine the presence of any new findings or adverse events related to the air flow. The same ENT that performed the initial examination (pre-cooling) also performed the post-cooling examination.

In addition to the core and tympanic temperatures, all patients had continuous hemodynamic monitoring with arterial blood pressure and oxygen saturation data throughout the study. Shivering was monitored visually and scored using a Bedside Shivering Assessment every 10 min. Scale (0—no shivering, 1—mild localized shivering of the neck/thorax, 2—moderate shivering of neck and thorax, 3—severe generalized shivering) [11]. Patients were closely monitored for 24 h after the completion of the study for any adverse events. Study-related adverse events were defined as any unanticipated event during the study period. Continuous electrocardiogram, blood pressure and oxygen saturation were monitored according to NCCU protocol. Patients were examined every 10 min for nasal or oral bleeding, shivering and any skin discoloration due to the mask itself. A data safety monitoring board (DSMB) comprising of three senior physicians who were not involved with the study monitored the study procedures and outcomes. It was acknowledged that any unanticipated or adverse events occurring during the study and up to 24 h after study completion would be considered as study-related adverse events unless adjudicated otherwise by the DSMB.

Study Statistics

The primary outcome of this study was to assess the feasibility of using high flow of ambient air transnasally in a unidirectional fashion (in the nose and out of the mouth) to lower the core and tympanic temperatures from baseline values down to < 37.5 °C over a 2-h time period. A secondary outcome was to assess the safety of the transnasal airflow in this patient population. Data are represented as mean ± SD. Each subject acted as his/her own control. Data were analyzed using paired Student t tests. A p value of < 0.05 was considered significant.

Results

Baseline characteristics of the study population are shown in Table 2. Nine patients were enrolled in the study, but only seven completed the protocol and were included in the final analyses. The family of one subject withdrew consent after initial consent and enrollment, but before the cooling protocol was initiated; a second subject could not start the study protocol due to technical difficulties with the esophageal temperature probe placement. Of the seven patients who completed the protocol, the mean age was 40 ± 14 yo and 72% (5/7 patients) were men. Mean body mass index was 29 ± 0.6 kg/m^2 (range

Table 2 Baseline characteristics and temperatures before, during and after therapy

Patient	Age	Sex	Weight (kg)	BMI (kg/m^2)	Underlying neurologic condition	Temperature (°C)											
						Baseline		*T*-30 min		*T*-60 min		*T*-90 min		*T*-120 min		*T*-150 min (after therapy)	
						Tymp	Core	Tymp	Core	Tymp	Core	Tymp	Core	Tymp	Core	Tymp	Core
1	27	M	82.7	28	Transverse myelitis	36.4	38.2	36.1	37.9	35.8	37.8	35.4	37.6	35.4	37.5	36.3	38.0
2	29	M	70	22.2	Intracerebral bleeding	37.5	39.7	37.4	38.5	37.4	38.5	37.4	38	37.4	37.9	37.5	39.1
3	29	M	70	22.2	Intracerebral bleeding	36.5	38.3	36.2	38.0	35.8	37.4	35.9	36.6	35.9	37.5	35.6	38.1
4	41	M	105	28.1	Intracerebral bleeding	37.7	38.5	37.0	38.4	37.0	38.2	37.1	38.3	37.1	38.3	37.8	38.8
5	30	M	93.9	28.9	Anoxic brain injury	36.8	38.4	36.6	38.3	36.4	38.0	36.0	37.8	36.0	37.2	36.8	38.4
6	69	F	87.4	32.1	Intracerebral bleeding	36.7	37.9	36.4	37.7	36.1	37.4	36.0	37.5	36.0	36.7	36.2	37.9
7	54	F	110.1	41.5	Intracerebral bleeding	37.1	37.9	37.2	37.7	36.9	36.9	36.8	36.2	36.8	36.5	37.7	38.1
Mean	39.9		88.4	29.0		37.0	38.4	36.7	38.1	36.5	37.7	36.4	37.4	36.4	37.4	36.8	38.3
SD	14.9		14.6	6.1		0.5	0.6	0.5	0.3	0.6	0.5	0.7	0.7	0.7	0.6	0.8	0.4

BMI body mass index, *SD* standard deviation, *Tymp* tympanic, *T-30* 30 min into cooling therapy, *T-60* 60 min into cooling therapy, *T-90* 90 min into cooling therapy, *T-120* 120 min into cooling therapy, *T150* 30 min after termination of cooling therapy

22.2–41.5). Five patients had intracerebral or intraventricular bleeding, one subject had transverse myelitis, and the remaining patient had anoxic brain injury due to cardiac arrest. None of the subjects had invasive brain monitoring prior to, or during the study. All patients were initially hemodynamically stable except for one patient with intracerebral hemorrhage. This patient was hypertensive pre-enrollment, requiring intravenous nicardipine for blood pressure control. All but one of the patients were endotracheally intubated and on mechanical ventilation. Two of the seven patients were comatose, and five were responsive to verbal commands. Baseline ENT examinations were normal in all subjects. Subjects 2, 3 and 5 had surface cooling in addition to acetaminophen during the 24 h prior to study entry. The other subjects only received acetaminophen.

Figure 2a shows the gradual increment in airflow, and the steady airflow achieved at the peak pressure of 20 cmH_2O through the CPAP machine. Figure 2b shows the esophageal and the tympanic temperature in the same subject superimposed on the airflow rate. Once the air supply was turned on and incremented gradually up to the maximum of 20 cmH_2O, the mean airflow rate achieved was 57.5 ± 6.5 LPM. Mean baseline temperature prior to start of therapy was 38.4 ± 0.6 °C. Figure 3a shows the change in core (esophageal) temperature for all seven subjects over the course of the 2 h of transnasal airflow, as well as the 30-min recovery period after cessation of the airflow. Compared to baseline, core temperature was significantly lower in the overall group at the end of the 2-h nasal airflow (38.4 ± 0.6 °C vs. 37.3 ± 0.5 °C; $p < 0.002$). Core temperature increased significantly within 30 min of cessation of airflow and was similar to the pre-cooling baseline core temperature (38.3 ± 0.4 °C vs. 38.4 ± 0.6 °C; p = NS). Figure 3b shows the core temperature normalized to baseline temperature showing a consistent decrease in all the subjects. The mean rate of decline in temperature was approximately 0.6 °C per hour (range 0.4 °C–1.2 °C). Baseline tympanic temperature was significantly lower than the core temperature in all subjects (36.9 ± 0.4 °C vs. 38.4 ± 0.6 °C; $p < 0.01$). Similar to the core temperature, there was a significant decline in the tympanic temperature at the 2-h time point when compared to baseline (36.9 ± 0.4 °C vs. 36.3 ± 0.6 °C; $p = 0.04$); however, the absolute decrease in temperature was less than the decline in core temperature.

Effect of Airflow on Hemodynamics and Oxygen Saturation

Baseline mean systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse rate were 139 ± 18 mmHg, 64 ± 18 mmHg and 78 ± 11 beats per minute, respectively. No statistically significant changes were observed in SBP or DBP during peak airflow (SBP

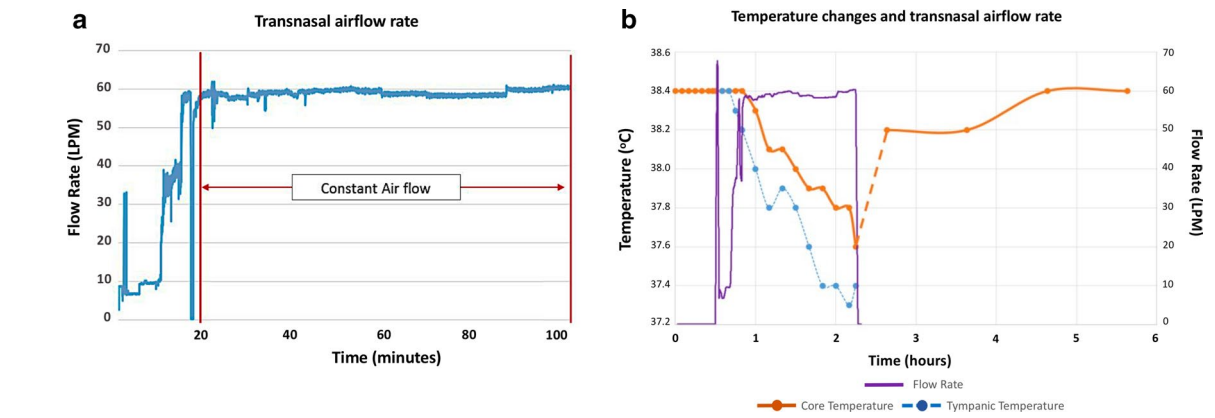

Fig. 2 Transnasal airflow rate and temperature changes. Left panel shows the recorded airflow from the CPAP device (**a**). Note the gradual ramp up of airflow to maximum flow rate maintained for 2 h followed by cessation of airflow. Right panel shows the esophageal and tympanic temperatures superimposed on the airflow (**b**). Note the gradual decline in the temperatures, which promptly returns to baseline upon cessation of airflow

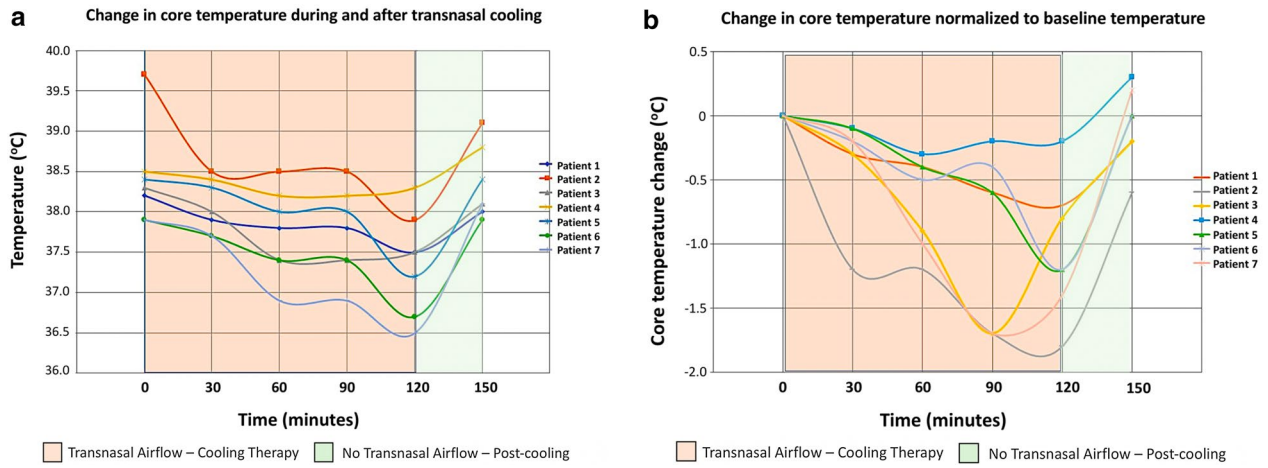

Fig. 3 Core temperature changes during and after transnasal cooling. Absolute (**a**) and normalized (**b**) change in core temperature of all the seven subjects during and after cessation of airflow

149 ± 18 mmHg and DBP 64 ± 16 mmHg, respectively, p = NS compared to baseline). One subject was hypertensive pre-enrollment and remained hypertensive throughout the study duration. Baseline oxygen saturation was > 95% in all subjects, throughout the study protocol.

Efficacy End Point

The primary end point of achieving normothermia (core temperature < 37.5 °C) was met in five of the seven subjects. Two of the seven did not achieve normothermia in the 2-h treatment window. One patient (patient 2) had severe neurologic injury with a starting core temperature of 39.7 °C. During the 2-h period, he cooled to 37.9 °C but failed to achieve normothermia (37.5 °C). The other subject (patient 4) started with a core temperature of 38.5 °C. However, therapy was discontinued several times during the 2-h period, due to displacement of the nasal mask and dislodgement of the esophageal temperature probe. This subject cooled only 0.2 °C mainly related to the technical issues around delivering the transnasal therapy. No shivering was noted in any of the subjects during the entire study despite lowering of core temperature (average bedside shivering assessment scale = 0).

Baseline tympanic temperature was significantly lower than the core temperature in all subjects (36.9 ± 0.4 °C vs. 38.4 ± 0.6 °C; $p < 0.01$). Similar to the core temperature, there was a significant decline in the tympanic temperature at the 2-h time point when compared to baseline (36.9 ± 0.4 °C vs. 36.3 ± 0.6 °C; $p = 0.04$); however, the absolute decrease

in temperature was less than the decline in core temperature.

Safety End Point

No protocol-related adverse events occurred during the study or during the first 24 h of completion of the study protocol. No significant increase was seen in blood pressure due to the use of the cooling process. Mild hypertension (systolic pressure > 30 mmHg from baseline) was noted in one subject immediately after starting the nasal airflow. It was subsequently discovered that this subject had labile hypertension before enrollment and was started on a nicardipine infusion, which was discontinued for unclear reasons prior to the start of the protocol. Blood pressure promptly normalized as soon as the nicardipine therapy was restarted. No subject had bleeding or nasal discharge based on the ENT examination post-cooling. No dryness/desiccation or ulceration of the mucosa was visible on anterior speculum examination.

Discussion

This exploratory study demonstrates the feasibility, and efficacy of using transnasal air in reducing core body temperature in febrile patients unresponsive to conventional antipyretic therapies. Over a 2-h period, five of seven subjects were rendered normothermic by this novel intervention and no adverse events were seen. The transnasal air was well tolerated even in non-sedated patients, and none of the patients had any adverse mucosal changes 2 h post-dry air therapy. Finally, no shivering response was elicited by the transnasal cooling method, which is a significant advantage compared to surface cooling methods, obviating the need for anti-shivering agents and sedatives.

The mechanism behind our method has been previously described in pigs [15]. High flow transnasal dry air induces cooling of the nasal mucosa due to evaporation of nasal mucosal water, which in turn results in convective cooling with reduction in the brain and body temperature in porcine animals. Similar results have also been reported using cooling balloons in the nasopharynx that circulate cold saline [16] and by using perfluorocarbon (PFC) nasal spray which also causes evaporative cooling [17]. However, both cooling balloons and the PFC approach require deep cannulation of the nasal passages in addition to the risk of cold-induced injury to the nasal passages with the PFC exposure.

Other commonly used methods used in the NCCU setting such as ice packs, cooling blankets and cooling pads for maintaining normothermia are sub-optimal and require significant nursing intervention [9]. Surface cooling causes shivering and cutaneous vasoconstriction that counteracts the cooling effects [17]. Intravascular cooling, although effective, is expensive and associated with delayed post-arrest hypothermia, also induces shivering and is limited in its use to critical conditions in tertiary centers [18–20]. Administration of cold saline for fever control is an adjunct for inducing normothermia in refractory febrile patients, but volume is difficult to estimate, and this method lacks a closed-loop system based on continuous temperature-controlled feedback [21]. We carefully monitored shivering response in our subjects using a well-validated shivering score [11]. None of our study subjects required anti-shivering agents and/or skeletal muscle paralysis which is a significant advantage of this method. The exact reasons behind the lack of shivering response are unclear. Skin cooling results in shivering response due to cutaneous thermoreceptor activation, which is distinctly absent in the transnasal cooling process. It is possible that the direct effects of selective brain cooling might account for lack of shivering although this is speculative and was not investigated in this study. Finally, using anti-shivering agents and neuromuscular blockade may result in prolonged length of stay in NCCU and negatively impact on morbidity and cost of cooling therapy [22]. As such, our method of temperature lowering using transnasal air has the advantage of being inexpensive and easy to use, thereby potentially increasing the utilization of normothermia therapies.

Selective brain cooling was reported using transnasal dry air flow by prior investigators [23–25]; however, none of these studies appreciated the mechanism behind cooling as such they did not exploit the evaporative cooling mechanism. One of the main determinants of evaporation is air flow rate. All of these studies used air flow rates of 5–10 LPM which is very sub-optimal for evaporation. In our study, we used up to 50 LPM which is an order of magnitude higher than what has been previously tested and we were able to demonstrate core cooling in our study which was not seen in the prior studies.

Studies that used PFC nasal spray also used high flow of oxygen (50–70 LPM) to induce hypothermia [26, 27]. Liquid coolant (PFC) along with oxygen was sprayed into the upper airway and evaporated with the help of high flow oxygen. The Pre-ROSC IntraNasal Cooling Effectiveness study in cardiac arrest patients showed significant survival benefit to patients presenting with ventricular fibrillation as the primary rhythm in a sub-analysis [17]. It is quite possible that similar results would have been obtained using the high flow dry gas alone as the rate of cooling in that study is comparable to the cooling achieved in our patients. It is also important to note that this study was not optimized for transnasal cooling. The air used with the subjects was provided from a medical grade wall port, with relative humidity levels of $32 \pm 8\%$ which limited the evaporative energy exchange process.

Less humid air is expected to significantly increase the energy exchange (loss) from the body.

This was a small exploratory study and is limited by the fact that only a 2-h exposure to 60 L/min dry nasal flow was assessed and core temperature increased back to pre-cooling baseline within 30 min of cessation of airflow. Longer durations of exposure will be needed to assess the effect of extended exposure of the nasal mucosa to dry gas at high flow and to determine feasibility of this procedure for fever control over longer time periods. Another limitation is that all but one patient was tracheally intubated and on mechanical ventilation. Although it is not anticipated that this device will be limited to intubated patients, further study on non-intubated patients will be needed to determine whether high dry gas flow has deleterious pulmonary effects on the airway when not protected by intubation. The one subject who was not intubated was fully awake and seated during the exposure and had no aspiration. As there is the risk of aspiration with use of noninvasive positive pressure ventilation in patients with poor neurologic status and/or poor ability to control secretions, this needs to be studied in larger populations. The use of CPAP in intubated subjects has also not been studied. There were no adverse effects during short-term exposure. A larger study is underway with 24 h of exposure under an investigational device exemption protocol.

Finally, several technical issues deserve mention. Although the position of the esophageal temperature probe in the esophagus was confirmed visually, it cannot be excluded that the temperature sensor might have been in the upper part of the esophagus or even in the larynx leading to erroneous temperature readings. However, we have also tested this device in normal volunteers with the esophageal probe placed under fluoroscopy in the gastroesophageal junction and had similar results suggesting that the gradual decline is due to change in core temperature drop and not directly due to the effect of airflow on the temperature sensor [28]. One intubated patient did not experience a drop in temperature due to repeated mask discontinuation and esophageal probe displacement in the oropharynx resulting from an orogastric tube which took up most of the posterior oropharynx. These technical issues will need to be considered in planning larger studies.

Conclusions

In conclusion, this study demonstrates the feasibility of using a high flow of ambient air through the nasopharynx in a unidirectional fashion (in the nose and out of the mouth) to lower core body temperature in febrile patients in the NCCU setting. No adverse events were seen, and the process showed no signs of shivering or any other serious side effects during short-term exposure. We believe this cooling mechanism may be useful as an acute intervention or for the initiation of fever control and that further study is warranted for both short- and long-term use.

Abbreviations

NCCU: Neurocritical care unit; ENT: Ear, nose and throat; CPAP: Continuous positive airway pressure; LPM: Liters per minute; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; PFC: Perfluorocarbon.

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Author Contribution

WZ analyzed the data and wrote the manuscript. DS collected the data. FRA analyzed the data and reviewed the manuscript. HT analyzed the data and wrote the manuscript. RGG supervised the project, analyzed the data and reviewed the manuscript.

Source of Support

Funding was provided by Key Technologies Inc.

Conflict of interest

Harikrishna Tandri is the founder of CoolTech Inc, which is developing a transnasal device for hypothermia. Other authors declare that they have no conflict of interest.

Ethical Approval/Informed Consent

This study was approved by the Johns Hopkins University Institutional Review Board (IRB00086134).

Human and Animal Rights

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent

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

Publisher's Note

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