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Prolonged unintended brain cooling may inhibit recovery from brain injuries: Case study and literature review

George P. Ford^{1ABCDEF}, David C. Reardon^{2ADEFF}

¹ Institute for the Minimally Conscience, Rye NY, U.S.A.

² Elliot Institute, Springfield, IL, U.S.A.

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Summary

Background:

Tracheal intubation of comatose patients is common, but contrary to most standards for respiratory care, heated nebulizers are not always used. This deviation from recommendations appears to be widespread.

Case Report:

In the case examined, a tracheotomized patient suffering from severe anoxic brain injury was unintentionally exposed to chilled air, 17°C (63°F) at the cannula, for a period of 31 months. A month after upper respiratory tract warming was restored the vegetative state lifted, as marked by the patient's ability to verbalize responses to questions.

Conclusions:

This clinical experience led us to a review of the literature. Among other findings, we learned that brain temperature is strongly affected by the temperature of arterial blood flow. Arterial blood, in turn, is strongly affected by the air temperature in the lungs. Experiments have shown that the introduction of colder air in the lungs will produce rapid cooling of at least some surface brain tissues. Chilled aortic blood is also more viscous and less efficient in transfer of oxygen. Hypothermia of brain tissue may significantly affect the endocrine system and neurochemistry. Through inferences from the literature, we also identify other possible effects. We hypothesize that intubated delivery of air into the lungs at a temperature significantly below body temperature, especially over a prolonged period, is likely to inhibit recovery and may even produce iatrogenic effects. We recommend the use of heated nebulizers. Research strategies are recommended.

key words:

brain temperature • respiratory care • tracheal intubation • vegetative state • pituitary dysfunctions • encephalomalacia • growth hormone • coma • selective brain cooling

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Author's address:

George P. Ford, Institute for the Minimally Conscience, 48 Clinton Ave, Rye, NY 10580, U.S.A.,
e-mail: gford@mine4ever.net

BACKGROUND

For patients requiring prolonged respiratory therapy, humidified air heated to between 95° and 97.8° F (35° and 36.6° C) is recommended [1–4]. While the harmful effects of unhumidified air on respiratory tissue is well known, the portion of these recommendation regarding the warming of the air to near body temperature appears to be chiefly motivated by concerns regarding patient comfort rather than any known harmful effects of associated with prolonged exposure to cool intubated air. This observation may help to explain why the use of humidified air without heated nebulizers appears to be common, especially for non-responsive, intubated patients in long-term care.

Motivated by the case described below, we queried respiratory care staff at 10 hospitals and 10 extended care facilities in New York and Connecticut asking how frequently they used nebulizer heaters when giving moisturized oxygen via tracheotomy to non-responsive patients. As seen in Table 1, most indicated that heaters were rarely used. Explanations offered for this practice reflected the assumption that moisturized oxygen will spontaneously warm to room temperature before entering the cannula. Many staff members also appeared to unaware of the fact that the oxygen supply does not originate from compressed gas but is instead drawn from bulk liquid oxygen tanks (–183°C). In fact, in the absence of a heated nebulizer, the temperature at the point of delivery to the patient may actually be many degrees below room temperature [5].

The above query and following literature review were motivated by reflection on the following case which brought the possibility of deleterious effects arising from prolonged exposure to unintended brain cooling to our attention.

CASE REPORT

A 53-year-old female experienced respiratory failure and cardiac arrest concurrent to an overdose of proscribed Tylenol with Codeine #4 for back pain. CPR was begun approximately four to six minutes after the arrest and continued until arrival of paramedics. The patient, suffering from cerebral hypoxia, was placed on mechanical ventilation. Two days after the brain injury, the patient was responsive to commands and able to raise her arm but soon became non-responsive. Sixty-six days after the cardiac arrest, the patient, diagnosed with persistent vegetative state, was treated with a gastrostomy and tracheotomy and transferred to a long-term care facility.

For the next thirty-one months, oxygen was delivered through an unheated nebulizer set to provide moisture and 28% oxygen with 6 liters of flow per minute through a three meter large bore hose to a T connected to an unfenestrated cannula directly into the trachea. The setup is shown in Figure 1. During the thirty-second month the assisted oxygen was removed following the observation that the temperature of the air at the unheated nebulizer was 15°C (59°F) and only 17°C (63°F) at the cannula. It was hypothesized that bypassing the upper respiratory system with oxygen below body temperature might cause localized hypothermia of the lungs, heart, and brain even though the patient's rectal body temperature was in a normal range. The cannula was

replaced with a plugged fenestrated cannula and it was observed that the patient tolerated unassisted breathing well, with blood oxygen remaining at 98 percent.

One month after removal of the unwarmed oxygen, the patient exhibited her first signs of being able to respond to questions with a simple yes or no. Later, she was able to reply to the question "Do you feel like talking?" with "I don't wanna," and on another occasion with "I no power." Verbalization was sporadic, however, and was frequently interrupted by months of silence.

Subsequent review of the patient's record revealed that no entry was made for the patient's temperature on the first and second day after the cardiac arrest, while she was on a ventilator. The first temperature (rectal) recorded in the charts, on the morning of the third day, was 26°C (78.8°F). The next measurement, approximately two hours later, 35°C (95°F) followed by a brief dip to 31°C (87.8°F). Thereafter, for the remaining 22 days on the ventilator, the records show the rectal temperature remained in the range of 33–35°C (91.4–95.0°F). While in the long-term care facility, records show the patient's rectal temperature was typically recorded between 97° and 100°F (36–38°C).

The record review also revealed that the blood tests performed just before transfer to long-term care revealed traces of opiates though the patient's last known exposure to opiates would have been at the time of the overdose that triggered the cardiac arrest. It would seem that this could only be possible if the function of the patient's hepatic metabolic system was suppressed, which is a symptom of hypothermia [6].

DISCUSSION

Hypotheses and observations of additional cases

We hypothesize that long-term exposure to intubated air below body temperature may cause localized hypothermic reactions in the brain and heart that may slow or inhibit recovery of brain function. Alternatively, healing of brain injuries may be masked by iatrogenically induced symptoms. There is also the concern that prolonged cooling may contribute to encephalomalacia. These hypotheses are circumstantially supported by a small, non-random observation of tracheotomized patients in non-responsive states lasting over six months among whom we observed that the only seven who recovered did so after oxygen had been removed. We are unaware of any recoveries when unheated nebulizers were in use at the time of the recovery. As noted, however, these are non-random observations that caught our attention because of the case reported and our developing interest in the above hypotheses.

We also hypothesize that many non-responsive patients may be receiving intubated oxygen beyond the time that is necessary to stabilize the patient's condition. In such cases, providing assisted oxygen has no beneficial effects that would offset the hypothetical risks associated with delivery of below room temperature gases directly into the trachea. In the case reported above, the patient's improvement followed restoration of upper respiratory tract conditioning, not the installation of a heated nebulizer. In the last few months, we have become aware of a similar case involving a much

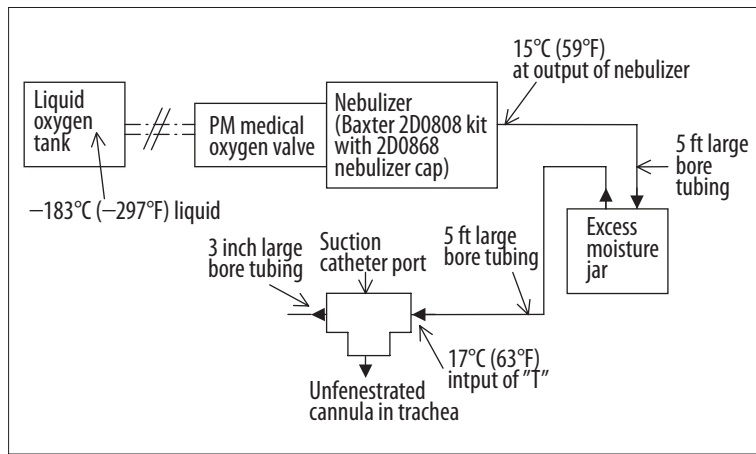


Figure 1. Connections and temperatures of oxygen for the tracheotomized patient.

Table 1. Is a heated nebulizer used when providing assisted oxygen to a comatose or non-responsive tracheotomized patient via a nebulizer? Responses from the directors of respiratory care or nursing at a convenience sample of ten hospitals and ten extended care facilities in New York and Connecticut.

	Hospital	Extended care facility
1	No	No
2	No	No
3	Rarely	Only if secretions are thick.
4	No	No
5	Occasionally	No
6	Not a standard	Generally NO
7	No	Only on ventilator*
8	Off ventilator, no	No
9	No	No
10	It depends on thickness of secretions	No

* This respondent is also the director of respiratory care at a second extended care facilities and one hospital.

more complete recovery following removal of unwarmed oxygen. In this case, for which we do not have access to patient records, one of the authors (Ford) had an opportunity to observe, in a non-professional capacity, a tracheotomized 28-year old male receiving unwarmed oxygen. The patient had overdosed on drugs and had been non-responsive for at least 2-months and had been diagnosed to be in a persistent vegetative state. Following Ford's questioning regarding the patient's blood oxygen level, which was reported as 98.99, assisted oxygen via tracheotomy was subsequently removed. Whether Ford's comments actually initiated reconsideration of the assisted oxygen is unknown, but we have confirmed the fact that it was removed and approximately six weeks later the patient began moving his arm and several weeks later began to speak and is now participating in a rehabilitation regimen.

Literature review

In our literature review of articles related to brain temperature, it appears that nearly all prior research interest has been focused on short-term interactions between brain temperature and hypothermia or hyperthermia. We have been unable to identify any literature, either of a hypothetical or experimental nature, related to prolonged shifts in brain temperature caused by exposure to below body temperature air delivered into the trachea over an extended period of months or even years. However, the existing literature, much of which has been collected within the last ten years, appears to support our hypotheses.

As described in mathematical detail by Yablonski and colleagues [7], the energy required for proper brain function is principally produced by the reactions of glucose and oxygen and ATP hydrolysis, and in normal circumstances the resulting heat is primarily removed by the cooling of arterial blood. In a resting person, the temperature of cerebral arterial blood is around 0.3°C lower than cerebral venous blood, and the heat exchange provided by this blood flow accounts for 95% of the cerebral heat removal required to maintain thermal equilibrium [8]. As noted by Yablonski, "by manipulating incoming blood temperature, the brain temperature may be changed temporarily" [7]. It is also evident that prolonged manipulation of incoming blood temperature would cause prolonged changes in brain temperature.

The temperature of cerebral arterial blood, for its part, is strongly associated with esophageal temperature [8]. This association can be readily understood by noting that the exposure of hot, oxygen depleted venous blood over the large surface area (approximately 70 to 100 square meters) of the lungs' 300 million alveoli is conducive to both rapid oxygenation and rapid heat transfer.

In normal circumstances, the upper respiratory tract is an efficient conditioner of the air and carotid arterial blood will be only a little below the core body temperature [8-10]. In such normal conditions, the temperature of the heart and great vessels will closely track esophageal temperatures [9].

For a thermally stable person, relaxed oronasal breathing of cold (-1°C) or warm (41°C) air for short periods of time

does not appear to have an effect on brain stem temperatures as indirectly estimated by the measurement of interpeak latencies of using auditory-evoked brain stem responses [11]. This finding is a testament to the ability of the upper respiratory tract's to properly condition air under normal circumstances.

But the respiratory system's ability to condition air can be overcome by a number of conditions. For example, breathing of very cold air (-18°C) will produce thermal changes in the upper respiratory tract that extends into the lungs [12]. Also, rapid breathing, common in cases of exertion, may reduce the time that air will be exposed to the warming conditions provided in the upper respiratory tract and may even cause a chilling of respiratory tissues. Any drop in the temperature of air in the lungs due to rapid breathing would therefore produce a related drop in arterial blood temperatures. In the case of exertion, this drop in arterial blood temperatures may be beneficial in helping to remove additional heat caused by exertion.

The link between inspiration and brain tissue temperatures has been demonstrated in an experiment with post-operative neurological patients before, during and after removal of an of an endotracheal tube, in which Mariak found that rapid breathing of cool air (22°C) for only a three minute period produced a significant drop in the surface temperature of the human brain as measured between the frontal lobes and cribiform plate (mean 0.07°C per minute) [13].

Other researchers have also observed the association between esophageal temperatures and brain temperature [14,15]. The only study known to us that identified a significant deviation in trending patterns of esophageal temperatures and brain temperatures was another experiment by Mariak [16] in which 20–25 percent of the brain surface of neurological patients was exposed to ambient air. In this unnatural condition, esophageal temperatures were unchanged while brain temperatures were significantly affected by exposure to ambient air and a warm saline bath.

Since rapid breathing will temporarily cool at least some areas of the brain, it is extremely likely that bypassing the upper respiratory tract with cool air delivered via intubation would also produce cooling effects. These cooling effects of chilled arterial blood would most likely be more pronounced on the brain, compared to other body parts, because the relatively short pathway of the carotid artery minimizes tissue warming of the blood before it reaches the brain [8,17]. Also, there is evidence that there is very little heat exchange across the walls of major arteries and veins with diameters exceeding a few millimeters due to high flow rates and small surface area per length [18].

While we do not question the general assumption that the brain temperature will be similar to the core body temperature under normal circumstances, in abnormal circumstances, rectal, oral and even tympanic temperatures may be significantly different than the brain temperature [18]. Indeed, in some experimental situations cooling of brain tissue has been accompanied by a rise in the rectal temperature [13,16]. We speculate that abnormal temperature variations in the brain due to bypass of the upper respiratory tract may cause the hypothalamus to regulate the body

temperature in ways that may obscure the effects of chilled aortic blood on both the body and the brain.

Possible implications of prolonged brain cooling

There are many possible implications of prolonged brain cooling by intubation of air in the range of 17°C (63°F). It is well known that even relatively small changes in temperature can significantly effect chemical reactions, and this is also true of neurochemical reactions [19]. Brain temperature, in turn, also appears to be affected by brain activity. Magnetic resonance imaging has shown functional stimulation of the visual cortex will produce up to 1°C changes in localized brain temperature [7]. Direct measurements have also shown that there is a natural temperature gradient within the human brain, with the central parts being warmer than the surface, and the brain can be several degrees different than the core body temperature [20]. A shift in these normal temperature gradients may have significant effects on brain function and neurochemistry.

Localized cooling of brain tissue may produce many of the effects normally associated with hypothermia, including confusion, disorientation, lethargy, inattentiveness, a reluctance to speak, and stupor [6], even while core temperatures appear normal. Oxygen demand for cold tissue decreases by 7% for each degree centigrade fall in temperature [6]. Even modest hypothermia (0.4°C) is associated with a 7% increase in packed cell volume, a 21% increase in blood viscosity and a rise in blood pressure [6]. Since there is evidence that local brain activity will produce changes in the brain temperature due the increase in neurochemical reactions in the activated portion of the brain [7], it reasonable to hypothesize that cooling of the brain tissue may alter or inhibit the neurochemistry associated with proper brain function. Moreover, if brain activity is suppressed, this would have the additional effect of reducing the heat generated thereby further tipping the equilibrium to a lower temperature.

Yet another negative reinforcement of lower brain temperatures may occur if the chilled carotid blood triggers constriction of cerebral capillaries. Under normal conditions of hypothermia caused by external cold, a reduction in metabolic rates following constriction of cerebral capillaries may produce a beneficial, even life saving, effect if body warmth is restored in a reasonably short period of time. In the case described above, however, the patient's external environment was warm and any constriction of cerebral capillaries would have occurred only due to chilling of the carotid blood. If such cerebral capillary constriction did occur, it would have the net effect of diverting the chilled blood to deeper regions of the brain where additional chilling of tissue would occur. The chilling of carotid blood in the condition described may therefore produce a self-reinforcing trend: chilling of tissue, constriction of capillaries, reduced metabolic heat output, deeper penetration of the chilling blood, chilling of tissue, constriction of capillaries, further penetration of the chilling blood, et cetera. A new thermal equilibrium would be established, of course, but the net change might be significantly greater than that which would be expected from the heat carrying capacity of chilled blood alone. Suppression of metabolic rates and reduced penetration of the chilled blood through constricted capillaries

would effectively serve to extend the chilling of brain tissue. Of some potential interest in this regard is a three person study of induced ice cream headaches in which a 20 to 30 percent drop in the middle-cerebral-arterial flow velocity was observed, as measured using transcranial Doppler ultrasonography, suggesting cerebral vasoconstriction as a response to the thermal shock [21].

It is also known that hypothermia affects hormone balances, including almost the complete suppression of the growth hormone (GH) [22]. The symptoms of growth hormone deficiency syndrome [23,24] are consistent with the physiological deterioration observed in many patients in a vegetative state, including the patient described above. While research has shown that growth hormone deficiency and other pituitary dysfunctions is common among victims of brain injuries [25–27], it does not appear that investigators have identified, or looked for, any association between suppressed pituitary function and the temperature of inspired gases.

Other literature we have examined [28–34] also suggests that many other biochemical and physiological effects which may be associated with moderate hypothermia of brain tissue might have a deleterious impact on health. It is evident that any negative effects may worsened if unintended brain cooling were to persist over a long period of months or years. Localized hypothermia may also negatively impact efforts to measure brain function [35] and may also be a factor contributing to misdiagnosis of vegetative state [36].

Regarding the reluctance of some facilities to use nebulizer heaters, we speculate that the decision to forgo their use may in part be due to fears of malfunctions that may overheat the air and damage the trachea. Another disincentive may be that the use of heated air might require more frequent checks using a calibrated analyzer [37].

CONCLUSIONS

Based on the cases discussed and our literature review, we make two clinical recommendations. First, heated nebulizers should be used to ensure that the air delivered into the trachea is only a few degrees below body temperature, no less than 30 to 33°C, which is the normal range for upper tracheal temperatures [38], and perhaps more preferably in the range of 35 and 36.5°C, which is the recommended standard [2]. Second, the ability of intubated non-responsive patients to breath without intubation should be periodically checked so normal conditioning of the air through the upper respiratory tract may be restored as soon as possible. Neither of these recommendations involves any known risks to the patient. Moreover, in light of the case study and literature review presented, it is very possible that both recommendations may prove to be beneficial.

We also strongly urge seven lines of research, none of which are within the capacity of the authors. First, esophageal and cerebral venous blood temperatures should be measured as described by Nybo [8] and compared between inactive healthy patients, non-responsive patients without respiratory assistance, and non-responsive intubated patients receiving unwarmed oxygen in the range of the case examined. This comparison would confirm or refute the underlying

concern that the failure to use a heated nebulizers with intubated non-responsive patients may contribute to lower esophageal temperatures resulting in lower cerebral venous blood temperatures. Second, cerebral blood flow of cases and controls should be measured with Doppler ultrasonography as this may be an indicator of both increased blood viscosity [21] and vascular constriction with comparisons done for blood flow rates in carotid, brain, and core organs. Third, MRI techniques should be employed to examine differences cerebral blood flow, blood temperatures, and brain activity in nonresponsive intubated patients receiving oxygen at 17°C and 34°C. Fourth, estimates of brain temperature in intubated patients might be examined measuring interpeak latencies of auditory-evoked brain stem responses as described by Jessen and Kuhnen [15]. Fifth, animal experiments should be conducted using thermocouples placed at numerous points intracranially. A coma may be induced by drug or surgical trauma and ventilation provided through tracheotomy. An experimental group should be given chilled, humidified air, while the control group would be given warmed, humidified air. To examine the possible long-term effects, it is advisable that such a study should include at least a subset of animals exposed to sub-body temperature air through a cannula for a period exceeding one or even five years. Sixth, a retrospective, record-based study should be conducted of patients in coma, vegetative, and minimally conscious states to determine if different recovery rates are associated with different patterns of respiratory care, with particular attention to the use of warmed or unwarmed air. Seventh, the treatment recommendations described above should be implemented for a cohort of intubated non-responsive patients and any changes in condition should be examined for improvements. In addition, based on a number of circumstantial bits of information not reported herein, we also recommend exploration of any possible associations between prolonged brain cooling and symptoms consistent with idiopathic recurring stupor (IRS) [39].

While additional research is required, we conclude that the general recommendation for intubated patients to be given humidified air heated to near body temperature is appropriate and should be more universally followed [1–3].

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