A Cold Nose *and* a Cold Brain?
The RhinoChill: A New Way to Cool the Brain Quickly

By Mike Darwin

We scientists are difficult, cranky, and above all, maddeningly frustrating people. Want to turn lead into gold? No problem, we can tell you how to do that, and in fact have even done it already: the only catch is that the cost of such 'nuclear transmutation' is many times that of even the most expensive mined gold. You say you want to travel to the moon? Done! That will be ~$80 billion (in 2005 US dollars). Want to increase average life expectancy from ~45 to ~80 years? Your wish is our command, but be mindful, you will, on average, spend the last few of those years as a fleshpot in the sunroom garden of an extended care facility.

And so it has been with an effective treatment for cerebral ischemia-reperfusion injury following cardiac arrest. Thirty years ago, laboratory scientists found a way to ameliorate most (and in many cases all) of the damage that would result from ~15 minutes of cardiac arrest, and what's more, it was simple! All that is required is that the brain be cooled just $3^{o}C$ within 15 minutes of the restoration of circulation. The catch? Well, this is surprisingly difficult thing to do because the brain is connected to the body and requires its support in order to survive. And the body, as it turns out, represents an enormous heat sink from which it is very difficult to remove the necessary amount of heat in such short time. Thus, the solution exists and has been proven in the laboratory, but it has been impossible to implement clinically. This may be about to change as a variety of different cooling technologies, such as cold intravenous saline and external cooling of the head begin to be applied in concert with each other. Separately, they cannot achieve the required $3^{o}C$ of cooling, but when added together they may allow for such cooling in a way that is both effective and practical to apply in the field. A newly developed modality that cools the brain via the nasal cavity may provide the technological edge required to achieve the $-3^{o}C$ philosopher's stone of cerebroprotection.

In 2009, the RhinoChill, a new noninvasive method for rapid induction of mild therapeutic hypothermia (MTH) under development by Benechill, Inc., began clinical trials.[1] The RhinoChill uses a novel method to achieve intra-cardiac arrest cooling; transnasal evaporative cooling, wherein a liquid coolant–oxygen or air mixture is sprayed into the nasal cavity and frontal sinuses where the liquid is rapidly evaporated with high-flow compressed gas (typically O_2). The heat of vaporization of the perfluorocarbon azeotrope causes cooling of the nasal passages and brain. The device is highly portable, can be used on a patient within minutes of cardiac arrest, and has been demonstrated to be safe for use in humans in the hospital setting.[1],[2]

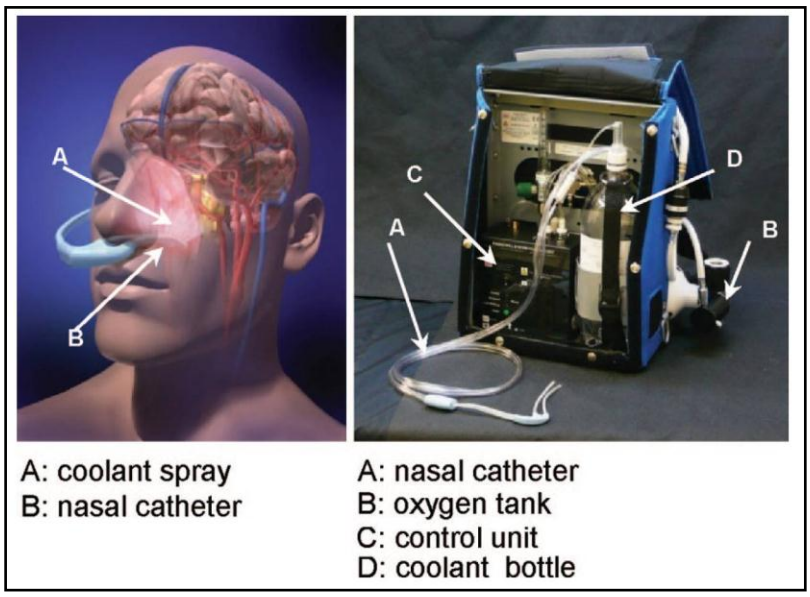

Figure 9-38: *The RhinoChill device (R) and the anatomical areas cooled by the evaporation of the PFC refrigerant from the nasal cavity and sinuses.*[2]

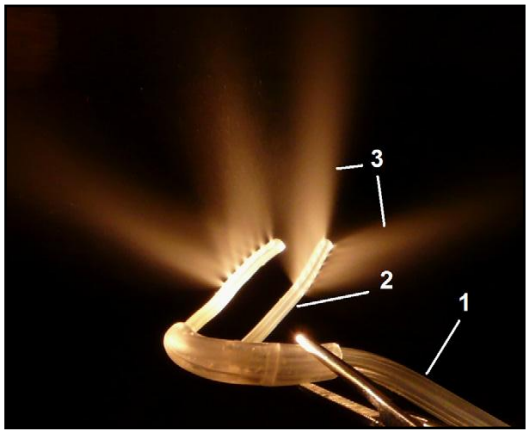

Figure 9-39: *Photograph of RhinoChill nasal cannulae used for nasopharyngeal cooling. The perfluorochemical (PFC)-oxygen mixture is delivered from the oxygen tank and the PFC reservoir in a single tube (1) that then bifurcates into a left and right nasopharyngeal cannula (2). The perfluorochemical-oxygen spray (3) exits in dorsal and lateral direction from the distal end of the cannulae.*[3]

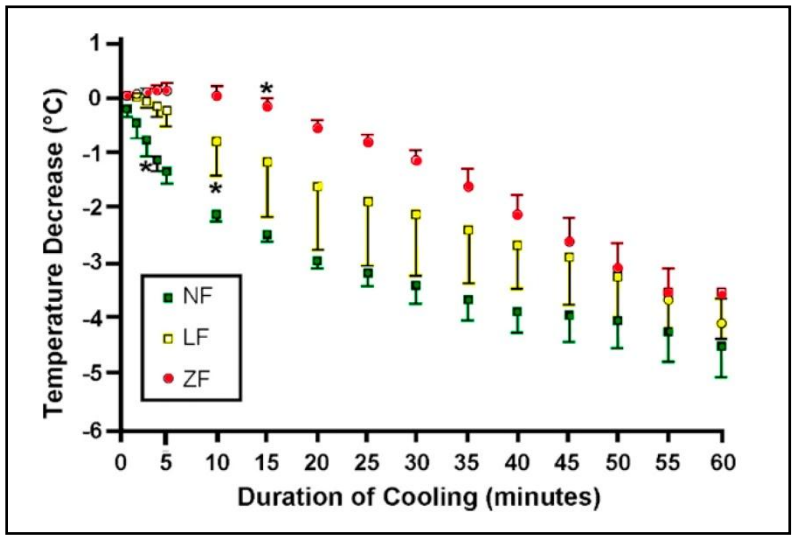

Figure 9-40: *Change in brain temperatures from baseline (mean ± SD) during untreated cardiac arrest (ZF; n = 3), CPR (LF; n = 4) and anesthesia (NF; n = 3) over the course of 60 min of nasopharyngeal cooling. *indicates first significant decrease from baseline (<0.01).*[3]

Perfluorochemical (PFC) is delivered via a proprietary cannula the two legs of which are passed through the nares and into the nasal cavity. PFC is delivered at a rate of 1 mL/kg/min while oxygen is co-administered at a rate of 1 L/kg/min. When circulation is present, heat is removed from the brain predominantly hematogenously, through the submucosal nasal venous plexuses by the rich subepithelial vascular plexus to the deep venous sinuses of the brain, and secondarily by direct convection. The device can reduce tympanic temperature (a surrogate for brain core temperature) at the rate of 2.4°C per hour. Systemic cooling proceeds more slowly at a rate of 1°C per hour.

The liquid evaporates instantaneously, thereby removing heat. The coolant is a proprietary perfluorochemical or perfluorochemical mixture (azeotrope) the composition of which is not disclosed. No patents appear to have been filed disclosing the PFC chemical structure, or mixture of PFCs being use as the refrigerant. The PFC used by Benechill must have a temperature well below the freezing point of water since inadvertent freezing of the nasal mucosa is a complication of operation.[2] Perflourochemicals are a family of chemicals that are generally regarded as both chemically and biologically non-reactive. These chemicals are among the least acutely toxic compounds known, although they are known to be potent immunomodulators and inhibit white blood cell chemotaxis at fentogram concentrations.[4],[5],[6] They cannot reach appreciable concentrations in tissues of air-exposed animals since they have limited ability to dissolve in biological media. Many are highly volatile and have a high air–blood partition coefficient, which facilitates their rapid elimination through pulmonary expiration (more information is available via 3M Specialty Materials. Robust summaries and test plan: perfluorocompounds, C5–C18; revised summaries. EPA Report 201-14684B, Aug 2003). The cooling and safety profile associated with the specific perfluorochemical used in the coolant was determined by Wolfson et al., in an ovine model, where no damage to the epithelial surface was noted.[[7]

The nasal cavity with its proximity to the cerebral circulation, basal brain regions, hippocampus and the brain stem, offers an approach that allows for preferential cooling of some of the most selectively vulnerable areas of the brain.[8] The device has been tested in a porcine model of prolonged ventricular fibrillation cardiac arrest both with and without cardiopulmonary resuscitation (CPR). In the CPR group, jugular venous temperature, which was used as surrogate for brain temperature, dropped from 38.1^{o}C to 34.2^{o}C within 5min of the onset of CPR and cooling. Importantly, the rate of brain cooling as measured by a temperature probe placed in the center of the right frontal lobe was almost the same at 60 min in the zero flow (no CPR) group as it was in the groups with spontaneous circulation and low flow (CPR) circulation (see **Figure 9-37**).[3] When perfusion is absent, cooling of the brain is by conduction, via the cribiform plate and frontal sinuses.

The RhinoChill device (**Figure 9-38**) consists of the tubing set, the control unit, and the coolant bottle. The tubing set delivers oxygen and coolant to the patient. The cooling cannulae rest in the nasal cavity adjacent to the chonchae and have spray ports on their dorsal surface (**Figure 9-39**). The coolant is nebulized by turbulent mixing with oxygen at the spray ports. A battery operated control unit controls coolant flow rate and acts as an over-pressure shut-off

valve. The patient pressure safety circuitry switches the system to a standby mode if the pressure in either nasal cavity exceeds 60 cm H_2O. Coolant delivery is maintained at a constant ratio to oxygen flow such that cooling level is controlled by setting the oxygen flow rate between 0 and 80 L/min. The patient's mouth is kept open to provide venting of the coolant vapor. Duration of nasopharyngeal cooling in the clinical trial has been 60 minutes (50;90; range 25–195 min), and the amount of refrigerant per-patient used was 3.5 liters (2.0; 4.0 L).[2]

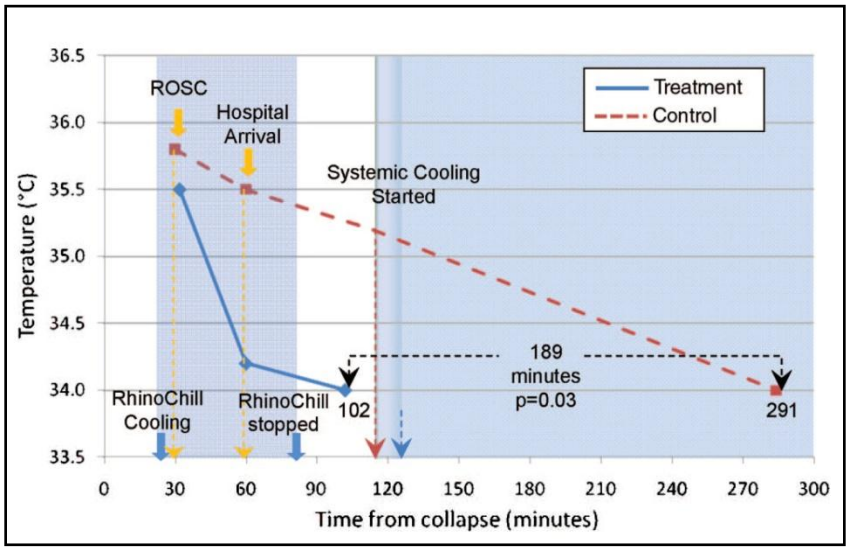

Figure 9-41: *Time to target temperature (tympanic) of 34°C in minutes (median) from the cardiac arrest in the treatment and control groups among those patients admitted to the hospital.*

In the latest human trials a tympanic temperature of 34°C was achieved by a median of 102 minutes (interquartile range 81 to 155 minutes) in the treatment group compared with 291 minutes (interquartile range 183 to 416 minutes, P0.03) in control patients (**Figure 9-41**). Median time to target temperature (core) of 34°C in the treatment group was 155 minutes (interquartile range 124 to 315 minutes) versus 284 minutes (interquartile range 172 to 471 minutes) in control patients (**Figure 9-41**). The time required to apply the device was ~2 min. The improvement in outcome in neurologically intact survival is shown in **Figure 9-42**.[4]

These cooling rates may not seem impressive, and the relevance of this device to human cryopreservation may seem questionable. Undoubtedly the cost of the device and the PFC refrigerant will be prohibitive if the device is FDA approved for widespread clinical application. However, neither the likely high cost nor the modest cooling rate should obscure the fact that this technology demonstrates that a substantial increase in the rate of brain cooling can be achieved by using the heretofore unutilized surface area of the nasopharynx and frontal sinuses. Whether exploited by evaporative PFC cooling, or by the use of an aqueous heat exchange medium, this surface area should be exploited in inducing hypothermia in cryopatients, and in particular in cooling the brain. The advantages that the RhinoChill system has of not requiring bulky, heavy equipment and of leaving the nasooropharynx (NOP) devoid of liquid are also substantial. Introducing saline or other liquids into pharynx carries with the risk of aspiration in the mechanically ventilated patient.

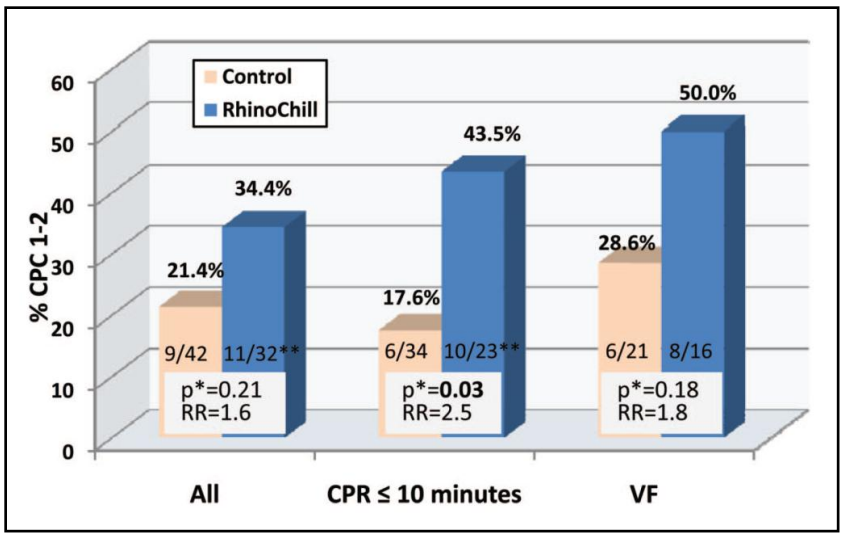

Figure 9-42: *Rates of neurologically intact survival (defined as having a cerebral performance category [CPC] of 1 or 2) in the treatment and control groups among those patients admitted to the hospital for the entire group, those who received rescuer CPR within 10 minutes, and those with a presenting rhythm of VF. RR indicates relative risk.*
**Unadjusted X_2 test.*
***In one admitted patient, outcome data were missing.*[2]

While the RhinoChill uses compressed oxygen and a fairly sophisticated delivery device, it is easily possible to substitute compressed air for oxygen, fabricate a less expensive delivery system, and presumably find an acceptable azeotrope of PFCs to use as the refrigerant. Perfluropropane and one or more of the 3M Fluorinert liquids would seem to be a good starting place. Alternatively, chilled saline can certainly be used as it was in the RhinoChill swine pilot study. While liquid assisted pulmonary cooling (LAPC) may seem an attractive alternative to transnasal cooling, there are many problems with this approach including the risk of serious systemic embolization with PFC during closed chest CPS in patients with friable or seriously injured lungs.

Finally, it is important to keep in mind that, with due consideration to cost and logistics, the various approaches to cooling mentioned earlier are complementary and synergistic, rather than opposing or exclusive. As is the case with cold IV saline and external cooling, the RhinoChill, as a standalone method for rapid induction of hypothermia (-3^{o}C in ≤ 15 min), will not suffice. However, in combination with other easily applied and non- or minimally-invasive modalities it may prove the long sought answer to the problem of cooling the brain by 3^{o}C in (ideally) 10 minutes at most.

REFERENCES

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