Alcor A-3450

Case Report

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Table of Contents

1. Summary

Information was derived from multiple sources and was all converted to Mountain Standard Time (MST). For de-identification, dates are not shown. T-0 represents the date of pronouncement of legal death, T-X represents occurrences before T-0, and T+X represents occurrences following T-0.

A-3450 was a 67-year-old member with neuro cryopreservation arrangements. The cause of death on the death certificate was cancer. The member is estimated to have gone into cardiac at 13:40 hrs and was within one minute pronounced legally deceased in Virginia at 13:40 hrs on T-0 days in 2022.

After stabilization and Field Cryoprotection (FCP), the patient was air transported to Alcor for cryogenic cooldown. The patient arrived at Alcor at 12:55 hrs on T+2 days. The cryogenic cooldown was initiated on T+2 days at 13:15 hrs and terminated on T+7 days at 10:18 hrs. The patient was transferred to long-term maintenance at liquid nitrogen temperature on T+73 days at 14:03 hrs. CT scans were made of the patient's brain while in liquid nitrogen at 11:18 hrs on T+109 days.

2. Patient Assessment

T-1 days

The member had not communicated with Alcor about current medical status and Alcor only became aware when called by the member's nurse. The member had a history of multiple strokes, pneumonia, hypoxemic respiratory failure, anemia, potential aspiration, and was Legionella positive, for which broad spectrum antibiotics had been prescribed. The member had undergone recent cyber knife treatment for one of the brain metastases. At 14:43 hrs Alcor's Medical Advisor had spoken with the member's physician and reported that the member had been admitted late the previous evening with stable vital signs.

The member was drinking small amounts of liquids, making some concentrated urine, and was receiving blood transfusions and antibiotics. At this point, the member was a full code, but the hospital was approaching the family to reverse this. The member was not yet critically ill enough to be moved to the intensive care unit (ICU), but assessment of how the member would respond to treatment would help determine when a deployment would be advisable.

3. Deployment and Stabilization

T-0 days

The hospital reported at 07:02 hrs that the member was in steady decline and would be switched to comfort care only. Alcor's Deployment Committee called a Level-1 deployment. International Cryomedicine Experts (ICE), one of Alcor's strategic partners for providing standby, stabilization and transport (SST) as well as field cryoprotection, was immediately deployed.

Sidebar:
The medical personnel on the Alcor Deployment Committee have determined a list of medical indicators that have either a Level-1, or a high probability of death within seven days, or a Level-2, a medium probability of death within seven days. The Deployment Committee voting members use these criteria when considering if a deployment is necessary.

The member went into cardiac arrest, was pronounced legally deceased by hospital personnel, and was covered with ice at approximately13:40 hrs. The ICE team was still enroute. The funeral home that had been contracted was alerted to pick up the patient, transport to the funeral home, and to continue cooling with water ice until the ICE team arrived. No portable ice bath was used (see the Discussion section).

The ICE team arrived at the funeral home at 23:05 hrs. Mechanical chest compressions using the ROS-Q device were started at 23:13 hrs. An intraosseous device was placed in the tuberosity of the left leg to access the vasculature for the administration of stabilization medications. The first medication was administered at 23:17 hrs (see the below Table of Medications Administered for the names of the medications, the dosages, and the times of administration) and the last medication was administered at 23:30 hrs.

4. Field Surgery and cryoprotection

At 23:35 hrs the surgical trays were ready and the perfusion system with bladders of precalculated concentrations of M22 cryoprotectant had been set up. Cardiopulmonary support was discontinued at 23:38 hrs. The data logger was not working so the patient's nasopharyngeal temperature (NPT) could not be recorded (see the Discussion section). The patient was prepped for surgery at 23:42 hrs. The first incision for the burr holes was made at 23:44 hrs. The right burr hole was completed at 23:48 hrs using a Codman perforator and chilled saline to cool the Codman perforator and the skull. The left burr hole was similarly established at 23:53 hrs. The burr holes were cleaned of debris and a thermocouple was placed in the right burr hole to obtain temperatures and was sutured to the scalp as a surgical stapler was not in the kit.

T+1 days

The right carotid artery was isolated and raised at 00:01 hrs and cannulated with a rigid, 18 French (Fr) cannula at 00:03 hrs. The left carotid artery was isolated and raised at 00:07 hrs and cannulated with a rigid, 18 French (Fr) cannula at 00:08 hrs.

At 00:08 hrs 25,000 IU of streptokinase, a thrombolytic used to break up existing blood clots, was added to the first bladder to be used for cryoprotectant perfusion. The gravity-induced perfusion flow was initiated at 00:12 hrs with Bladder #2 containing nM22 cryoprotectant with a concentration of 0.05 concentration needed to vitrify (CNV) (see the Table of Concentrations (Brix) of nM22 Solution, for the times the bladders were started, the precalculated concentrations of each bladder, and the refractive index of effluent samples taken).

The cephalic isolation was started at 00:12 hrs and finished at 00:14 hrs using a mallet and microtome. The vertebral arteries were draining, which confirmed that the Circle of Willis was intact and there would be reasonable perfusion pressure at the back of the brain. An

attempt to cannulate the vertebral arteries was not successful as the cannulae kept slipping free of the vessels. The vertebral arteries were clamped off to keep the Circle of Willis pressurized and thereby optimize brain perfusion (see the Discussion section).

By hanging two bladders with different cryoprotectant concentrations on a teeter-totter atop an elevated tripod, a smoother transition of increasing concentrations of cryoprotectant can be achieved (see the Discussion section for a more detailed explanation of the field equipment).

The height of the bladders on the teeter totter was 39 inches which is (39" x 2.054 mmHg per inch of height =) 80 mmHg maximum arterial pressure at the infusion site. The goal is to have the pressure between 70 and 80 mmHg and the bladders can be raised or lowered as needed to optimize flow and protection of the vasculature.

Sidebar:
Per the cryoprotection protocol, the ramp is to be paused at 30 Brix (50% of the desired terminal concentration) to allow the patient to come to osmotic equilibrium. When the bladder system is used, bladders 6 & 7 represent the pause. The cephalic/patient enclosure and the chiller are switched from +3°C to -3°C operation. At the end of the 30-minute pause, the ramp is resumed at the maximum addition rate (maximum without losing total volume in the circuit) to go to 105% of the desired end concentration (52.5 Brix) and held between 102% and 105% concentration until the terminal concentration is obtained.

Bladder #6 was started at 01:55 hrs and ethylene glycol antifreeze was added to the water in the heat exchanger at 02:02 hrs to bring the perfusate below 0°C. At 04:45 hrs the refractive index (RI) of the effluent was 50 Brix, and the one-hour countdown to termination of cryoprotectant perfusion was started. Cryoprotectant perfusion was terminated at 05:47 hrs. The final RI concentration was 51.2 Brix.

An eyebolt was placed in the patient's vertebra for handling and the patient was moved to the dry ice shipper at 06:08 hrs and covered with approximately 8 lbs. of dry ice, the maximum the shipper would hold, at 06:10 hrs. The ICE team left the patient at the funeral home to make travel arrangements to transport the patient to Alcor the next day.

5. Patient Transport

T+2 days

The ICE team returned to the funeral home to pick up the patient. They left the funeral home at approximately 06:45 hrs to transport the patient to the airport. The patient's nasopharyngeal temperature (NPT) was -71.95°C. No transit permit was needed as the neuro patient was checked in as baggage. The ICE team was on the same flight, which left for Phoenix at 07:12 hrs.

6. Cooling to Liquid Nitrogen Temperature

The patient arrived at Alcor at 12:55 hrs. The nasopharyngeal temperature was -76°C and the burr hole temperature was -69°C.

Computer controlled cryogenic cooldown was initiated at 13:15 hrs on T+2 days, plunging to -110°C and descending thereafter at -1°C/hour to liquid nitrogen temperature. On T+7 days, an uneventful cooldown was terminated. On T+73 days at 14:03 hrs the patient was transferred to long-term maintenance at liquid nitrogen temperature. On T+109 days at 11:18 hrs CT scans were made of the patient's brain while in liquid nitrogen.

7. Timeline and Time Summaries

Timeline

T-0	13:40	Estimated time of cardiac arrest
T-0	13:40	Pronouncement of legal death
T-0	23:05	Team arrived at funeral home
T-0	23:13	Start of mechanical chest compressions
T-0	23:15	Placement of intraosseous device
T-0	23:17	Administration of first medication (20 g sodium citrate)
T-0	23:30	Administration of final medication (200 ml deca/THAM)
T-0	23:38	Termination of cardiopulmonary support
T-0	23:44	Start of field surgery
T+1	00:10	End of field surgery (estimated)
T+1	00:12	Start of open circuit cryoprotection (FCP)
T+1	00:14	Completion of cephalic isolation
T+1	01:55	Start 30-minute pause for equilibration
T+1	04:45	Start of one hour countdown to termination of perfusion
T+1	05:47	End of open circuit cryoprotection (final RI = 51.2 Brix)
T+1	06:10	Start of dry ice cooling
T+2	07:12	Departure of patient from airport
T+2	12:55	Arrival of patient at Alcor (NPT -76°C)
T+2	13:15	Start of patient cryogenic cooldown
T+7	10:18	End of cooldown
T+73	14:03	Transfer of patient to long-term care at LN2 temperature
T+109	11:18	CT scan at LN2

Time Summaries

Event Duration hr:min		days	time	
FIELD STABILIZATION				
00:00	From:	T-0	13:40	Estimated time of cardiac arrest
	Till:	T-0	13:40	Pronouncement of legal death
09:33	From:	T-0	13:40	Estimated time of cardiac arrest
	Till:	T-0	23:13	Start of mechanical chest compressions
09:37	From:	T-0	13:40	Estimated time of cardiac arrest
	Till:	T-0	23:17	Administration of first medication (20 g sodium citrate)
00:13	From:	T-0	23:17	Administration of first medication (20 g sodium citrate)
	Till:	T-0	23:30	Administration of final medication (200 ml deca/THAM)
FIELD SURGERY AND CRYOPROTECTION (FCP)				
10:04	From:	T-0	13:40	Estimated time of cardiac arrest
	Till:	T-0	23:44	Start of field surgery
00:26	From:	T-0	23:44	Start of field surgery
	Till:	T+1	00:10	End of field surgery (estimated)
10:32	From:	T-0	13:40	Estimated time of cardiac arrest
	Till:	T+1	00:12	Start of open circuit cryoprotection (FCP)
05:35	From:	T+1	00:12	Start of open circuit cryoprotection (FCP)
	Till:	T+1	05:47	End of open circuit cryoprotection (final RI = 51.2 Brix)
06:32	From:	T-0	23:15	Placement of intraosseous device
	Till:	T+1	05:47	End of open circuit cryoprotection (final RI = 51.2 Brix)
00:30	From:	T-0	23:44	Start of field surgery
	Till:	T+1	00:14	Completion of cephalic isolation
00:28	From:	T-0	23:44	Start of field surgery
	Till:	T+1	00:12	Start of open circuit cryoprotection (FCP)
06:03	From:	T-0	23:44	Start of field surgery
	Till:	T+1	05:47	End of open circuit cryoprotection (final RI = 51.2 Brix)
DRY ICE AND LIQUID NITROGEN COOLDOWN				
31:28	From:	T+1	05:47	End of open circuit cryoprotection (final RI = 51.2 Brix)
	Till:	T+2	13:15	Start of patient cryogenic cooldown
47:35	From:	T-0	13:40	Estimated time of cardiac arrest
	Till:	T+2	13:15	Start of patient cryogenic cooldown
47:15	From:	T-0	13:40	Estimated time of cardiac arrest
	Till:	T+2	12:55	Arrival of patient at Alcor (NPT -76°C)
00:20	From:	T+2	12:55	Arrival of patient at Alcor (NPT -76°C)
	Till:	T+2	13:15	Start of patient cryogenic cooldown

8. Table of Medications Administered

T-0 days

TIME	MEDICATION	DOSE	PURPOSE
T-0 days 23:17 hrs	Sodium citrate	20 g Note 1	Anticoagulant; prevents blood clot formation.
23:19 hrs	Streptokinase	250,000 IU Note 2	A thrombolytic used to break up existing blood clots.
23:23 hrs	Heparin	50,000 IU	Anticoagulant; prevents blood clot formation.
23:27 hrs	Decaglycerol/THAM	200 ml Note 3	Decaglycerol inhibits cerebral edema.
23:30 hrs	Minocycline	200 mg	Antibiotic; reduces microbial overgrowth during long transport times.
T+1 days 00:08 hrs	Streptokinase	250,000 IU Note 2	A thrombolytic used to break up existing blood clots.

Notes:

1. The standard formulation for sodium citrate is 20% w/v, in sterile packaging provided by the manufacturer. 10 grams of sodium citrate are given to patients who weigh less than 40 kg, and 20 grams are given to patients who weigh over 40 kg. This patient weighed more than 40 kg and received 20 grams of sodium citrate.

2. The standard administration of streptokinase is 250,000 IU dissolved in 5 mL of 9% sodium chloride. This medication previously needed to be infused through a 0.2 µ filter. The medication now in use is already sterile filtered and can be reconstituted in the vial.

3. Decaglycerol/THAM is administered as a custom formulation of 20% w/v decaglycerol and 4.5% w/v THAM (tromethamine) in water(pH = 10.4 and pKa = 8.3).

9. Table of Concentrations (Brix) of nM22 Solution

A-3450 step-ramp, nM22									
Preferred endpoint is over 49.9 Brix from both jugulars for 1/2hr									
2L Bag label number	[nM22], CNV	Molarity of penetrating CPAs*	Brix (calc)	Bag start hh:mm, MST	hrs post pronounc-ement	Bag avg. flow rate, mL/min		Sample time hh:mm, MST	Effluent Conc., Brix
2	0.05	0.47	11.81	0:28	7.58	142.9		2:44	41.6
3	0.08	0.78	13.14	0:42	7.82	76.9		3:00	42.8
4	0.14	1.29	15.35	1:08	8.25	76.9		3:24	47.3
5	0.23	2.15	19.03	1:34	8.68	95.2		4:14	48.1
6	0.50	4.67	29.85	1:55	9.03	90.9		4:45	50
7	0.50	4.67	29.85	2:17	9.40	76.9		5:02	50.4
8	1.06	9.91	52.306	2:43	9.83	125.0		5:30	50.4
9	1.06	9.91	52.306	2:59	10.10	87.0		5:47	51.2
10	1.06	9.91	52.306	3:22	10.48	87.0			
11	1.06	9.91	52.306	3:45	10.87	80.0			
12	1.06	9.91	52.306	4:10	11.28	74.1			
13	1.06	9.91	52.306	4:37	11.73	83.3			
14	1.06	9.91	52.306	5:01	12.13	71.4			
15	1.06	9.91	52.306	5:29	12.60	142.9			
16	1.06	9.91	52.306	5:43	12.83	500.0			
END				5:47	12.90				
* does not account for concentration of non-penetrating CPAs									

When the bladders with precalculated concentrations of cryoprotectant are made up in the lab, the first bladder in the series contains only the B1 carrier solution with no cryoprotectant and was intended to be used for purging air bubbles. Bladder #2 contains the lowest concentration of cryoprotectant. Limited experience with the bladder system, however, has shown that better edema control is provided when the initial perfusion is done with cryoprotectant. As a result, cryoprotectant perfusion is initiated with Bladder #2. When there is sufficient experience to make this the standard protocol, the lab procedure for creating the Bladders will be changed so that Bladder #1 will contain cryoprotectant.

10. Discussion

Standby and Stabilization

No portable ice bath was used on this case. The contractor has been educated about the importance of the ice bath and will always use it on future cases.

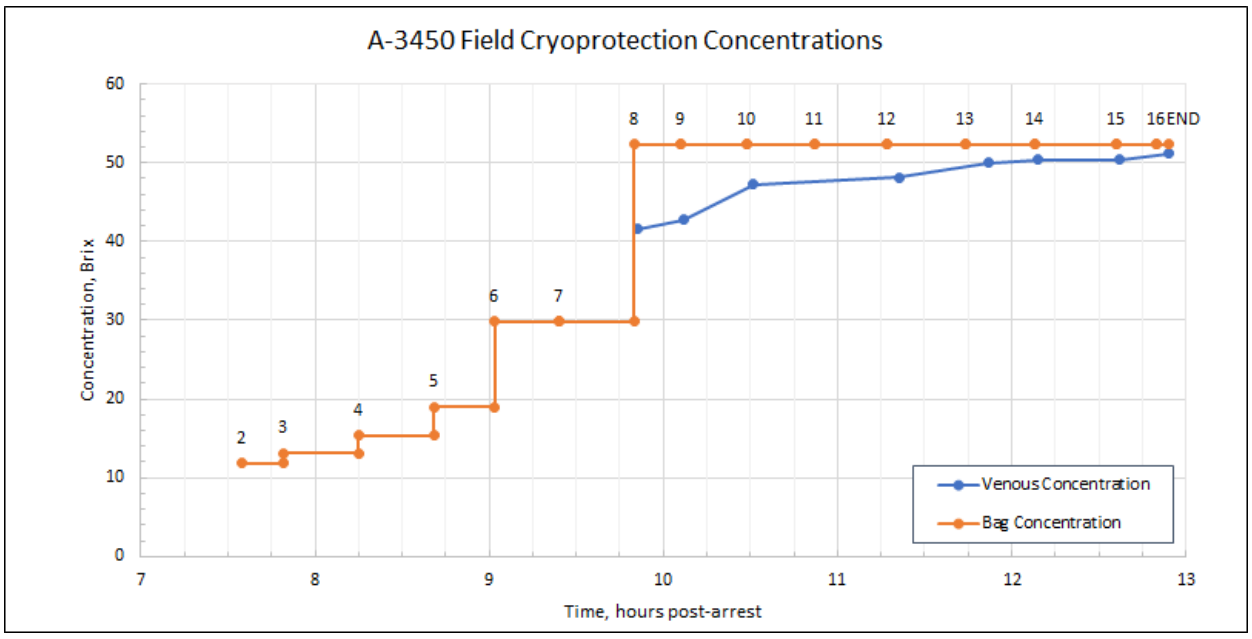
Data was periodically lost from the left nasopharyngeal temperature (NPT) probe during perfusion, transport, and cooldown. The temperature probes appeared to be functioning upon arrival to Alcor, so the left nasopharyngeal probe was randomly chosen of the two probes to be connected to the cooldown computer. This loss of temperature information was not noted during the case, and a definite cause for the gap in the data has not been determined. Due to the fact that data loss was intermittent even when the logging device was changed, it is suspected that the thermocouple may have been defective or had a loose connection internally.

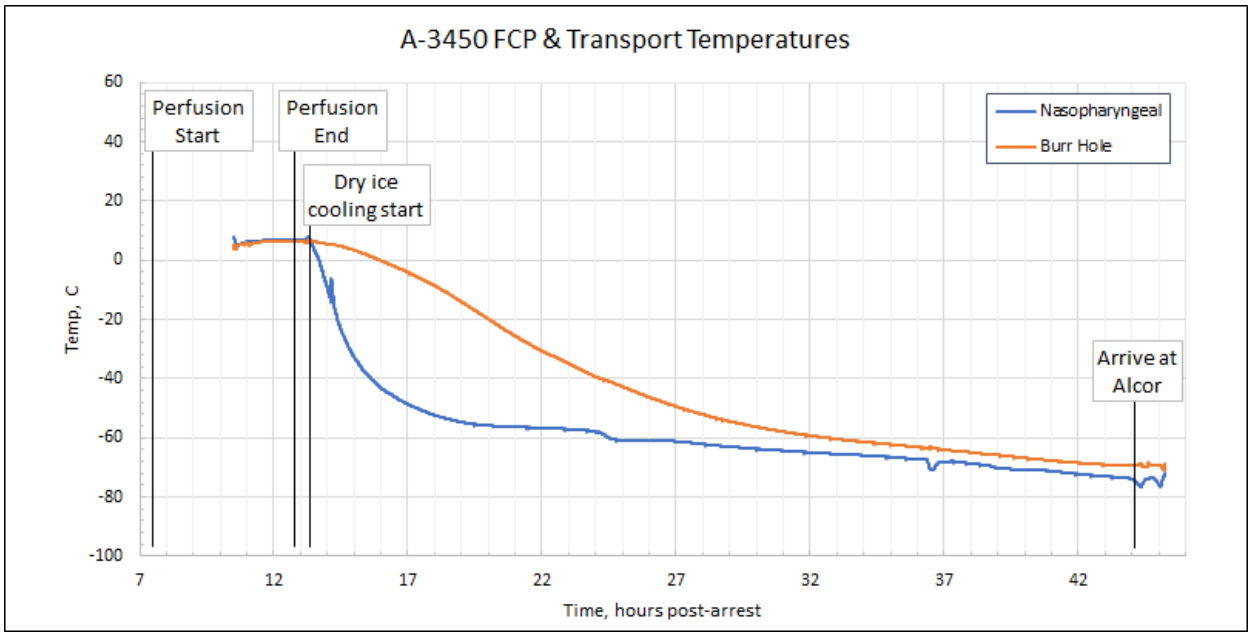
Streptokinase was administered twice to this patient. The contractor has been given additional training so that the second dose will not be administered in the future.

Field Surgery and FCP

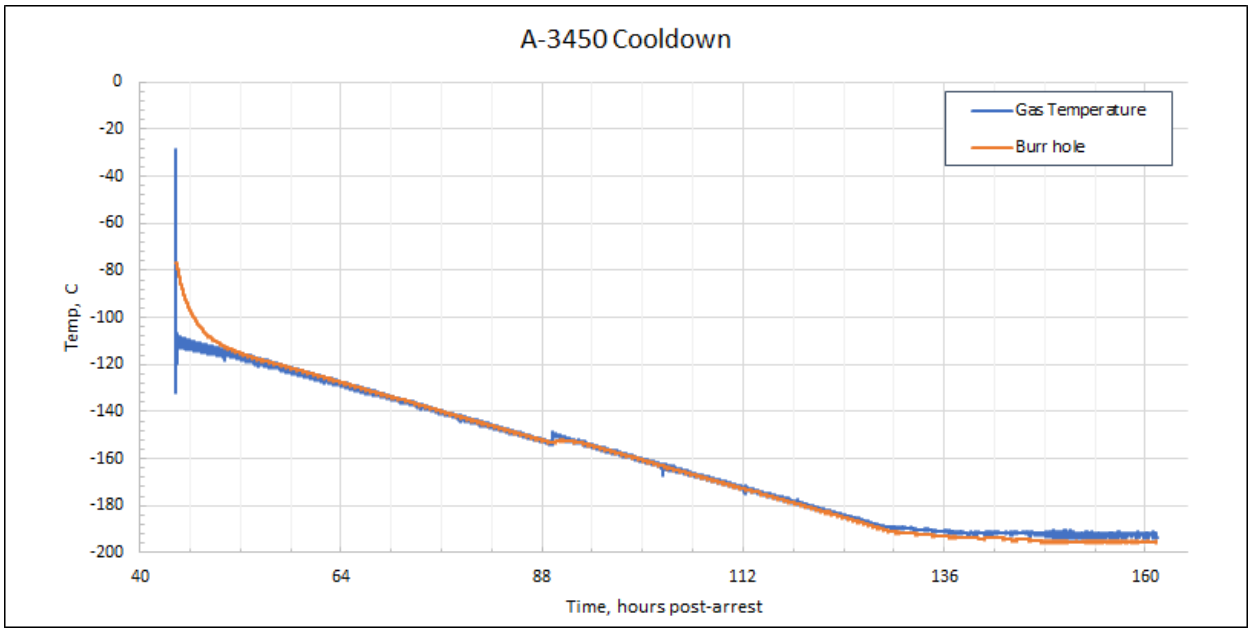
The cannulae in the kit would not stay in the vertebral arteries but kept slipping free of the vessels. Alcor staff is currently working on designing and printing new vertebral artery cannulae to prevent this from occurring in the future.

11. Cryoprotection and Temperature Graphs





The FCP temperature log did not begin until 3.2 hours after the start of step ramp cryoprotection because the data logger was not functioning, and the backup had to be restored at the funeral home via computer.



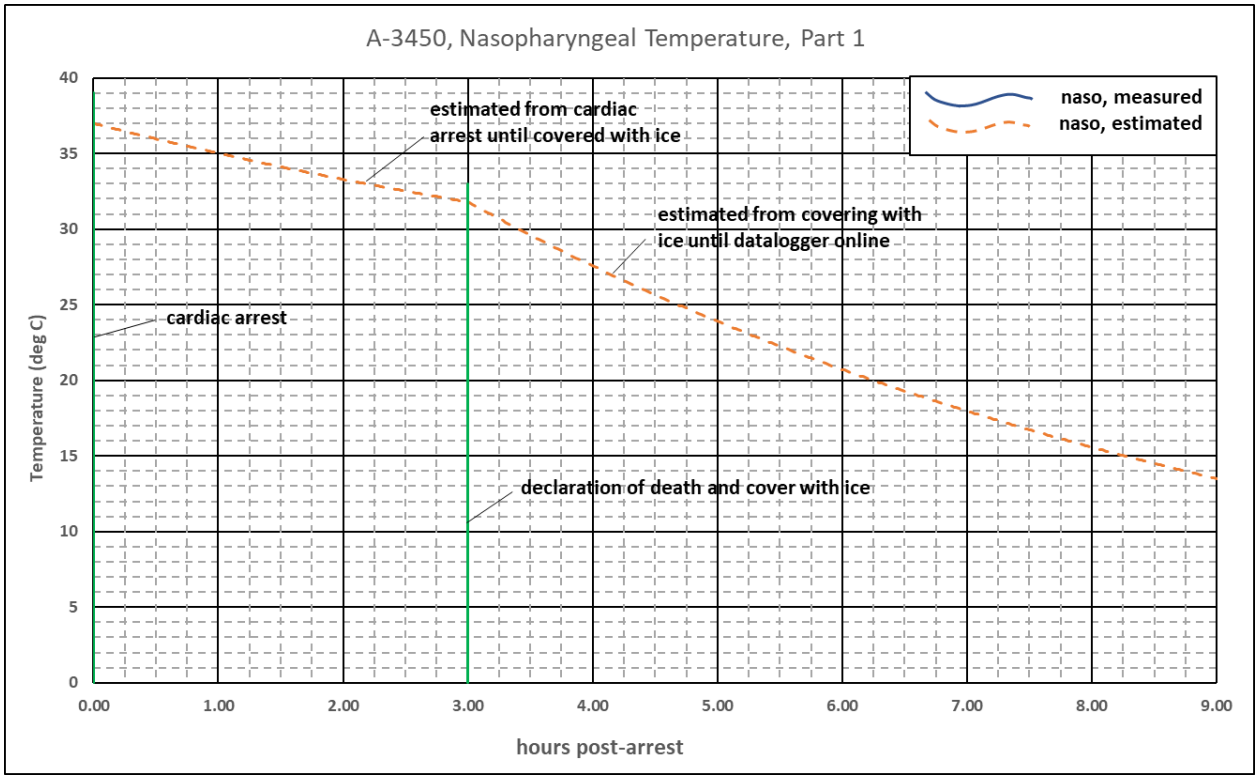
The cooldown graph shows a typical cooldown from dry ice temperatures, with a small deviation observed around 90 hours into the procedure. The cause of this deviation is not known.

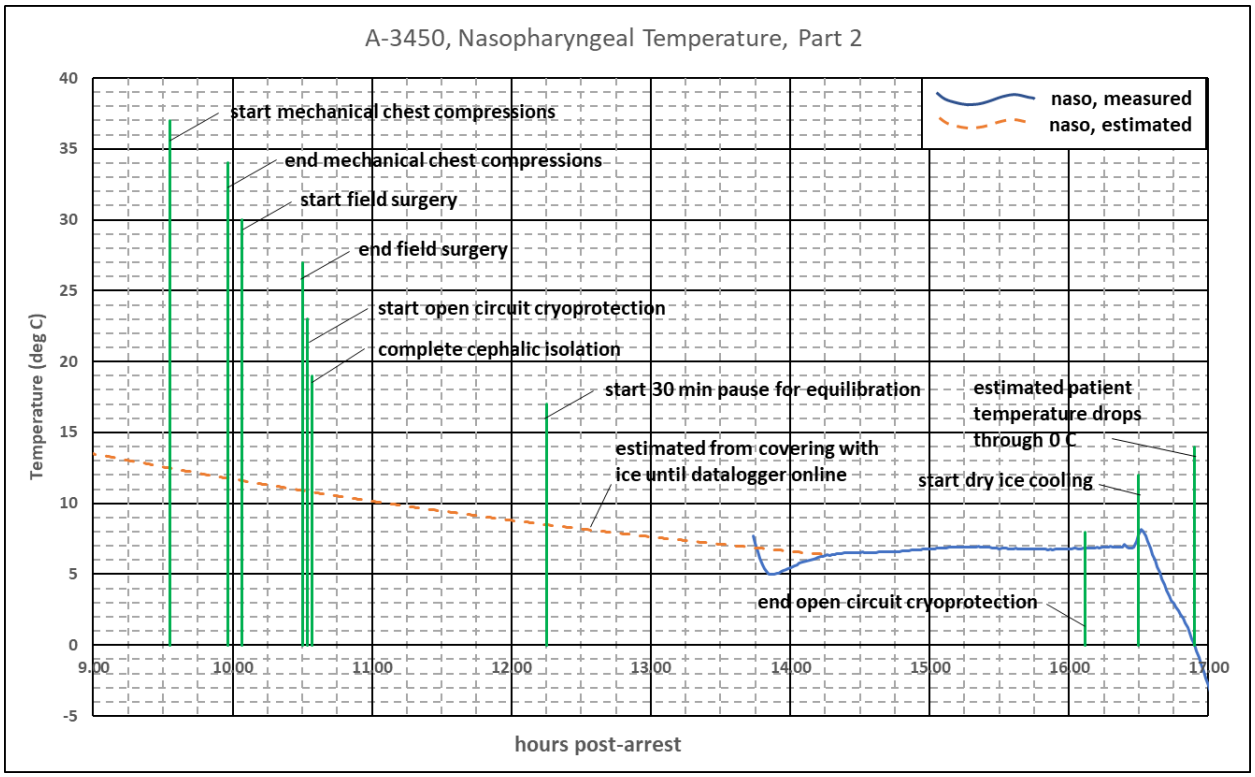
12. S-MIX

The Standardized Measure of Ischemic Exposure (S-MIX) expresses the total ischemic exposure prior to the start of cryogenic cooling as the equivalent duration of normothermic ischemia. An S-MIX of 00:00 (hh:mm) is the ideal case of no ischemic damage. The higher the S-MIX time, the more damage. Factors that improve the S-MIX, and that are quantitatively accounted for in the below table are: shorter times at higher temperatures, ventilation during cardiopulmonary support (CPS), and oxygenation during blood washout. The duration from cardiac arrest to 0°C is 16:54. As shown below, and due to lowering of the body temperature, S-MIX duration is shorter, at 05:46.

event	ment #	(T+X)	duration	arrest	(deg C)	ventil.	oxygen.	(hh:mm)
Estimated time of cardiac arrest		T-0	13:40	00:00	37.0			
	seg 1		03:00	03:00	-5.2	no	no	02:29
Pronouncement of death & covered with ice		T-0	16:40	03:00	31.8			
	seg 2		06:33	06:33	-19.3	no	no	02:17
Start of mechanical chest compressions		T-0	23:13	09:33	12.5			
	seg 3		00:25	00:25	-0.7	no	no	00:04
Termination of cardiopulmonary support		T-0	23:38	09:58	11.8			
	seg 4		00:06	00:06	-0.2	no	no	00:01
Start of field surgery		T-0	23:44	10:04	11.6			
	seg 5		00:26	00:26	-0.7	no	no	00:04
End of field surgery (estimated)		T+1	00:10	10:30	10.9			
	seg 6		00:02	00:02	-0.1	no	no	00:00
Start of open circuit cryoprotection (FCP)		T+1	00:12	10:32	10.9			
	seg 7		00:02	00:02	-0.1	no	no	00:00
Completion of cephalic isolation		T+1	00:14	10:34	10.8			
	seg 8		01:41	01:41	-2.3	no	no	00:15
Start 30-minute pause for equilibration		T+1	01:55	12:15	8.5			
	seg 9		03:52	03:52	-1.7	no	no	00:29
End of open circuit cryoprotection		T+1	05:47	16:07	6.8			
	seg 10		00:23	00:23	1.0	no	no	00:03
Start of dry ice cooling		T+1	06:10	16:30	7.8			
	seg 11		00:24	00:24	-7.3	no	no	00:03
patient temperature thru 0deg C		T+1	06:34	16:54	0.5			
totals:			16:54	16:54	-36.5			05:46

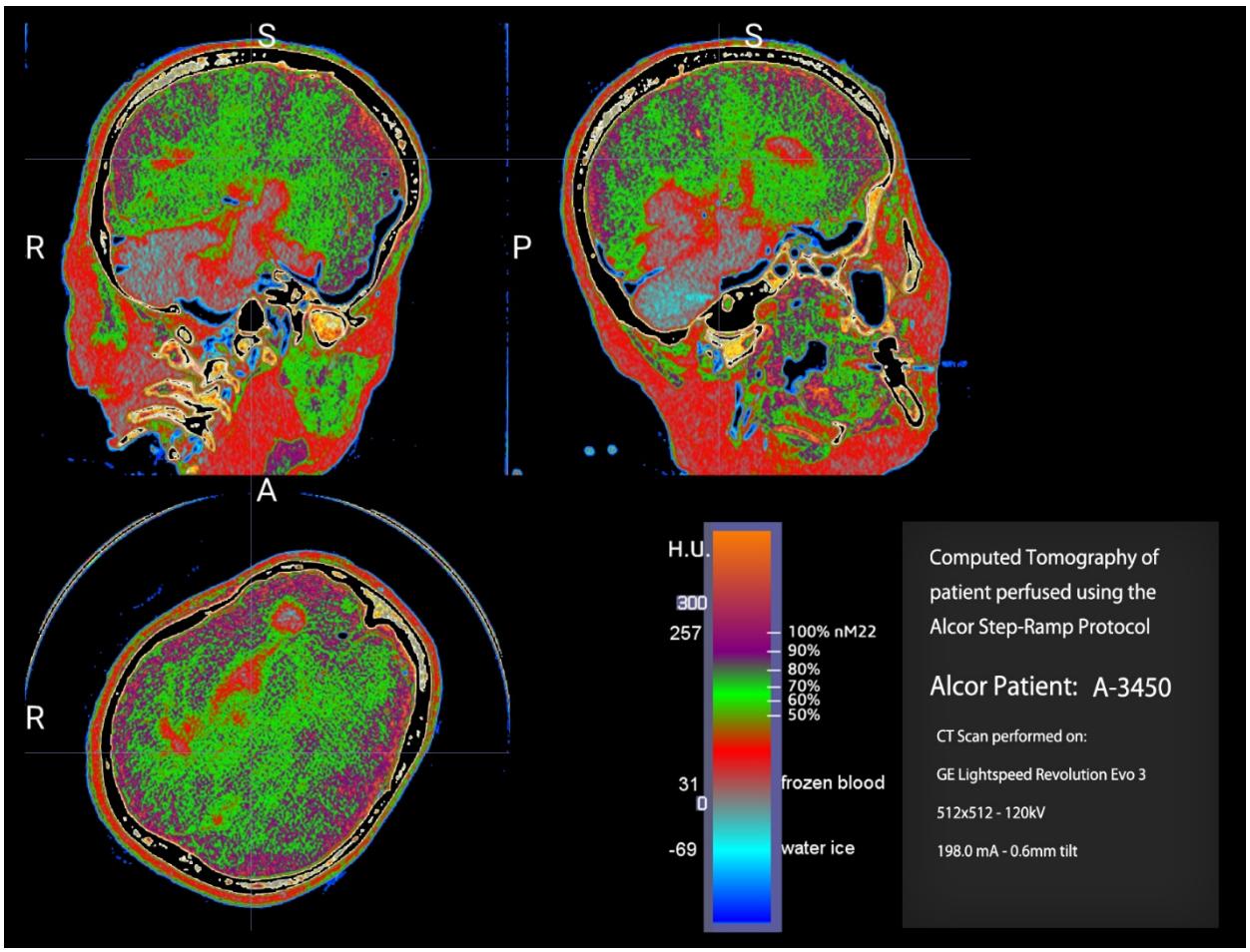
The below plots show events related to the S-MIX calculation. A delay in datalogger operation necessitates the estimation of body temperature in two phases. Shown below are Newtonian temperature declines, first from cardiac arrest at room temperature until ice is applied, and second, from the application of ice until the datalogger is online.


A-3450, Nasopharyngeal Temperature, Part 1
naso, measured
naso, estimated
estimated from cardiac arrest until covered with ice
estimated from covering with ice until datalogger online
cardiac arrest
declaration of death and cover with ice
Temperature (deg C)
hours post-arrest
0
5
10
15
20
25
30
35
40
0.00
1.00
2.00
3.00
4.00
5.00
6.00
7.00
8.00
9.00


A-3450, Nasopharyngeal Temperature, Part 2
naso, measured
naso, estimated
start mechanical chest compressions
end mechanical chest compressions
start field surgery
end field surgery
start open circuit cryoprotection
complete cephalic isolation
start 30 min pause for equilibration
estimated patient temperature drops through 0 C
estimated from covering with ice until datalogger online
start dry ice cooling
end open circuit cryoprotection
Temperature (deg C)
hours post-arrest
-5
0
5
10
15
20
25
30
35
40
9.00
10.00
11.00
12.00
13.00
14.00
15.00
16.00
17.00

13. CT Scans

Cryoprotectant Distribution (Post-cryopreservation CT scan)



The post-cryogenic cooldown CT scan was obtained on T+109 days; the patient was at liquid nitrogen temperature (-196°C).

Notably, there was no brain shrinking caused by dehydration. This lack of dehydration is more commonly observed in patients with cancer. Cryoprotectant perfusion appears incomplete to non-existent in the left posterior portion of the occipital lobe, cerebellum, medulla oblongata and cerebellar cortex. The areas of the brain that were perfused with cryoprotectant achieved approximately 80% to 100% CNV. An uneven and somewhat incomplete cryoprotectant perfusion is indicative of brain edema consistent with approximately 6 to 7 hours of ischemia prior to surgical access and subsequent field perfusion.