14. Monitoring

This section concerns monitoring and data collection during cryonics stabilization procedures. Monitoring of the patient during stabilization will be broadly defined, and we will include the collection of data during deployment and standby.

Data collection during other phases of human cryopreservation is discussed in other sections, as follows:

Blood gas analysis	Section 15
Blood washout and substitution	Section 16
Cryoprotection	Section 18
Cryogenic cooling	Section 19

Feedback from Cryonics Procedures

One of the biggest myths in cryonics is that only the future can tell us how good our procedures were. It is of course correct that the objective of cryonics is to revive and restore patients in good health. In this strict sense, only the future will tell us whether this ultimate goal has been achieved. But when we look at the actual cryonics procedures that are employed to place a patient in cryostasis, we will find that many of these procedures have specific objectives that allow for data collection and evaluation today.

For example, one of the objectives of cardiopulmonary support is to generate sufficient blood flow to the brain to support metabolic demand. One of the objectives of blood washout is to increase the cooling rate of the patient. The objective of cryoprotection is to protect the patient against ice formation. During each of these procedures, data can be collected to assess how well the

objectives have been achieved. This will also allow us to compare protocols and cases and identify areas for improvement.

Another important objective of data collection and monitoring is to identify strengths and weaknesses in standby teams and personnel.

In an ideal situation the objective of a cryonics organization to meet these objectives would be treated in the same way as the objective of keeping a patient alive in mainstream medicine. Unfortunately, there is a real difference between keeping a patient alive and viable and checking off a number of quantitative goals on a data collection sheet during a cryonics case. If a hospital would be incompetent and understaffed in a case, the potential result could be the death of the patient, which would trigger a host of emotional, legal, and financial responses. In cryonics there is not a distinct point at which such a response would be triggered. Cryonics organizations and their members do not even necessarily agree on how much effort should be expended to prevent any additional damage after pronouncement of legal death.

All cryonics patients will need some treatment in the future to address the cause of death, and this requirement is often invoked to argue that the same technologies should be able to repair any additional damage that is sustained during cryopreservation. The perspective at Alcor, however, has been to resist such reasoning and to aim for minimizing the additional damage that the patient incurs during cryonics procedures. In short, the objective is to sustain viability of the brain as far downstream of our procedures as possible, and when this objective can no longer be achieved, to secure the best ultrastructural preservation of the brain as possible. It is this perspective that informs the discussion of data collection and monitoring in the remainder of this chapter.

Data Collection

Data collection starts when a member joins Alcor. On the application form, the member can enter physiological and health information that will be filed with cryopreservation contracts. Alcor encourages members to update this information if circumstances change. The information can not only assist

Alcor in estimating the risk of terminal illness of a member, but can also be used to inform deployment, stabilization, and cryopreservation decisions.

The real collection of data, however, typically starts when Alcor is notified of the pending death of a member. At this point staff will start gathering up-to-date information about the patient's health condition (a topic that is discussed in more detail in Section 7) to make standby and deployment decisions.

It is routine in cryonics that staff members dealing with the case keep a written record of the case as it develops. In circumstances where written notes are not possible, a voice recorder is a good option. The collection of data continues during the case either by people making notes, or through the use of (monitoring) equipment. After completion of the case all the data are organized and used to create a case report.

Voice Recorders

The use of voice recording is a powerful tool for data collection in a cryonics case. Their advantage in cryonics is that they allow team members to report about the case while performing other important tasks such as standby procedures or surgery. During procedures such as surgery or intubation, only the person who is doing the work has a good look at what is going on, and voice recording allows these procedures to be recorded. In some cases it is not even necessary that the person dictates directly to the equipment; even the recording of a conversation during a procedures (such as the priming of the washout circuit or surgery) can provide valuable information about the procedure.

Most modern voice recording equipment also provides timestamps. This will tell the writer of a case report not only what is going on but when it happened. This is particularly important when there is an omission in the data collection sheets, and to note crucial points during a case (cardiac arrest, start of cardiopulmonary support, administration of the first stabilization medication, and so on.) Reading the events and timestamps allows the case report writer to construct a timeline of the case. It is important to recognize here that team members should make a deliberate effort to synchronize their

watches and (recording) equipment to allow for a smooth reconstructing of the important events in a case.

Until quite recently voice recording required purchase and maintenance of specialized voice recorders that utilized special software to download the recordings to a computer. With the widespread adoption of cell phones, there is less need for such specialized equipment, and a phone can of course store video as well as audio.

Note, however, that a headset is necessary to record audio when the person is using both hands in a procedure. While many phones enable a headset to be connected via a USB cable, a suitable app may be needed to enable the phone to recognize the headset. Also, voice-actuated recording is helpful so that anyone transcribing audio subsequently will not have to listen to long periods of dead space. For these reasons, a separate, dedicated voice recorder still has some advantages.

Either way, there are few excuses to avoid audio and video recording in case work today. The lack of it shrouds cryonics in an aura of secrecy that damages credibility and makes it difficult to factually defend actions of cryonics team members if that should be necessary.

Temperature Monitoring

Cryonics is all about time and temperature. We would like to stabilize the patient at cryogenic temperatures without ice formation as quickly as possible after pronouncement of legal death. At the end of a case we should be able to graph the temperature of the patient as a function of time. Unlike other procedures, such as ventilation or cryoprotective perfusion, temperature data can be collected from the start of procedures until the patient is placed into liquid nitrogen (or intermediate temperature storage). Therefore, in a well-run cryonics case we should expect to see temperature data for all parts of the procedures, including transport.

This does not mean that the collection of temperature data is equally important throughout all parts of the procedure. While there is usually no good excuse to omit gathering temperature data in any part of our procedures, collecting temperature data during the initial stages of stabilization is of

crucial importance. As soon as the patient goes into circulatory arrest (and sometimes before that point) energy depletion of the brain will set off a cascade of events culminating in injury and perfusion impairment in the brain. The most potent strategy to counter this injury is to cool the patient as quickly as possible. Temperature monitoring is the only credible means to assess how successful initial induction of hypothermia has been, and how different (external) cooling methods compare.

The need to collect temperature throughout all parts of procedures requires that we log the temperature automatically instead of taking intermittent readings from the patient. During stabilization and transport this means the use of a portable temperature logging device, and during cryoprotective perfusion and low temperature cooling temperature probes in the patient will communicate data directly to a computer.

Another important requirement of good temperature monitoring is the ability to measure temperature at different locations in the patient. This can be achieved by using two temperature loggers, but the preferred solution in cryonics is to use a logger that receives inputs from two separate temperature probes. For a considerable period, the temperature logger of choice at Alcor has been the Digi-Sense DualLogR (SOP for cryonics use is available here: http://www.alcor.org/Library/pdfs/dualogr.pdf). The DualLogR is no longer available but has been replaced by the Oakton Temp-300 Dual-Input Datalogging Thermocouple Thermometer that retains the same functionalities and also allows direct uploading of the data to a USB port on a computer. See Figure 14-1.

Figure 14-1. The Oakton Temp-300 Dual-Input Datalogging Thermocouple Thermometer.

These devices not only permit time-stamped temperature logging of two temperature probes but also have the ability to change the logging interval, so they can be used in situations where the logging interval needs to be relaxed to prevent running into the maximum number of data points, such as during transport of the patient.

While the newer Oakton dual-input temperature logger seems more robust in terms of water damage, one of the challenges during cryonics stabilizations has been to prevent temperature logger malfunction as a result of immersion in the portable ice bath. For this reason some cryonics organizations have used water-proof cases to protect the logger against mechanical shock and fluids. Pelican brand cases are waterproof, and very small sizes are available, appropriate for most loggers.

There are a number of reasons for wanting to log temperatures measurements in different parts of the body. One reason is redundancy. If one temperature probe gets dislodged during movement of the patient, or transport,

temperature logging will not be interrupted. Over the years there have been multiple cases without reliable temperature data during a part of the procedure because a temperature logger did not work or the probe was disconnected. Such scenarios will be greatly reduced if multiple temperature probes are placed. Another reason for placing multiple probes is to ensure the collection of reliable data. If one temperature probe is incorrectly placed and not inserted far enough the result will be that the probe will just be measuring the temperature of ambient air or ice water. In both cases, temperature data will not be reliable.

Yet another reason for using multiple temperature probes is to identify (transient) regional temperature differences. For example, rectal temperatures have often been observed to lag core brain temperature. Finally, in procedures such as blood substitution we do not only need to log the temperature of the patient but monitor the temperature of the arterial and venous fluid as well. In such circumstances the use of multiple dual-input logging devices is recommended.

Temperature data are also useful for comparing the efficacy of different methods of cooling. Most of our knowledge about the relative effectiveness of different cooling methods in cryonics has been obtained from comparing case temperature data. For example, temperature data collection has allowed Alcor to rank internal and external cooling methods from least effective to most effective as follows:

1. External cooling with ice bags (slowest)
2. External cooling in ice bath with CPS (cardiopulmonary support by chest compressions)
3. External cooling in ice bath with CPS and with recirculating water ice (squid)
4. Cyclic lung lavage with CPS (liquid ventilation) under development
5. Extracorporeal cooling (fastest)

A comparison of different cooling methods in cryonics is shown in Figure 14-2. Because this figure shows cooling curves from three patients of

different body weight, the results are not strictly comparable, but they do suggest that an extracorporeal cooling device, colloquially known as a "squid," should be used in an ice bath. See Section 11, which discusses the induction of hypothermia.

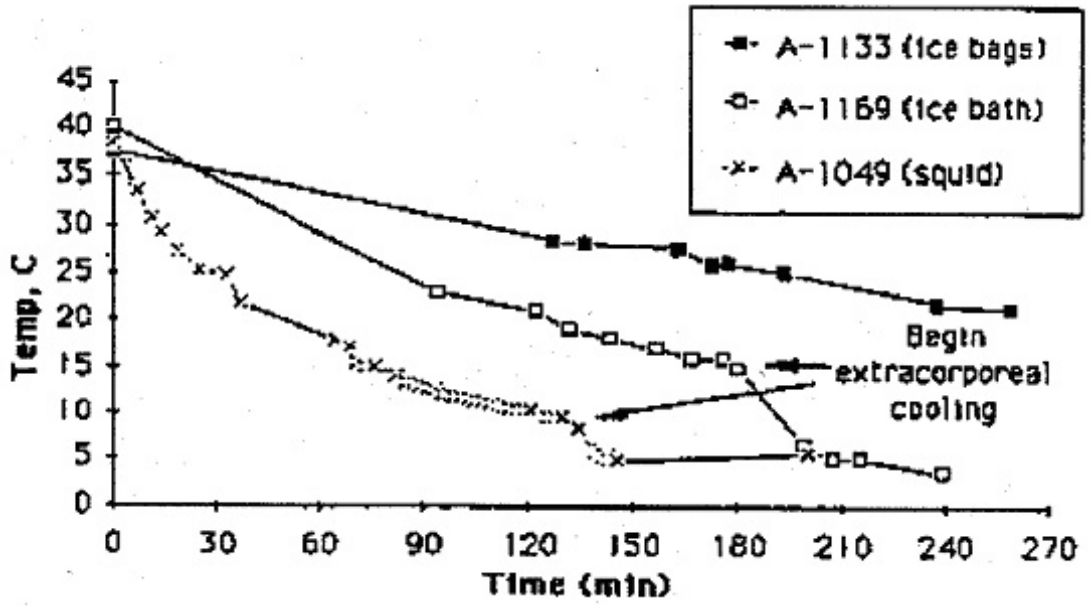

Figure 14-2. Cooling of patients in three Alcor cases. See text for caveats regarding this data.

While some people have a good intuitive grip at the efficacy of different cooling methods, collecting the actual data can still be revealing. For example, throughout the history of cryonics there have been multiple debates about the values of adding a submersible pump to circulate the ice water in the ice bath. But as this graph shows, the substantial gains in cooling rates are definitely worth the additional effort. Achieving rapid cooling rates at the start of stabilization procedures is one of the most effective tools we have to protect the patient against warm ischemia and associated perfusion impairment during washout and cryoprotective perfusion.

Cardiopulmonary Support Monitoring

The effectiveness of cardiopulmonary support (CPS) can be monitored regardless of which device is used. The most straightforward indication of restoration of circulation is to observe the patient's response to chest compressions and ventilations. Visual signs of restoration of perfusion include change of skin color and capillary refill times. Because a patient in cardiac arrest or poor circulation will look pale, CPS should return a pink color to the skin (look at inner eyelids, lips, and nail beds). Circulation can also be assessed by pressing and releasing the nail bed and counting the seconds for a pink color to return. Normal capillary refill time should be two seconds or less. However, capillary refill checks are typically done in pediatric patients, and their value for adults in clinical situations is controversial. Another straightforward sign of perfusion is to check the patient's skin temperature and condition simply by touching the forehead.

As the last example indicates, many of these traditional measurements are only of limited use in cryonics. Whereas a paramedic would consider a cool and clammy skin a sign of shock, in a cryonics patient we would hope to see a cool and "wet" forehead as this would indicate rapid induction of hypothermia and use of circulating ice water. A pale skin color is not necessarily a bad thing either because this might be the result of cooling and vasoactive medications (such as vasopressin) instead of inadequate perfusion. One solution to these problems would be to leave a portion of one extremity (like a part of the arm) unexposed to ice or water but this may present a logistical challenge and would still not counter the effects of vasoactive medications on peripheral blood flow. And even if such visual methods of assessing perfusion would work, the nature of this information would be qualitative, not quantitative in nature, and generally insufficient to refine or change procedures.

There are many different techniques for giving chest compressions and some techniques generate better cardiac output than others. In cryonics, CPS techniques range from manual chest compressions by hand to mechanical high impulse active compression-decompression CPS (HI-ACD CPS). See Section 9 for more details.

Conventional cardiopulmonary resuscitation (CPR) typically generates only one-third to one-quarter of normal cardiac output, even when vigorously applied. This is generally not sufficient to meet cerebral energy demands and should only be used as a bridge to defibrillation (in conventional medicine) or blood washout (in cryonics).

In cryonics patients cardiac output may be further compromised because many patients are atherosclerotic and/or have gone through a prolonged period of shock or multiple organ failure prior to pronouncement of legal death. In ideal cases, securing cerebral viability may still be feasible, however, if aggressive multimodal techniques are used. An example of such a scenario would be a case where the team is able to intervene immediately after pronouncement of legal death; circulation and ventilations are promptly restored using a mechanical device capable of active compression-decompression CPS; a respiratory impedance valve is attached to the airway to improve venous return to the heart; blood pressure is supported by vasopressin and/or epinephrine; and rapid administration of neuroprotective medications and induction hypothermia are started to protect the brain until blood substitution or cryoprotection is possible.

Normal Mean Arterial Pressure (MAP) is between 70 and 110 millimeters of mercury (mmHg). Lower MAPs of ~ 50 to 60 and higher are still associated with cerebral viability, but manual CPR is rarely higher than 40 mmHg. Although measuring MAP (or even normal blood pressure) is generally too invasive or impractical during stabilization of the patient, some indirect measurements of the effectiveness of CPS can be obtained by pulse oximetry, end tidal CO2 measurements, and blood sampling.

Pulse Oximetry

A pulse oximeter can be attached to a finger or earlobe to monitor pulse rate and oxygen saturation. See Figure 14-3. It is usually included in a cryonics standby kit as an option to monitor the patient prior to pronouncement, although permission must be obtained from any attending medical personnel, as explained in Section 7.

Figure 14-3. A pulse oximeter opens on a spring-loaded hinge so that it can accept a finger tip to assess oxygenation of the blood.

A pulse oximeter displays the percentage of arterial hemoglobin in the blood. Normal saturation readings at or near sea level range between 95% to 100%. A lower reading is acceptable at significantly higher altitude, such as 5,000 feet or above.

Using a pulse oximeter after pronouncement and during CPS is controversial, as readings may be erratic. It is also recognized that pulse oximetry readings become less reliable when the readings drop below 70%.

Pulse oximetry is also not a good measure of ventilation. This situation may be aggravated in cryonics as a result of aggressive vasopressor use and hypothermia. Another important caveat in the use of pulse oximetry is that it does not reflect insufficient hemoglobin in the blood (anemia). As a

consequence, oxygen saturation levels may look good but there is not enough oxygen to meet the metabolic demands of the patient. Still, in light of the ease of taking pulse oximetry readings, pulse oximetry may be worthwhile to look for trends or serous deficiencies in ventilation.

End Tidal CO2 Monitoring

The best non-invasive indicator of cardiac output and oxygenation during cardiopulmonary support (CPS) is end tidal carbon dioxide (ETCO2). ETCO2 is the partial pressure of carbon dioxide (CO2) at the end of an exhaled breath. Until recently, cryonics standby kits were equipped with disposable colorimetric ETCO2 detectors of the colorimetric type shown in Figuree 14-4. This detector can be attached directly to the endotracheal tube, or any other kind of compatible secure airway, to monitor exhalations. Some limitations of disposable ETCO2 detectors of this type are that they are not quantitative, not continuous, hard to read in the dark, and can give false readings.

Figure 14-4 Easy Cap disposable ETCO2 detector, which changes color to provide an approximate indication of the partial pressure of carbon dioxide gas at the end of each exhalation.

In 2006 this situation changed when Alcor started using the CO2SMO (pronounced “cosmo”), a sophisticated monitoring device that can give a complete respiratory profile of the patient. The CO2SMO does capnography, pulse oximetry, and gives a comprehensive non-invasive, continuous respiratory profile. It operates by connecting a respiratory sensor to the patient's ventilation circuit while also connecting the pulse oximeter sensor to a finger or earlobe. See Figure 14-5.

Figure 14-5. The CO2SMO system, showing the unit, its display, and associated cabling.

Although this represents the state of the art in respiratory monitoring, its cost, size, and complexity will limit routine use of this equipment in remote cases.

In August 2007 Suspended Animation, Inc. added the Capnocheck to its standby equipment. This was similar in size to the older colorimetric disposable detectors but gave quantitative and digital readings for ETCO2 and respiratory rates using infrared technology. ETCO2 readings were shown in mmHg and the respiratory rate was given in breaths per minute. This device is no longer being manufactured, but the Capnocheck II, shown in Figure 14-6, is larger and uses a sensor connected by a wire to the display.

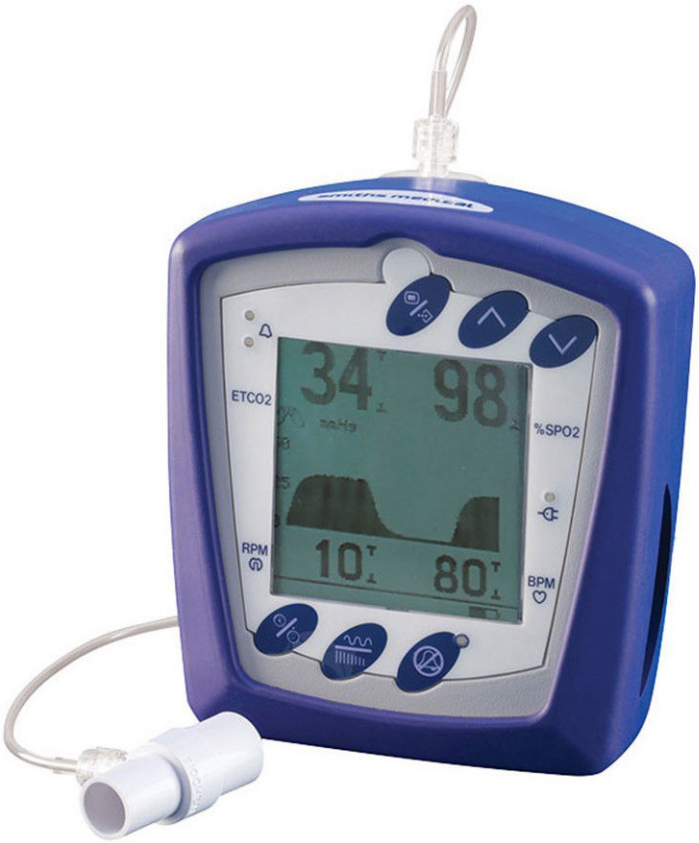

Figure 14-6. The Capnocheck II.

ETCO2 can be used to evaluate the effectiveness of chest compressions and as a predictor of outcome during cardiopulmonary resuscitation. Studies have found that patients with restoration of spontaneous circulation (ROSC) have higher ETCO2 levels than patients that could not be resuscitated (levels <10 mmHg). Normal ETCO2 levels are between 35 and 45 mmHg. Because numeric readings of ETCO2 have rarely been obtained and analyzed in cryonics, and knowledge about what ETCO2 levels to expect and not to expect are currently unknown. At this point in time, meticulous note taking of ETCO2 levels during CPS is essential to generate more data about the efficacy of cardiopulmonary support.

Another important use of ETCO2 monitoring is that it can be used to validate correct placement of the endotracheal tube (or Combitube). If the endotracheal tube has been placed in the esophagus, or has become dislodged,

we expect to see negligible ETCO2 readings. Another issue that needs to be taken into account is the effect of stabilization medications on ETCO2. For example, administration of the vasopressor epinephrine will decrease ETCO2 readings although cerebral blood flow may be improved.

One concern that has been raised about the use of ETCO2 monitoring is that it adds another adjunct to the endotracheal tube. If the ETCO2 detector is the only adjunct used during a case there should not be a problem, but adding the ETCO2 detector to an inspiratory impedance threshold valve (such as the ResQPOD Circulatory Enhancer) can create an unstable "tower" of adjuncts on the endotracheal tube (or any kind of ventilation tube). Because both adjuncts are important in cryonics stabilization protocol, this remains an ongoing challenge.

Some cryonics technologies such as liquid ventilation appear to be incompatible with ETCO2 monitoring altogether. One way around such challenges is to consider measuring oxygen saturation directly in the brain. ETCO2 monitoring does not give direct information on how well the brain of a cryonics patient is being perfused, but there are now technologies that can specifically address this question.

Cerebral Oximetry

As a rule of thumb one should expect evidence of effective ventilation (such as good ETCO2 values) to indicate that the enough oxygen and other energy substrates are delivered to the brain. However, there are a number of reasons why apparent adequate ventilation may fail to meet the metabolic needs of the brain.

The most likely obstacle to good cerebral oxygenation in cryonics is inadequate cerebral perfusion. As discussed above, conventional chest compressions often fall short of generating enough blood flow to the brain to meet metabolic demand. Mechanical chest compression devices such as the LUCAS may do a better and consistent job, but even the efficacy of such methods may decline during a case.

Another reason why delivery of oxygen to the brain can falls short of need is the presence or development of cerebral edema. If intracranial pressure

exceeds arterial pressure, the brain will not be perfused, even if chest compressions are vigorous enough to meet metabolic demand under normal circumstances. Even if cerebral edema does not prevent blood flow to the brain, blood flow can still be limited in specific areas of the brain as a result of compression of (micro) vessels. Other factors that can limit blood flow to the brain include vasoconstriction, blood coagulation, red cell aggregation, brain tumors and ischemia-induced perfusion impairment.

Oxygenation of the brain can be directly measured by taking blood samples from a catheter in the jugular vein. This approach is invasive, labor-intensive, requires advanced medical skill, and is not compatible with the field logistics that characterize a typical cryonics stabilization case.

A recent non-invasive technology that can be used to measure oxygenation of the brain directly is cerebral oximetry. Cerebral oximeters measure transcutaneous oxygenation of the frontal cerebral cortex by exploiting the property of hemoglobin to absorb light. The blood that is measured for oxygen is estimated to be 70% venous and 30% arterial. Because the frontal cerebral cortex has high metabolic demands and limited oxygen reserve, oxygen deficiency in this area can indicate poor delivery of oxygen to the brain as a whole. Measurements of cerebral oxygenations are displayed as a regional oxygen saturation value called rSO2.

The dominant commercial cerebral oximeter on the market today is the Somanetics INVOS system. The INVOS can be used on adult, pediatric, infant, and neonatal patients and can assist patient management in a range of medical treatments ranging from cardiac surgery to emergency out-of-hospital situations. It can operate down to 16 degrees Celsius, which permits collecting cerebral oxygenation data in cryonics during stabilization and the initial stages of blood substitution. The INVOS is available as a two-channel or four-channel device, and sensors are available for all typical patient sizes. The four-channel version allows for simultaneous monitoring of cerebral and somatic oxygenation, which can alert the cryonics team to peripheral / cerebral oxygenation imbalances and cerebral perfusion problems.

Figure 14-7. Four-channel version of the INVOS 5100C Cerebral/Somatic Oximeter showing adult-size and child-size sensors.

Collecting data on cardiopulmonary support and ventilation has historically been a challenge during cryonics stabilization procedures. As discussed in Section 10, the only quantitative information that we have about the efficacy of these procedures has been obtained in a few selected cases in which blood gases were collected and analyzed. During the cryopreservation of patient A-1049 Alcor sought to overcome this challenge by using the CO2SMO, but the device was not used to guide treatment in the field and was never deployed again. Cerebral oximetry may be the first new technology that could be routinely used during cryonics stabilization procedures.

The INVOS system consists of a monitor, pre-amplifier, disposable sensors (2 or 4) and sensor cables. The disposable sensors are attached to both sides of the patient's forehead , and should be protected from (extreme) moisture. The monitor measures 24 cm (height) 29 cm (width) 19 cm (depth) and weighs around 5 kg. Since the system would be used in conjunction with a portable ice bath, and a separate portable roll stand would be inconvenient during transport, a method to secure the device to the ice bath would have to be established. Alternatively, the INVOS could be used exclusively in the Alcor transport vehicle (and OR).

There is only limited clinical evidence for using the INVOS (or similar devices) during resuscitation and/or hypothermic procedures, but its theoretical advantage is that it could help a cryonics organization assist in answering one of the most fundamental questions involving cryonics stabilization: is the brain kept viable by contemporary medical criteria? With hospital or hospice approval, the device can also be used to monitor the condition of the brain during the agonal phase, which would be useful in establishing a baseline for stabilization procedures.

Bispectral Index

An even more robust measurement of the condition of the brain could be achieved by conducting EEG measurements on the brain of the patient during transport. Obviously, such an approach would only be feasible in cases in which the patient has been pronounced legally dead by cardiopulmonary criteria and the standby team can start procedures promptly after pronouncement. In cases where the patient is pronounced by brain dead criteria, or where stabilization procedures start after a prolonged period of ischemia, EEG measurements are not likely to produce meaningful information.

Electroencephalography (EEG) is the recording of electrical activity along the scalp by measuring the ionic activity of neurons. Whereas EEG recordings in small (research) animals typically require time-consuming invasive surgical procedures, the procedure in humans can be conducted non-invasively by securing electrodes to the scalp of the patient, either individually or by using a cap or net in which the electrodes are embedded. The use of EEG in cardiopulmonary resuscitation is uncommon because the urgency surrounding CPS does not allow for placing the electrodes on the scalp and obtaining the readings. Another limitation of using EEG for out-of-hospital CPR is that mechanical chest compressions and defibrillators can generate artifacts in the EEG waveform. Most of the information we have about electrical activity in the whole brain comes from in-hospital cases in which the patient’s heart stopped while EEG monitoring was conducted, or cases where

EEG monitoring (or a variant thereof) is used during procedures that require anesthesia and/or hypothermia.

The logistics of doing EEG during cardiopulmonary support would not favor this form of monitoring in cryonics. Another complication is that while it has been established that the brain responds to artificial attempts to restore blood flow to the brain, the resulting brain waves would not provide simple actionable information and interpretation of data that lies on the continuum between isoelectric (flat line) and normal values would be hard to interpret. One approach that gets around this challenge is for a computer to process the EEG into a simple numerical score that expresses the degree of brain activity. The need for such a simple measurement has been driven by procedures that require measurement of the depth of anesthesia.

Bispectral index (BIS) is one the dominant commercial technologies that aims to measure the depth of anesthesia by calculating a single number from electroencephalographic measurements. The BIS index ranges from 0 (equivalent to electrocerebral silence) to 100 (equivalent to fully awake and alert). A BIS value between 40 and 60 indicates an appropriate level for general anesthesia. An additional advantage of BIS monitoring are the BIS sensors, which, like the INVOS sensors, are simple and can be non-invasively applied to the forehead of the patient.

Emerging studies on the use of BIS during in-hospital and out-of-hospital CPR are aimed at establishing whether BIS scores during CPR can predict successful resuscitation and neurological recovery. In cryonics, resuscitation is not an endpoint of stabilization procedures. However, continued monitoring of BIS could provide meaningful information about the effectiveness of chest compressions and ventilation. BIS monitoring can also be used to assess the effects of medications administration, in particular the administration of general anesthetics (such as Propofol) and vasoactive medications.

In an ideal cryonics case we would expect to see robust EEG activity during CPS, a change of pattern during Propofol administration, and a gradually flattening EEG as deep hypothermic temperatures are approached. Similarly, in an ideal cryonics case with BIS monitoring we would expect to see an initial high BIS score, followed by a drop to an anesthetic plane after

Propofol administration, and a further, progressive, drop as deep hypothermic temperatures are approached.

One potential drawback of the use of BIS monitoring is that it could draw attention to the not widely known (or appreciated) phenomenon that subsequent recovery of electrical activity in the brain is compatible with pronouncement of legal death. A positive BIS score might raise concern about restoration of awareness of the patient. Cerebral oximetry monitoring may be preferable from this standpoint, but because both clinicians and laypeople recognize that delivering oxygen to a brain of a "dead" person is possible and could support viability of individual neurons, and because anesthetic is used as part of cryonics stabilization procedures, it should be possible to ally concerns about brain activity measurements.

Monitoring of Stabilization Medications

Of all three basic stabilization procedures—induction of hypothermia, cardiopulmonary support, and medication administration—monitoring and evaluating medications administration has received the least attention in cryonics publications (including case reports). This situation is somewhat remarkable because the long list of stabilization medications that characterizes Alcor's stabilization protocol has no precedent in conventional medicine. In fact, despite many years of research and clinical trials there is no single neuroprotectant that has been approved for stroke or cardiac arrest. Monitoring of stabilization medications of cryonics involves two distinct aspects: administration and efficacy.

The most basic form of medication administration monitoring is to document the timing and administration of all the individual medications. This aim has been achieved in many Alcor cases. The most important objective of documenting the time of administration of the individuals medications and solutions is quality control but documenting the time of administration can also help the cryonics organization in evaluating whether a protocol is realistic and/or effective. For example, there have been a fair amount of cryonics cases where administration of the medications was delayed, incomplete, or abandoned. Some medications require re-constitution or administration

through a syringe filter. In some cases reconstitution or filtration was not successful, which necessitated changes in protocol. Documenting the timing of medications administration is also important because some medication are presumed to be only effective during the early stages of ischemia or are most important when the patient is still at normal body temperature.

The most neglected aspect of medications administration monitoring involves assessing their efficacy. While it is not possible to evaluate the effectiveness (or degree of effectiveness) of all medications, it should be possible to do this for a number of the medications in Alcor's stabilization protocol.

As a general rule, the effectiveness of stabilization medications can be assessed by looking for (expected) physiological responses or outcome measures during a case. For example, a vasoactive medication should be effective in raising blood pressure and an anti-coagulant should prevent clotting of the blood after pronouncement of legal death. In some cases the effects of a medication can be assessed immediately after administration; in other cases the effectiveness can be assessed upon the start of washout or cryoprotective perfusion procedures.

It is not always possible to differentiate the effects of individual medications when they serve the same aim and are given shortly after one another. Many neuroprotectants fall in this category. Assessing the efficacy of such medication will require more rigorous research in a lab. For medications for which individual assessment is possible, the data of one single case do still not give definitive answer regarding efficacy. For example, if no blood clotting is observed after administration of heparin this can be both attributed to the medication, promptly restoring circulation, or even the possibility that blood does not coagulate as a result of stasis.

With these caveats in mind, we are listing some of the individual medications in Alcor's stabilization protocol with notes describing how they can be monitored and what clinical questions we would like to answer.

Propofol

The most important reason for administration of Propofol is to reduce metabolic demand. Since Propofol has adverse effects on blood pressure, it is

important to know whether we achieve this aim. The only kind of monitoring in this document that would be able to help address this question directly is to monitor the bispectral index (BIS) of the patient prior, during, and after administration of the medication.

Streptokinase

Streptokinase is administered to break up existing blood clots. Absence of blood clots is not evidence of the efficacy of streptokinase unless it is reasonable certain that (large) clots were present in the patient prior to administration. The best opportunity for looking for clots is during the initial stages of washout and cryoprotective perfusion. The right atrium is known to have large clots in "dead" patients without anticoagulation.

Heparin

Heparin is administered to prevent the formation of blood clots. Absence of blood clots is not evidence of the efficacy of heparin because restoring normal circulation rapidly can also be assumed to prevent blood clots. The best opportunity for looking for clots is during the initial stages of washout and cryoprotective perfusion. The right atrium is known to have large clots in "dead" patients without anticoagulation.

Vasopressin

Vasopressin is administered to increase blood pressure, and this medication should affect cerebral oxygenation and end tidal CO2 values. If vasopressin and epinephrine are both administered at the same time, it is not really possible to evaluate the relative contribution or interaction of these medications.

SMT (S-methyl-isothiourea)

SMT is a neuroprotectant that is difficult to evaluate on a case-by-case basis but its positive effects on blood pressure may provide evidence of successful administration.

Minocycline

This is an antibiotic that is used to protect the patient from microbial overgrowth during long transport times. Its efficacy might be assessed by comparing bacterial cultures from patients who received the medication and patients who did not after long transport times.

Vital-Oxy

This is a proprietary emulsion of antioxidants and anti-ischemic compounds. As a neuroprotectant it is difficult to evaluate the efficacy of this medication in a single case, but a comparison of a large number of cases might reveal differences in the degree of edema or ice formation after administration or omission of this agent. A more sophisticated approach would be to look at specific biomarkers of ischemia in the blood.

Hetastarch

The most important property of Hetastarch is as a volume expander and we would expect to see improvement of blood pressure, ETCO2 values, and cerebral oxygenation, especially in dehydrated patients.

THAM

As the only agent explicitly aimed at maintaining and restoring physiological pH, blood gas analysis should reveal the efficacy of this medication.

Decaglycerol

The most important objective of decaglycerol administration is to decrease cerebral edema (or prevent it) by osmotic force as its predecessor medication, mannitol, did. If cerebral edema is present at the start of stabilization procedures, the effects of decaglycerol should be closely monitored.

Maalox

The most direct way to look at the efficacy of Maalox would be to inspect erosion of the stomach wall, or stomach contents outside of the stomach. The absence of Maalox administration could also express itself in (aggravated) abdominal swelling during whole body perfusions.

Monitoring of ischemia

There are a number of approaches to monitoring the presence and degree of ischemia. The most reliable indicator is to directly measure oxygenation of the brain with a technology such as the INVOS cerebral oximetry system. If oxygenation is sufficient to support normal metabolism of the brain (other things being equal) a cryonics patient could be claimed to suffer no ischemia. It is important to recognize that aggressive cooling may relax the oxygen requirement criteria for the brain. So a patient who's cerebral oxygenation is slightly below normal may not be ischemic if (s) he is cooled rapidly as well. In absence of cerebral oximetry, end tidal CO2 measurements may be a good indicator of the degree of ischemia. A flat EEG or a low bispectral index score (prior to Propofol administration) is also indicative of ischemia.

One of the most robust indicators of the degree of ischemia in a case is the degree of perfusion impairment during cryoprotective perfusion, edema formation, and ice formation after subzero cooling. The cryonics research company Advanced Neural Biosciences is conducting ongoing studies on the effect of ischemia on the brain and have found that, as a general rule, as the duration of (warm and cold) ischemia increases so does perfusion impairment, (abdominal) edema, and ice formation after subzero cooling. Recent CT scans at Alcor have further corroborated this relationship between ischemia, distribution of the vitrification agent in the brain, and ice formation.

Cryonics organizations would benefit from a simple (compounded) "grade" for each case that integrates all the data collected to assess the overall quality of the case. A number of writers in cryonics have attempted to create such a score to estimate the total amount of ischemia. This topic and other issues concerning comparing cases will be discussed in Appendix 1: Evaluating the Quality of Patient Care and Appendix 2: Writing Case Reports.