Feb 22, 03

Initial Cooling in Cryonics

From Body Temperature to Ice Temperature:

Physiologic and Physics Theory, Quality Control Proposals, Historical Cryonics Case Analysis Examples, Lab Experimental Results, Literature Review, Numerical Recipe Examples, and Practical Summaries and Recommendations for the Future.

Steven B. Harris

Abstract. There are problems with quality control in cryonics, and some of these problems are due to general under-appreciation of the fact that brain damage rates during brain ischemia are a high-order exponential function of failure to cool immediately after circulatory arrest. To remedy this situation, an exponential function of brain damage with time and temperature is here derived and proposed. This function "outputs" a time-equivalent index number (the "**E-HIT**"), which is expected to be a more proportional representation of amount of ischemic brain damage in the early phases of cryonics treatment (i.e., during transport and before cryoprotective perfusion). The **E-HIT** should be valid generally for situations of brain anoxia— states in which blood is not flowing to the brain, or it is flowing but carrying no oxygen. With suitable modifications, the **E-HIT** can also be made to model brain damage with partial oxygenation as well.

In the essay, heat transfer problems and inferences of temperature time-constants in cryonics are discussed, as well as the critical importance of supplying oxygen to the brain while metabolic rate is still high, during the first phase of cryonics treatment. Data from three real and contrasting cryonics cases are discussed, with abstraction of the kinds of information which the author would like to see calculated or estimated for all cryonics cases, where possible. Studies of postmortem conductive head cooling in the forensic literature are discussed, as they apply to cryonics. An appendix gives abbreviations, equations, mathematical approaches and numerical computational methods with some illustrative **BASIC** programs. Some theoretical and experimental results are also given, showing a fair match from known human forensic and cryonics data.

Major conclusions of this essay are: 1)

INTRODUCTION (To Skip Philosophizing, Go to Next Section)

There is an apocryphal story about a University President who complains to the Chemistry Department chairman about the high cost of equipment budgeting for chemistry: "Why can't you chemists be like the Math Department? They only ask for paper, pencils, and erasers? Or like the Philosophy Department, which doesn't even ask for erasers..?"

Those who have worked through the years to keep cryonics from being just another religion or art form, have similarly had to struggle with the basic question of just what it is that separates philosophies, fashions, and religions from the more objective enterprises such as engineering and the physical sciences. One answer to this question has been argued by cryonics thinker Mike Darwin, who holds that it comes down to a question of *feedback* in objective pursuits, and particularly in cryonics. Quality must be measured and quantitated before it can be dealt with. In business management language, therefore, the essential difference between engineering and religion is a matter of objective quality control loops, where *quality* is something that can be more or less universally agreed-on.

In short, it seems that many religious, ethical, and aesthetic debates suffer from the basic problem that there is little agreement about what constitutes *improvement* in the product under discussion. For example: How is a person to know if his or her metaphysical philosophical view is better than someone else's? Or even (to remove the competitive element) how is a person to know whether his present philosophy is better than the one he held last year, before doing all that reading and thinking? It's a problem.

Without any way to measure quality, there is no way to close the quality-control feedback loop which is so necessary to objective progress in business, technical, and scientific pursuits. This is the basic problem of cybernetics. As business managers can tell you, if you can't measure the extent of what's wrong, it's rather difficult to tell if you're making any worthwhile progress as you work to fix it. And if this sorry state happens, then organized feel-good religion will result, and all objective measures of quality which are connected with expenditure of work, time, or money, will then atrophy and disappear. What is left will resemble cargo-cult riturals: people will go through the old motions, but no real progress will ever be made.

We all know many historical examples of what tends to happen when people have no good way to reduce progress into some kind of good and readily identifiable parameter which they can get a grip on. It is for this reason, above all others, that religious, political, ethical and legal debates often lead nowhere but to polarization and bad feelings. Throughout most recorded history we observe that such debates have too often led to group scission and flight, or else violent conflict. Large scale violence for reasons other than simple theft, in particular is a sure sign that somewhere someone has run out of good persuasive, logical, and empirical arguments **[1].**

Though there has yet to be violence, more than a little scission and polarization has happened in cryonics. The question before us is: what concrete progress have cryonicists made in the art and the science of the practice of cryonics itself? Arguments in science lead to dead theories. Thanks to some progress in politics, arguments in religion no longer lead to as many dead bodies as they used to--but religious disagreements still lead too often to new religious sects, and little else. Cryonics disagreements lead to new cryonics organizations, but is there more? Where are our dead cryonics theories? Surveying the field, the author can point to more dead cryonics organizations than dead cryonics theories and practices, and that's a bad sign.

Yogi Bera used to say that it's hard to make predictions, especially about the future. Cryonics as an enterprise has one foot in the uncertain future, and thus suffers from all of the epistemological and predictive questions that plague any science or business, plus some of the additional problems that plague philosophy and theology. In particular, cynics in the cryonics community have long pointed out that the role of savior and God Almighty is played in the cryonics world by the promise of "nanotechnology." This *"Deus Ex Machina*" is the coming micro-repair technology which in cryo-mythology is due to arrive in somewhat the same salvational manner as The Second Coming of Jesus. As personified in the helpful image of "**Our Friends In the Future**," nanotechnology will supposedly be able to fix anything in a damaged brain which is necessary to fix. **Our Friends In the Future** will know, just for example, how to recover the memory traces which have been stored on neurons which have been digested by their own internal enzymes, blasted into lacunae by extracellular ice crystals, and whirled up in a litter of disrupted synapses by currents of solute displacement during freezing.

If cryonics has a "Big Answer," this is it. Since **Our Friends in the Future** will fix it up for us, being dead and cryopreserved is not quite as desperate a situation as would first appear. Even being warm and dead is not so bad as we might first have thought.

Which is strangely lucky for us, because it so happens that the process of getting freshly-declared dead people rapidly frozen, not to mention vitrified, is very, very difficult. People do not die on schedule, even when they know they have a terminal problem. Even if they are cryonicists, they do not like to plan for the event, or even think about it. Their families, even less so. Because of unpredictability, arranging to have a team of cryonicists standing by at a cryonicist's death, which may occur far from any major cryonics facility, is a logistics nightmare. No matter how much planning has been done, there are almost inevitable legal and social problems in gaining physical control over a human body in the first minutes, or even hours, after death has been legally declared. It all costs a lot of money, it is emotionally and physically draining, and (even worse) the immediately tangible payoff for managing it well, is almost nil. A superbly-preserved cryonics patient looks much the same (and sometimes cosmetically even worse) as one who didn't get nearly so good a job. The differences, such as there are, might only be find-able on electron microscopy which is expensive and difficult to do, and which isn't routinely done. And which would not tell the whole story, even if it were done.

Under such circumstances, it's very hard to make a maximum effort in cryonics. Motivation sometimes, is lacking. To begin with, we do not really know how much effort is needed. We cannot even define the problem well. We *do* know that the difficulties of cutting down "warm and dead" time rise rapidly and nonlinearly, the closer one gets to the moment of death. This happens for social, financial, legal, psychological and physiological reasons. An organization which pushes too hard at this task may find itself (along with its already cryopreserved patients) at some risk, merely as a result of making the effort. And there is risk also (albeit of another kind) in not making the effort. So there's a tradeoff involved, and it's a difficult tradeoff, because nothing about it has been quantitated. Some of the ill-defined risk in *not* making the effort lies in the existence of plenty of people with scientific and/or business managerial experience out there, watching cryonics, wondering if cryonicists are simply crazy. This, at the same time that the cryonics organization's chief "work-product"-- a set of preserved memories in a cryonics patient-- is not directly measurable by anyone at the present time.

This is not a problem which will go away by pretending it doesn't exist. One should be especially suspicious of philosophical ideas that present themselves as solutions to difficulties which are otherwise dire and terrible. Our Friends in the Future seem to qualify as one of these. The desire to avoid wishful thinking about death was the historical motivation for cryonics in the first place. But if cryonics is simply another way to fix death-anxiety by even *more* wishful thinking, then we've made no progress at all.

INFERRING ISCHEMIC DAMAGE FROM THE KNOWN TEMPERATURE DEPENDENCE OF THE ISCHEMIC DAMAGE RATE

It is our aim to make progress on the question of how to think about trade-offs in cryonics between brain-damage-done, and effort-and-money spent. In order approach this calculation, we first need to take some baby steps to quantitate the brain damage which results from delays in cooling and/or oxygenation, during field transport in cryonics. To do this, we will not argue from electron micrographic studies, because (in the first place) we do not have these, and (in the second place) they are too crude to tell us what we want to know, anyway. Instead we will argue from what we know about ischemic ("no blood flow") brain damage, as discovered in resuscitation studies with animals.

Here is a very abbreviated synopsis about brain damage in ischemia: When the heart stops, blood flow in the brain stops in about 5 seconds (the elasticity of arteries moves blood for a bit of time). After that, there is enough oxygen in the capillaries in the brain to run the brain's normal metabolism perhaps 5 more seconds. After this 10 seconds have passed, consciousness is lost. Without oxygen, neurons simply cannot do the heavy work of moving sodium and potassium ions across nerve cell membrane concentration gradients of these ions. This movement is the process which constitutes what we need to do, in order to think and be aware. If we interrupt it, the mind shuts down almost as fast as a desk computer does, when the power plug is pulled. In case you have ever wondered, this is about as much time as guillotined people got to contemplate their position, after the blade had fallen. In modern times, this "useful consciousness" time after cardiac arrest or zero blood pressure, has been carefully documented in videotapes of people undergoing cardiac arrest during controlled tests of implant-able cardiac defibrillators.

Losing consciousness only means your neurons do not have enough energy to let you think, but it doesn't mean they have run out of energy completely. There is still some ATP left and some glucose to split into lactate, and all of this lets the neurons work sluggishly for about 2 minutes. By the end of this time, however, the usable energy is gone, and EEG ("brainwaves") will now be flat (not to worry-- if you supply oxygen again they will come back). Short term memory (the phone number you were repeating to yourself) also has evaporated like the last few lines of the word-processor document you were working on when your power went out, indicating that this much is stored by primarily electrical means. But your other memories, stored as something hardier than mere electrical impulses in your speech-phrase buffer file, are still there. There are many other changes in these first couple of minutes, also reversible. For example, all of the water between your brain cells will have been sucked into the cells as they swell because they cannot pump ions, but it too can be pumped back out. And less fixable things are also happening. Bad chemicals are being produced. After several minutes begins a cascade of many other kinds of damage that are not easily reversed by simply restarting the blood supply and oxygen.

For purposes of this essay, it doesn't matter what these many other kinds of damage are. You can't see any of the damage with any instrument, but it's there. Resuscitate somebody whose heart has stopped for less than two minutes, and rarely will there be lasting brain damage. After that, however, the chance of ultimate neuronal death increases linearly. By 6 minutes of arrest, 50% of ultimately resuscitated adults will suffer brain damage. By 8 minutes, we are up to 75% chance of severe damage. By 10 minutes of no blood pressure in adults, long term survival outside an institution for chronically vegetative patients is essentially zero, because even the people whose hearts are re-started (which are a surprising fraction) go on to suffer massive brain damage, swelling, and vegetative states or brain death. Even if their hearts are fine, 100% of these people will become, for all social intents and purposes, dead.

This does not mean the brain is in any sense dead exactly at 10 minutes of circulatory arrest. Far from it. The time only means that, in adult humans. the brain eventually suffers such initial damage that it essentially never comes back to normal function, if the heart is merely restarted and nothing else is done. Presently, only animal research offers clues as to what might be done in the future to resuscitate brains from longer ischemic times.

Dogs, when compared with humans, have brains of very similar time-sensitivity to anoxic damage. But dogs can be resuscitated from as long as 16 minutes of cardiac arrest if their brains are rapidly cooled AFTER resuscitation and cardiac restart, and a number of drugs are given to block free radical damage and inflammation (This has now been done to 4 animals at **Critical Care Research, Inc**., where the author works. All animals are well). No one knows what the limit of this kind of "low tech" resuscitation is, but it may be as long as an hour. At least one cat has been resuscitated to reasonably normal behavior after an hour of cardiac arrest at normal body temperatures. Though it had some brain damage, enough of its brain survived to suggest that with the proper treatment, most of the mammalian brain can probably be resuscitated from arrests this long. Clearly, much of the disappearance/death of neurons happens long after reperfusion after cardiac arrest, and clearly much of this process is susceptible to blockade with treatments far less sophisticated than full nanotechnology.

What happens after an hour of arrest is inferable partly from studies of stroke victims which have had part of their brains cut off from circulation by a clot, then re-perfused as the clot is disrupted. In humans, this process is beneficial up to 2 hours, and does not clearly reach the point of doing more harm than good until 4 hours. In the areas in which the clot causes blockage there may be a little bit of blood flow, but (again) not so much that we may guess than many cells have survived without any blood flow at all. We do know that apparently completely viable isolated neurons can be cultured from human brains after as long as 8 hours of death, without any special cooling precautions save normal hospital transport to the appropriate morgue for air cooling **[2].** Although some post-mortem cooling is undoubtedly involved in protection here (more on this below), the numbers suggest that many (we don't know what fraction) of neurons survive beyond 8 hours, even after low technology restorative efforts. This is not to say, however, that *memories* (which are probably encoded in connections between neurons) survive this much ischemic time.

Thus (and we cannot overemphasize this), the picture which many people have (even some physicians) of brain cells going *poof* after 4 to 6 minutes of no oxygen or blood flow, is completely wrong. For some *hours* after clinical "death" there are no changes in cells in the brain or any other organ which clearly signal that things have certainly gone beyond recall, even to presently available methods of recovery. We cannot yet do the recovery job with the whole brain, but there is no reason to be convinced it cannot be done.

It is only some time after several hours of death that some (not all) cells in the body's organs begin to show changes which no one has yet successfully reversed. But it is difficult to say which of these changes cannot be reversed in theory. Only after cells have exploded or been digested from within by cellular enzymes (the same process which tenderizes meat during "curing") can we make a guess that enough information has been lost that the cell might not be recoverable even with the ultimate (nano)technology. Presumably, chemical processes destroy information in quantum mechanical ways. Just how this happens is beyond the scope of this essay, but suffice to say that when a given state of matter is a possible identical product of many different possible causes, then information about the state which preceded it, is probably gone forever. Even in theory.

DAMAGE IS SLOWED EXPONENTIALLY BY BEING COOL DURING ISCHEMIA

The applications of hypothermia discussed above have all been used *after* brain resuscitation (restoration of oxygen and blood flow), so these studies have all used cooling as a treatment after the fact. In other words, hypothermia has been used in somewhat the same way as cold water is applied after injury to a sprained ankle or burned finger. However, many famous cases of victims (especially children) surviving severe hypothermia while in cardiac arrest, are the result of the brain being cool *before* and *during* the ischemic episode. This works even better, as might be expected. At least one child has survived drowning in an ice-water brook with little neurological damage after an hour of total immersion. Brain aneurysm operations lasting for as long as 45 minutes at brain temperatures near 15 ^{o}C have been documented. In experimental studies **[3]**, dogs have survived, without significant brain damage, 3 hours of cardiac arrest and brain ischemia at very near the temperature of ice (1 ^{o}C).

Animal studies suggest quantitatively how this works. For every 10 ^{o}C of temperature drop below normal body temperature of 37 ^{o}C, it is known that a dog brain's metabolic rate, and also probably ischemic damage susceptibility, decrease by a factor of 2.2. This factor of 2.2 is called the "**Q10**" and the **Q** simply means that the **q**uantity of oxygen being used per unit time, drops by 1/2.2 for a 10 ^{o}C drop. The **Q10** figure for the brain has been checked in humans down to 15 ^{o}C, and in dogs down to about 7 ^{o}C, and it seems remarkable that it is the same in both species. (There are some high temperature departures in rodents which we will ignore, and also in dogs in special circumstances—see note **[4]**). The **Q10** decrease is exponential, so that at -20 ^{o}C below normal body temperature, the decrease is about a factor of $(1/2.2)^2 = 1/4.8$. An exponential equation to model this **Q10** value is given below.

Due to the damage caused by freezing or the toxicity of chemicals used to prevent freezing, we cannot yet easily explore ischemia at temperatures below 0 ^{o}C in a whole animal. However, down to temperatures just above freezing, we can crudely extrapolate from dog experiments already published in the literature. These considerations lead us to conclude at just above the temperature of ice, metabolism and damage in the brain is sufficiently slowed that every hour is equal to:

1 hour = $(60 \text{ min})^* \, 2.2^{-3.7}$ = 3.24 minutes at normal body temperature.

Thus, 3 hours of arrest in a dog at 1 ^{o}C (which is 37 ^{o}C below a dog's normal body temperature) is equivalent to only 10 minutes at the dog's normal temperature, and can thus be survived (in fact, the dogs seem to do even better than predicted by a 10 minute arrest-- probably due to being kept cool during warming and circulatory resuscitation, which we know also minimizes damage). Possibly the factor of 2.2 is a bit conservative, for humans have survived up to 45 minutes of ischemia at 15 ^{o}C during brain surgery, and they seem to be in much better shape than would be predicted for 7.7 minutes of ischemic arrest. Again, however, the explanation for this may be that both dogs and humans in such extreme hypothermia experiments are often kept cool for hours after resuscitation, and such treatment after the fact is known to extend the duration of non-damage to10 minutes of equivalent hypoxic or ischemic time.

Let us then keep the 2.2 factor number as the best estimate and most conservative figure, and see where it leads. The importance of the **Q10** to cryonicists should be apparent. A few degrees drop in temperature is far more potent at preserving the brain from ischemic damage than dozens of brain-protecting drugs, even when used all at once. For a cryonicist being shipped air-freight on ice at 0 ^{o}C, the 6 hours of "real-time" while at ice temperature is equivalent to only 19 minutes of brain ischemic or hypoxic time at normal temperature (the time-stretch factor is about 18.5). This time is an amount which might even be survivable with resuscitation techniques to be expected in the very near future.

THE CONCEPT OF "E-HIT" : A CUMULATIVE DAMAGE SCORE PRIOR TO CRYOPROTECTIVE PERFUSION

With this is mind, we can now consider the idea of the equivalent brain ischemic "hit," or **E-HIT**. Homeotherms like ourselves struggle to keep our body temperature within a very narrow range, and a tiny over-temp or under-temp makes a significant metabolic rate change. We may thus construct a function **S** which depends on $\mathbf{\Delta T_n}$ (the temperature drop from normal) and which gives a proper "time-stretch factor" (**S** stands for "**stretch**") due to this degree of cooling. From our discussion of **Q10**, we require that our stretch factor **S** at a $\mathbf{\Delta T_n}$ **of** -10 ^{o}C must equal $(2.2)^{-1}$ = 0.46, and similarly, **S** at a $\mathbf{\Delta T_n}$ **of** -20 ^{o}C must equal = $(2.2)^{-2}$ = 0.20 (see **S** equation below). This means that at -20 ^{o}C below your normal temperature, your brain metabolism is just 0.20 = 20% of normal, and thus you can survive at least 5 times as long in cardiac arrest, without damage, as you could if you weren't cooled while suffering the period of no blood pressure.

How much damage-time do we accumulate, if the temperature itself (and therefore the stretch factor) is changing, during the time interval we're looking at? We need to do a bit of calculus to add the total damage up. What we will call the **E**quivalent **H**omeothermic **I**schemic **T**ime (**E-HIT**) is defined as the integrated **S** d**t** over the time of interest **t** = 0 to total ischemic time t = **t**. Calculation of **E-HIT** needs to be an integration, because over the time of interest the brain temperature is generally changing (decreasing). The time-stretch function **S** is a straightforward function of $\mathbf{\Delta T_n}$ from the **Q10** arguments above:

$$\mathbf{S}(\mathbf{\Delta T_n}) = 2.2^{-\mathbf{\Delta T_n} / (10oC)} = \exp -[\ln 2.2 * \mathbf{\Delta T_n} / 10^{o}C] = \exp -[0.079\ \mathbf{\Delta T_n}]$$

t t

$$\text{Thus } \textbf{E-HIT} = \int_0 \mathbf{S}\,(\Delta \mathbf{T_n})\,dt = \int_0 \exp -[\,0.079\,\Delta \mathbf{T_n}]\,dt \qquad \textbf{Eq [1]}$$

In order to evaluate this integral where the variable is the total ischemic time **t**, one still must have some specific equation for $\Delta T_n(t)$**,** which is to say, an expression for ΔT_n as a function of time (in other words, how the amount of cooling ΔT_n changes with t**)**. The construction of such functions from actual data, assisted by theoretical solutions of heat transfer equations, are a concern in what follows, and are also a major topic in the **Appendix**. Keep your eye on **Equation [1]** above, for every **E-HIT** we will calculate in this essay ultimately flows from this equation, or a modification of it (**Eqs. 3** and **7** below).

The units of **E-HIT** are *time*, and they represent equivalent ischemic time at normal brain temperature (37 ^{o}C in humans). For short transport times, the cryonics patient who is not getting oxygen gets most of his ischemic "hit" on the way down to ice temp, and the exponential nature of the time-stretch makes the first part of brain cooling especially critical, if transport times from then on are to be "short" (i.e., less than about 18 hours). On the other hand, if time to beginning of cryoprotectant perfusion, during which the patient waits at ice temperatures, are to be much longer than 18.5 hours (equivalent to about 1 hour at 37 ^{o}C), then the **E-HIT** time saved "up front" by good cooling techniques begins to be less important. The reason is that the damage done in transport, while the patient is waiting or being transported in ice at 0 ^{o}C, now becomes by far the main problem, and damage done by warmth during initial cooling takes a back seat to it. We'll explore these tradeoffs later.

At the end of the total calculation for **E-HIT** for a given patient, one obtains a single **E-HIT** time number which tells essentially how good a job was done in cooling for an ischemic brain, between the time of death and the start of cryoprotective perfusion which brings the temperature below 0 ^{o}C. This **E-HIT** number is a rough equivalent to how many minutes of warm-ischemia a given cryonics cool-down and shipping time is equal to, taking into account oxygenation, and both metabolic effects from cooling, and changing rates of cooling with time. The final **E-HIT** number, calculated from the patient cooling graphs and known presence or absence of oxygen delivery, may be used as a rough quality index of cryonics field services and transport. The larger the **E-HIT**, the more ischemic damage was done, by failing to oxygenate and cool rapidly enough, or by failing to transport and begin the sub zero part of perfusion fast enough.

The **E-HIT** number does not take into account any savings from the use of anti-ischemic drugs. From preliminary work with dogs, we believe that this number may cut the total **E-HIT** by as much as 50%, but since there is as yet no good published evidence for effects this large, we will ignore them in this essay. Also, the **E-HIT** number does not address or take into accout the (surely additional) damage done to brains by cryoprotective perfusion, or by temperatures below 0 ^{o}C. We know very little about any of these, and they are not treated in this essay.

The Practical Calculation of E-HIT

For constant temperatures, such as transport at constant ice temperature in circulatory arrest, the **E-HIT** damage integral amounts to just a multiplication by the proper factor of 1/18.5 = 5.4%. But for exponential cool-downs and for segments with different cooling time-constants, the integral must be computed numerically. For simple exponential (Newtonian) advective cooling, the $\mathbf{\Delta T_n}$ is exponential with time, and for certain kinds of conductive cooling, $\mathbf{\Delta T_n}$ can be represented by a series of exponential terms. Thus the total function to be integrated is at the very least an exponential of an exponential (see the mathematical **Appendix** for details) and this kind of "exponential integral" has been proven to have no closed-form analytic solutions. Fortunately, in these days of cheap computers and high-level programming languages, a small custom software program to do such integrations is not complex, and gives excellent numerical accuracy on desktop computers. Desktop computers are new fast enough that it usually takes more time to hand-enter the temperature parameters for a cooling segment, than it takes for the computer to numerically sum the most difficult integral we will encounter in this essay.

REAL-WORLD EXAMPLES TO FOLLOW

At the end of the main body of this essay, we will give four examples of **E-HIT** calculations on some data from four human cryonics cases. Following this, we will make a plea to the cryonics community to look at past and future data of this sort more carefully. But before we do so, we must make two more digressions, and then present some simple rules-of-thumb regarding calculation of **E-HITs.**

Digression 1) THE ROLE OF OXYGENATION

The first problem concerns oxygen. The **E-HIT** as we've discussed it so far applies to brains which aren't getting any oxygen at all, and are being protected from hypoxia by cold only. What happens when CPR is started, and some oxygen is given while cooling happens?

The short answer is that we don't exactly know.

[etc] Dilation on how much we don't know and why

Digression 2) COOLING

Finally, before we proceed, a digression on the nature of **cooling** in cryonics is necessary. The reason is that we'll be talking about **E-HIT**s for different kinds of cooling, and we will need to consider these different cooling modes first. Essentially, we will be using what we can measure from temperature drops, and what we can calculate from it, to construct various candidate $\mathbf{\Delta T_n(t)}$ functions for real cryonics situations. These, in turn, can be used in our time stretch function $\mathbf{S(\Delta T_n(t))}$, so that actual and theoretical **E-HIT**s can then be calculated for these scenarios. We can also add in the role of oxygen when necessary, for those scenarios which involve CPR or CPB with oxygenation.

First Rule: Cooling is more or less an exponential process. As a general law, heat energy flows in the direction of temperature differentials, and when it flows into a medium, it increases its temperature and thus causes these driving differentials to decrease. The resulting negative feedback relationship is exponential. Exponential relationships result in mathematics wherever the rate of change of a quantity is proportional to how much of the quantity exists. A familiar example is compounded interest on money.

Heating and cooling situations usually result in exponentially changing temperatures, when temperatures are allowed to freely equilibrate and evolve with time (this fact was historically noticed first by Newton, and simple exponential cooling is universally also known as "Newtonian cooling"). In such relationships, a constant *fraction of the temperature difference* Δ**T** between two reservoirs is abolished in some characteristic time **t**. If one waits *again* another such time **t**, then the *same* fraction of the *remaining* Δ**T** (whatever it was) is then abolished. Thus (for example), if it takes 5 minutes for half of the temperature difference between two reservoirs to disappear, then in 5 more minutes, half the *remainder* will be gone (now 75% of the first difference). In such cases, the 5 minutes is called a half-time or half-life, but there is nothing special about the 'half.' In any exponential decay there is a characteristic time for any given fraction (1/3rd or 1/4th, etc) to disappear (these times could be called a "third-life" or a "fourth-life," etc.)

A very useful characteristic time **t** to use in such situations is the "e-th life," which is the time for all but 1/e = about 36.8% of a temperature differential to disappear. The constant "**e**" = 2.71828... is the base of "natural" logarithms and it shows up in mathematics as a "natural" limit whenever infinitesimal quantities are compounded infinitesimally. For an example of how **e** shows up, consider your probability (risk) of losing a single game of Russian roulette (1/6). If you play 6 games, with a spin each time, you are not guaranteed to lose (as you might think at first), but rather have a total chance to survive of (5/6)^6 = about 33.5%. If you play 100 times at some other game where you have a 1% chance to lose at each game, your odds of winning every one of 100 games are almost the same: 36.6% The *limit* of this process, as we close in on infinity (say 10 million airplane flights, each with 1 in 10 million odds of killing you) is 1/e = about 36.8% that you will survive this many flights. Thus, the constant "e" enters in "naturally" to all problems involving differential probability.

In heat conduction, where at each instant the rate of heat transfer changes with the temperature difference, the constant "e" arises in the same way. If one has a system in which a small fraction (say 1%) of the temperature difference Δ**T** goes away in given time (1 minute), then one might at first think that one would have to wait just 100 minutes for it *all* to go away. But because the drop in temperature, as time goes on, causes the rate of temperature change to change, in fact about 37% of the temperature difference remains at 100 min. The limit to this process also is 1/e, and the time necessary to get to 1/eth of the original temperature difference is called the "time-constant." Again, one can think of the time-constant as the "e-th life" or the time it takes for all but 1/eth of something to be gone.

Because it takes longer to get rid of all but 36.8% of a temperature difference than it does to get rid of just 50%, the e-th life or time-constant (symbol "$\mathbf{t_o}$") is always longer than the half-life for any process. In fact, it is a fixed number ratio: 1/ln2 = 1.4427.. times longer than the half-time for the process. Because this ratio is of the two "lives" is fixed and constant, if you know one time value (half-life or e-th life), you can immediately calculate the other, for any exponential process.

Let us now look at an example, with numbers which might be seen in cryonics. The natural time-constant $\mathbf{t_o}$ for any exponential temperature change of the type we've been discussing, is simply the ratio of the temperature difference driving the change at a given time, divided by the rate of temperature change at that time. This is a simple equation which we'll be using over and over in what follows:

$$t_o = \Delta T / [d(\Delta T)/dt] = \Delta T / [dT/dt] \qquad \textbf{[Eq. 2]}$$

If (for example) we have a temperature difference of 37 ^oC driving a heat-transfer system (sudden perfusion of a patient at normal body temperature, with 0 ^oC fluid, say), and we find that the rate of temperature change dT/dt is 2 ^oC/min (a possible value for whole body perfusion), then the time-constant for the process t_o will equal 37min/ 2 ^oC/min = 18 minutes.

What does this mean? The time-constant value tells us that at the end of 18 min. we may expect that 36.8% of the initial gradient of 37 ^oC will remain. 36.8% of 37 ^oC is 13.6 ^oC, therefore this will be the temperature of the patient after 18 min of cooling.

If we prefer to think in terms of "half-times," then the half-time for this process is 18/ln2 = 18/1.4427 = 13 minutes, and that is the time at which one can expect temperature to have dropped to half of the initial temperature difference, or 37 ^oC /2 = 18.5 ^oC. At this point, the alert reader should be able to see that another 13 minutes will bring it to 18.5 ^oC /2 = 9.25 ^oC, and so on. These times (as we will see) are quite realistic for t_o values for brains of real cryonics patients during (heart lung machine) perfusion.

The defining differential equation for Newtonian cooling, which is a rearrangement of **Equation 2**, is:

$$dT/dt = d\Delta T(t)/dt = (1/t_0) * \Delta T(t)$$

Again this is just a restatement of the idea that cooling rate at any time in the process is proportional to temperature difference between object and cooling bath at that time, and that the constant of proportionality has units of "inverse time." This proportionality constant is $1/t_0$. The solution to this differential equation is found by rearranging and integrating, then removing the constant of integration with the boundary condition that ΔT at time zero is **"$\Delta T(0)$"**:

$$\Delta T(t) = \Delta T(0)\, e^{-t/to} \qquad \textbf{Eq. [3]}$$

Here, as usual, $\Delta T(t)$ is the T difference between object and bath, and $\Delta T(0)$, as already noted, is that initial difference at $t = 0$. A graph of the fractional cooling $\Delta T(t)/\Delta T(0)$ at times which are in multiples of t/t_0, is the familiar inverse exponential decay graph $f(x) = e^{-x}$.

[Graph of Newtonian cooling here]

This graph merely shows the preceding discussion in graphical form. One can see that the total fractional cooling to bath temperature is 63% at t_0, 86% at $2t_0$, and so on. If the $\Delta T(0)$ is 37 ^oC, as it often is between a patient at 37 ^oC and water ice at 0 ^oC, then 2 t_0 of cooling time will bring the temperature to about 5 ^oC. Thus, "two time-constants worth" of cooling time are a convenient interval to speak of, in cryonics. The reader should be able to see at this point that 3 time-constants of cooling will bring the temperature to 36.8%(5 °C), or 1.8 °C.

E-HITs for simple exponential/Newtonian cooling.

To calculate **E-HIT** for Newtonian cooling we still need a function which reads in terms of the amount of cooling from the initial or **normal** state, which we'll call $\Delta T_n(t)$. If $\Delta T(t)$ is the temperature difference between an object (the brain) and cooling bath T_b at any time **t,** then $\Delta T(0) = T(0) - T_b$. The expression for $\Delta T(t)$ which we know from **Equation [3]** needs to be related to the one which we've sought for $\Delta T_n(t)$, which we in turn want to put into our integral in **Equation [1]**. This gives us a function $S(\Delta T_n(t))$ for any **t**, and thus a grand time-dependent function with which to calculate the total ischemic **E-HIT** across a span of **t** for the brain.

To get the rest of the way we merely need to recognize that the temperature function $\Delta T_n(t)$ we seek needs to describe how much the brain is cooled *from normal.* Obviously, the temperature difference we want to use for the stretch function $S(\Delta T_n(t))$ involves the difference between present *brain temperature and normal*, not between present temperature and cold bath. The normal temperature we symbolize as $T(0)$. The $\Delta T_n(t)$ function must be the normal/initial temperature of the brain $T(0)$ minus the present temperature of the brain at time t, which is $T(t)$. So:

$$\Delta T_n(t) = T(0) - T(t)$$

or equivalently, subtracting the bath temperature T_b from both terms on the right side, and remembering that we've defined $\Delta T(t)$ to be $T(t) - T_b$

$$\Delta T_n(t) = T(0) - T_b - [T(t) - T_b]$$

thus $\Delta T_n(t) = \Delta T(0) - \Delta T(t)$

We can now see that the value of this temperature gap function is **zero** at time **t** = 0, as it ought to be (the brain hasn't cooled at all), and the value of the stretch function $S(t=0)$ at time zero is 1, again as it ought to be.

Inserting now the expression for $\Delta T(t)$ from **Eq 3** into the equation just above**:**

$$\Delta T_n(t) = \Delta T(0) - \Delta T(t) = \Delta T(0) - [\Delta T(0)\, e^{-t/to}] = \Delta T(0)\,[1 - e^{-t/to}]$$

Inserting this expression for $\Delta T_n(t)$ into our **E-HIT** integral of **Eq 1.** now finally gives a value for **E-HIT** as a straight function of cooling time, in Newtonian cooling:

$$\textbf{E-HIT (Newtonian)} = \int_0^t \exp -[\,0.079\,\Delta T_n]\,dt = \int_0^t \exp -[\,0.079\,\Delta T(0)\,[1 - e^{-t/to}]]\,dt$$

For ice bath cooling, **ΔT(0)** is 37 ^oC, so the dimensionless constant –0.079*37 which is 37 $^oK*2.2^{-3.7}$ min/min/ 37 ^oK works out to be –2.92. This gives us our final compact **E-HIT** equation for a **Q10** of 2.2 and Newtonian cooling to the ice point, from an initial body temperature of 37 ^oC:

$$\textbf{E-HIT (Newtonian, } \Delta T = 37\ ^oC\textbf{)} = \int_0^t \exp\ [\, -2.92\ (1- e^{-t/t_o})\,]\ dt \qquad \textbf{[Eq 4]}$$

The type of integral seen here, sometimes called an exponential integral, or double exponential integral, has no closed-form analytic solutions. However it can be easily evaluated numerically with a personal computer. A program written in **BASIC** to do this is given in the **Appendix**. Having used the computer program to calculate out some **E-HIT**s, let us now graph the **E-HIT** damage integral, in units of the t_o time, against "real time", which we will also express in the same natural multiples of t_o. Note that at the beginning of the graph, **E-HIT** rises at a slope of 1, which means that before cooling happens, the **E-HIT** is rising at one minute per minute of ischemic time. Later, as cooling happens almost completely on a scale of 3 to 5 t_o times, the slope of continued **E-HIT** rises at a 1/18.5 minutes per minute of real time, which is the maximal time-stretch at 0 ^oC.

[Insert graph of Newtonian **E-HIT** vs. t_o here]

Though, as we noted, the **E-HIT** integral has no closed-form solution, there is obviously a certain amount of **E-HIT** which happens during cooling, and then merely serves as an additive factor to further **E-HIT,** which happens at the standard 1/18.5 minutes per minute, once nearly-full cooling has occurred. How much **E-HIT** occurs as a penalty during cooling, assuming no oxygen gets to the brain in this time, can readily be calculated by computer, and not surprisingly comes out in terms of a constant fraction of t_o, across the cooling process. Here is the result:

NEWTONIAN HYPOXIC COOLING RULES OF THUMB

*The "cooling penalty" **E-HIT** for non-oxygenated Newtonian cooling to near 0 ^oC, with **Q10** of 2.2, and temperature gap of 37 ^oC, is* **0.42 t_o.**

Thus, for "long" cooling times (more than about **3 t_o)** where "nearly full" cooling has occurred, a good approximation of the value of the total **E-HIT** integral for the entire time, is this equation**:**

E-HIT (Newtonian) = 0.42 t_o + (ischemic time/18.5)

For shorter times, the approximation isn't quite as good, since some time is, in a sense, being counted twice in each term if the cooling hasn't finished. For a cooling time of 2 t_o, which is standard in cryonics to bring the patient to the transport temperature of 5 ^oC, the exact Newtonian **E-HIT** turns out to be almost exactly 0.5 t_o, or one quarter the time taken to cool.

Newtonian E-HIT (at t = 2 t_o) = 0.25 t = ½ t_o

Here's an example. If the $\mathbf{t_o}$ is 1.8 hours, which is typical for Newtonian cooling with a thumper (mechanical chest compression CPR device) and ice bath, then time taken for cooling to 5 ^oC will be 3.6 hours, and the **E-HIT** penalty, if oxygen can't be administered, is then 0.9 hours. This is the same as if the patent had gone 0.9 hours without being cooled at all. After the cooling, transport ischemia damage then continues at a rate of approximately $2.2^{-3.2}$ = 1/12.5 minutes per minute (it is not 1/18.5 because remember we're at 5 ^oC, not 0 ^oC). Of course, with further cooling, this drops toward the maximal 1/18.5 min per min.

Cooling with air (or ice on head only), with CPR but no oxygen. Here is the place to address the question of what happens if one attempts to cool ONLY the head conductively (such as putting ice bags around the head only) while continuing circulatory cooling by CPR without oxygen. The answer is that one might just as well save the time used to place the ice bags. Conduction through the head is so slow that advection from the warm body will overwhelm it, and essentially no cooling of the brain from the ice will happen at all. Rather, blood from the warm body will warm the brain faster than slow cold conduction through the scalp can cool it. What will end up happening, in these circumstances, is somewhat more rapid cooling of the head to room temperature than would happen in ordinary death, since with circulation maintained (assuming an anti-clotting agent has been used), the cooling of the entirely body will proceed with a skin temperature closer to life (roughly midway between room temperature and internal body temperature).

Although, to the author's knowledge, CPR has never been conducted on a non-iced (air cooled) patient for long enough to observe and record the resultant cooling behavior, one can calculate the result using an average body heat transfer coefficient of 6.8 watt/$^oK/m^2$ (see Footnote 1, **Appendix**). As noted in the footnote, this figure amounts to use of Newton's cooling equation, with an initial cooling rate of 2.4 ^oC/hr at a temperature differential of 13 ^oC (that between body temperature and room temperature). These figures imply (**Eq 3**) a time-constant of 13/2.4 = 5.4 hours for air cooling of a human body which is generating no heat (we assume no oxygen is being given) but still has circulation, in room air. Essentially, this solution amounts to doing the problem by "lumped capacitance techniques" in which the high inner conductivity of the body allows all but constant surface thermal contact resistance to be taken into account, and the cooling rate is set by this contact resistance, the surface area of the body, and the heat capacity of the body. The **E-HIT** which results is simply that for Newtonian cooling using a time constant of 5.4 hours; thus all of the equations and rules of thumb for Newtonian cooling discussed above, apply here.

Newtonian E-HIT Cool-down Penalty, with partial CPR effectiveness set at 50% (partial hypoxia down to body temperature of 28 ^oC)

What if oxygen *can* be administered to the brain, with CPR? Let us assume that CPR is capable of providing about 50% of the normal brain oxygen demand. Realize that this is an average figure, and will be much lower with bad CRP, and somewhat higher (perhaps as much as 75%) with really good mechanical chest compression systems.

If we use an average of 50%, we may then assume that when the value of our function **S** above reaches 0.5 or ½, then the "**E-HIT** rate" will afterwards go to zero, because after this point, the lowering of oxygen demand by the brain due to cooling, will have caught up with the oxygen delivery from CPR. How much total **E-HIT** does that give us? We must integrate it. It is easy to calculate that the condition of S = ½ happens when exp $[-2.92 \ (1- e^{-t/to})] = 0.5$. Solving for **t** in this expression gives t = 0.271 $\mathbf{t_o}$. The temperature at that time (**Eq. 3)** is 28.2 ^oC. This is about -9 ^oC below normal, because we're asking for 1/2 of normal metabolism, and using the Q10 rule that -10 ^oC gives 1/2.2 of normal metabolism.

If we make one more assumption that the rate of damage to the brain is linearly dependent on the difference between oxygen needed and oxygen available (see the discussion of CPR above), then we have enough information to do the calculation. The total **E-HIT** accumulated during this time (assuming that rate of otherwise totally ischemic brain damage at any temperature, is multiplied by the simple fraction of oxygen demand that can be supplied) is the following integral, taken over the (t = 0 to 0.271$\mathbf{t_o}$) during which ischemic damage is occurring:

$$\textbf{E-HIT (Newtonian, 37 }^o\textbf{C -28.2 }^o\textbf{C)} = \int_0^{0.271to} \{ \exp \ [-2.92 \ (1- e^{-t/to})] \} - ½\} \ dt \qquad \textbf{Eq 4a}$$

The total value of this definite integral can be evaluated with a slight change to **BASIC** program 1 (**Appendix**), evaluating up to the indicated time $\mathbf{0.271t_o}$ where the temperature falls to 28.2 ^oC, and also modifying the integrand to subtract **½** from the **E-HIT** rate function being integrated. When this is done, the value of the above definite integral for "half-oxygenated Newtonian cooling at full 37 C differential" is seen to be 0.057 $\mathbf{t_o}$.

RULE OF THUMB FOR "CPR+O_2" E-HIT

Thus, the empiric equation for CPR **E-HIT,** assuming 50% oxygenation all the way to 0 ^oC is:

50% effective CPR **E-HIT = 0.057 $\mathbf{t_o}$ + (circulatory arrest transport time at 0 ^{o}C/18.5)**

The initial cooling **E-HIT** term 0.057 $\mathbf{t_o}$ for the typical $\mathbf{t_o}$ of 1.74 hours of thumper/PIB CPR assuming 50% oxygenation turns out to be only about 6 minutes. Thus, in the 0.271*(1.74 h)= 28 minutes which it takes to drop 9 ^oC with a thumper/PIB system (thus cutting the metabolic rate in half), only 6 minutes of **E-HIT** will accrue if all of our assumptions have been correct. After that, so long as CPR remains effective enough to supply the lowering metabolic demand during cooling, no more **E-HIT** at all accrues, until CPR and brain perfusion and oxygenation are stopped. Then **E-HIT** again begins to accumulate at the rate set by the temperature, which can be as low as $1/18.5^{th}$ of a minute, per minute at 0 ^oC, as we have seen.

All of which leads to some interesting inferences. For one, we note that all of this may have some applications in standard medicine. If a person in cardiac arrest can undergo CPR and cooling at the same time, then any method of cooling which cools with a time-constant less than about 1.8 hours, can cool by 9 ^oC rapidly enough that no significant brain ischemia may ensues during cooling. And after that much cooling has been done, even standard poor-perfusing manual CPR may do, until the person can be put on cardiac bypass or otherwise rendered assistance (perhaps even given an artificial heart). Thus, a question for standard resuscitative medicine (not cryonics, necessarily) is: if CPR cannot be improved, why not cool the patient by so much in the first half hour of CPR, that even poor CPR will suffice for the next several hours? At present, there do not exist any methods of cooling patients at these rates outside of doing CPR on people in tubs of ice, but there do exist theoretical methods of cooling (see the section on lung lavage below) which might be able to do the job. If we had them, then many of our present problems of what to do with patients in cardiac arrest who cannot be defibrillated in the field, would disappear.

A second inference, which has to do with cryonics more directly, is that perhaps brain perfusion/oxygenation should never be stopped at all, if possible, during a cryonics transport. The 6 minutes or so of total brain ischemia which accrues in the first -9 ^{o}C of cooling by chest compression is probably survivable, even with today's resuscitation technology. If no more damage due to ischemia accrues during the rest of the cool-down, so long as good chest compressions are maintained, then it seems a shame to stop circulation entirely for a transport which will cause 3.25 min of equivalent ischemia per hour of transport. Another way to look at this is that if cryonics cool-down is done moderately well with oxygen, even without bypass the entire cool-down process does less ischemic damage than 2 hours of transport on ice. Which in turn means that any transport longer than 2 hours will do more damage than the entire cool-down, if circulation during transport cannot be maintained.

[Cryobago]

Adding Oxygen to CPR Where Ice-Cooling is Absent.

Air Cooling. Again remember that a human body which is getting oxygen by CPR will (unlike a patient in circulatory arrest with tissues getting no oxygen) still be generating metabolic heat, albeit only about half as much. At half-metabolic rate, the equilibration temperature in the interior of the body must be about 28 ^{o}C, because of the Q10 rule.

Because the temperature gap is small and does not change much with respect to absolute temperatures, the radiative part of the effective heat-transfer coefficient (thermal contact resistance) remains constant during this cooling (see the Stefan-Boltzman discussion in the **Appendix**), and the entire process can be modeled using the same time constant recovered from the human body's heat capacity, and the approximate metabolic power necessary to maintain it at the normal temperature differential with the environment that is seen in life.

However, the skin temperature to room difference does not fall by exactly half, because the radiative part of the heat transfer coefficient scales approximately as the cube of the absolute temperature, as we show in the **Appendix**, while the convective part falls approximately linearly.

Bathtub Cooling with CPR.

III. Conductive (non-Newtonian) Cooling

We'd like to turn now to the case of what happens with no circulation at all. Unfortunately for our mathematical ease, the human head without circulation doesn't cool by the simple Newtonian exponential cooling law (see **Appendix.** *Part III*). **E-HIT**'s for conductive (unperfused) cooling can be calculated also using **Equation 1** above, but we need to modify this using *heat diffusion equation* solutions (see **Appendix)** in order to give us our needed time-stretch or **S** function for this class of problems. For problems in which the head is cooled from the outside by heat diffusion (i.e., in cardiac arrest with circulatory arrest), we need the different equation because the cooling behavior at the center of the head is not Newtonian, if heat diffusion (or "cold diffusion") from outside to the inside is "slow". Which it always is, with biological materials.

While it is possible to have advective/Newtonian cooling with partial oxygenation, or even no oxygenation, the same is not true for conductive cooling. If a brain is cooling *only conductively*, it must be presumed that circulation has stopped, so that therefore there is no way that oxygen can be getting to it at all. Thus, for this part of the discussion, the "partial oxygenation" case of the preceding sections does not have to be treated, because never arises.

The human head may be usefully modeled for heat conduction problems (i.e., cardiac arrest no circulation problems) as a sphere with a 9 or 10 cm radius. The effect of rapidly cooling such a sphere by surface conduction is given by **T(r,t)** solutions for the heat diffusion equation for a sphere with moderate thermal surface conductivity and moderate interior diffusivity, subjected to a sudden surface temperature transient (see the **Appendix** for a more complete mathematical treatment of this model). Use of the first exponential term of the expansion solution for only the time-dependent part of the temperature solution, gives an equivalent time-constant $\mathbf{t_o}$ for cooling at the center of the human head, which is valid after a certain time-delay (which is caused by the time it takes for heat to get to the center of the head, and fully stable heat transfer gradient to be set up). This simple exponential function in turn gives reasonable figures for center-brain temperature after these cooling gradients have been fully established (this will be more extensively discussed later). Such figures for air and water cooling of the head are more or less comparable to temperatures observed in cadaver brains at varying times after death (see **Appendix**), and also in cryonics patients (see below). The actual thermal non-uniformity of the head (in particular, the presence of the skull) may, however, throw theoretical figures off by as much as 60%. We will correct for this semi-empirically in what follows.

Rule of Thumb for Conduction Cooling

We will show how to modify **Equation 1** to generate **E-HIT** for conductive (tissue-diffusion) cooling in the **Appendix.** Meanwhile, we can present the results, as a graph of resulting computer-generated **E-HIT** result for non-Newtonian, or conductive (heat-diffusive) cooling in the human head (remember, this means no brain circulation).

[Insert graph of conductive **E-HIT** vs. time in units of $\mathbf{t_o}$]

Our rule of thumb for conductive cooling is similar to that derived for Newtonian cooling, save that here we must make a number of assumptions, one of which is that we're talking about cooling at the center of a brain in a human head. How to do this occupies a large chunk of the mathematical Appendix, and won't be given here. The answer comes out again in terms of characteristic time-constant $\mathbf{t_o}$**,** but since this is not a Newtonian process it is reasonable to ask what this time-constant represents. The answer is that here $\mathbf{t_o}$ is the time-constant for the later part of the conductive cooling process, which does approach exponential behavior. If the time-constant is extracted from this portion of the curve, then we find:

Approx. E-HIT (Conductive, 37 ^oC gradient, head center) = $\mathbf{0.97\ t_o + time/18.5 \cong t_o + time/18.5}$

Here we see that the ischemic-conductive **E-HIT** cooling-penalty at the center of the head is 0.97/0.42 = 2.3 times what it is for Newtonian/advective/circulatory cooling, even for the same time-constant. The difference is due to the delay in "cold" getting from the cooling bath to the center of the brain, in conductive cooling.

IV. THREE REAL-WORLD CRYONICS CASES

We're now ready to discuss some real cryonics cases. These three cases represent a significant fraction of those known patients for which there was a relatively rapid transport, and for which there is good temperature data. This unfortunate fact is part of the reason this article was written. This data has usually not been collected! When collected, it hasn't been analyzed. *Yet we learn nothing qualitative about the basic cooling process in cryonic suspension, if these things aren't done.*

In discussing cryonics cases, again remember that there are two basic ways in which heat can be removed from the brain in cryonics. The first is pure *thermal conduction* a.k.a pure *thermal diffusion*, as discussed just above. This means in practice the diffusion of heat through the tissues without bulk movement of matter, until it is removed by a bath "fluid" (air or water, etc) outside the body, which is in contact with the scalp and facial skin. This is the only kind of brain-cooling that can happen during circulatory arrest, and as will be apparent from calculation and examples below, it's a rather slow process in adult humans. (Children have smaller heads and thinner skulls, which may partly explain the spectacular resuscitations of pediatric cold-water drowning victims).

Removing heat from the brain by blood circulation (also known as *forced convection* or "*advection*"), is the second, and by far the more rapid way to do the process. Let us look at some time-constants for advective processes, which are generally Newtonian for reasons explained in the **Appendix.** A heart-lung machine can cool a patient at an initial rate of 1 ^oC/min, and since this is 10 times the rate given above in our ice-water example, it implies a half-time of 0.43 hours for the cooling process. Thus, the patient would be at 9.25 ^oC and ready for cryoprotectant perfusion in only 0.86 hrs = 52 minutes, if some way were found for bypass to be done immediately at clinical death. This would imply an **E-HIT** of only 52 min/4 = 13 minutes, well within even today's no-significant-brain-damage resuscitation limit for experimental animals.

Of course, there is always some operative delay in instituting bypass, even if the machine and patient are immediately put together on pronouncement, which they were in the cryonics case discussed next.

Model Cooling Time-Constants in Patient C-2150

Now, finally, some real cryonics patients. We begin with CryoCare patient **C-2150**, a cancer victim cryopreserved by BioPreservation in 1995. This patient had mechanical chest compression ("thumper" machine support) and **PIB** (portable ice-bath) support immediately after pronouncement of death at this home by his hospice physician. Cryonics personnel were just outside the house in an ambulance at the time, and negligible time passed before the patient was in the ice bath, which had already been set up in the living room of his home. He was immediately intubated, submerged in ice water, mechanical "thumper" chest compression was begun, and he was given ice+saline lavages at several sites, including peritoneum. His brain cooling was therefore by both conduction and blood advection. Because of the strong advective component and no cooling delay, we use **Equation 2**.

Analysis of the first segment of **C-2150**'s tympanic cooling curves indicates that he initially cooled (in a temperature differential of 37 ^oC) at a rate of 7 ^oC over 20 minutes (= 21 ^oC/hr = 0.35 ^oC/min). The implied time-constant is 37/0.35 = 106 min = 1.8 hours. This is comfortably faster than pure conduction cooling. Since 20 minutes is too soon for much of the impact of *conductive* cooling to show up in the brain or interior head where the probe is, these data imply that nearly all of the cooling of the brain is being done here by thumper-circulation of blood carrying "cold" from ice-bath ice, through the skin over the body, then on to the body's core and of course, the brain. Again, this type of circulatory cooling is *advective.*

At less than 1 hour into this suspension, one sees from the cooling curve that something odd begins to happen-- something which has not (before this essay) previously been formally noted or quantitated. At about 55 minutes (0.9 hrs) into thumper support in the PIB, and still 90 minutes away from connection to circulatory bypass (heart-lung machine) cooling, **C-2150**'s cooling curve suddenly changes for the worse, for no reason that is apparent on later analysis of external events. The new cooling rate for these next 90 minutes becomes 2.9 ^oC /hr at a cooling differential of -22 ^oC. The implied $\mathbf{t_o}$ of 22 ^oC /[2.9 ^oC /hr] = 7.5 hrs indicates that from 55 min to the start of bypass at 143 min at 18 ^oC, **C-2150**'s brain cooled significantly more slowly than by pure conduction. *Which means in turn that brain perfusion during this segment had largely disappeared, at best, or is working against us, at worst.*

If brain perfusion has disappeared, this means that during this time the patient's chest compression, though still being mechanically done by “thumper” (mechanical chest compression device), has become ineffective. This was not noticed by the operating team at the time. Here we see one more reason for in-field data graphing; the only question being how to get enough people into the field to monitor and use the results. At the very least we see one of the reasons for extensive in-field data collection in cryonics.

On the other hand, if brain perfusion contines is in this segment, it would be now *preventing* brain cooling at the purely conductive rate, by carrying warm blood from the patient's body core to the head. This putative flow would be limiting the rate at which the head can cool, once temperature within it falls below 22 ^{o}C. Evidence for this is, of course, that brain cooling in this segment is considerably worse than it should have been with no blood flow at all. If this process had been known to be active, chest compression could have been discontinued to allow more rapid brain cooling. The price for this, of course, would have been to cut off brain oxygen. So CPR would have been discontinued only in the case where for some reason oxygen wasn't being delivered to the patient's lungs (there have been cryonics cases where lung bleeding has indeed made oxygenation by CPR impossible).

At 143 minutes into the suspension, Patient **C-2150** was finally femorally connected to cardiopulmonary bypass (CPB) cooling. This was done using a portable cardiac bypass cart, and physically happened while still in the patient's home (the patient had died in a "home hospice" style program). The 2.4 hour delay was partly a result of atherosclerotic changes in his arteries, and the relative inexperience of the surgical team (you get you pay for, etc). At the point of bypass initiation, we see that this patient's cooling rate drops drastically, and calculation over two segments in the next hour gives about 0.9 hr time-constants in both segments (the discontinuity between segments is small, and caused by a bypass oxygenator/ cooler which ruptured and had to be replaced on the fly). This 0.9 hr time-constant rate is the true in-field cardiopulmonary bypass (CPB) cooling rate, but in this case it was available only after this particular patient had already reached 18 ^{o}C by (only partly concurrent!) thumper and conduction cooling.

The return of the full CPB cooling-rate at this point in this patient proves that the circulation of this patient's brain was open to nearly full flow (at least at CBP pressures), BUT either that the thumper had not been effective, just previously, at driving blood through the brain. Or, as noted, that the blood it was driving was no longer being as effectively cooled by its trip though the body in the ice bath. If brain circulation had been lost after the first hour of clinical death, and then later regained— it is all for reasons unclear. In dogs, we have observed that whole-body capillary leak causes intra-vascular volume to drop drastically during long ischemia, and this may have been happening with this patient (in which case, something might have been done with a higher volume fluid infusion, had the cryonics team realized the problem). Just where and why the problem occurred for **C-2150** from 0.9 to 2.4 hours of thumper support (perhaps failure of brain or body microvascular bed, or failure of thumper CPR of some kind) was never determined.

After the institution of bypass cooling, patient **C-2150**'s temperature dropped to 5 ^{o}C (his transport temperature) by 210 minutes (3.5 hrs) into the suspension. The low average-cooling-rate here is more a product of the fact that the cooling differential is now dropping off severely, as the patient nears ice bath temperature. Had bypass cooling somehow been available at the very beginning of his suspension without any operative delay, the data suggest that this patient would have cooled to this transport temperature in only 2 time-constants for the bypass process, or about 1.8 hours. Instead, due to delay in getting him on bypass, he took 3.5 hours. Nevertheless, he remains the most rapidly-cooled patient known to record for a cryonics field transport.

Especially in light of this last fact, it is worth noting that the cryonics entities who performed this procedure in 1995 are now out of business, in part attributable to inability to sustain the level of remote standby technology necessary to accomplish a suspension like the above, given the support of only the small market demand available for it. Ultra-rapid cryonics field-cooling is possible, but we still face the question of who (if anyone) wants to pay for it. And how much are they (the patients and their families) willing to pay, and for how much cooling improvement?

Model Cooling Time-Constants in Case #2 (Patient A-1216)

Another cryonics moral follows. This particular Alcor patient, suspended December, 2000 wanted to pay for more than he got in the way of standby, but was prevented by his family from doing so. He probably more realistically reflects the average cryonics patient who cannot make active preparations for death, and receives no family assistance. This patient died in a hospital of natural causes, and (under remote instruction by his cryonics organization) had his head packed in ice bags by a sympathetic nurse and a mortuary attendant. He did not get CPR or thumper assisted cooling because there was nobody there to perform it, due to his family's unwillingness to pay for a remote standby. The patient himself was a well-to-do man who had been previously willing to pay for his standbys, and had already done so once (for a coronary bypass operation). But just before his death he was incapacitated by a stroke, and so was for the first time not in control of his medical or cryonics care. His relatives then proceeded to control his financial resources as a result, and refused to pay for the next standby. The patient therefore paid for first class service when he could choose, but got second-class service when he actually needed it most (but could not choose).

Do-it-yourself-ers take heed: You may not (indeed probably will not) be in control to the end of your life, and if you're not, you'll need to surround yourself with friends or family you can absolutely trust. If you don't have that, even very nasty lawyers cannot save you, because the time frame in which the legal system works to ensure your contractual obligations are met, is guaranteed not to be fast enough to affect the kind of early transport you will get. If you think some judge is going to sign a court order in the middle of the night or weekend, in order to force your family to do something with your body they really don't want to do-- think again.

Patient **A-1216** did not get to the care of volunteer cryonics team members until 8.5 hours after death, at which time his measured nasopharyngial temperature (a rough index of brain stem and deep core temperature) was 12.6 ^{o}C, i.e., he had cooled about -24.4 C. Since this patient was being cooled by both ice and air at 0 ^{o}C, it is possible to estimate his cooling differential as being the usual 37 ^{o}C. The fairly complicated cooling **Equation [6]** (derived in the **Appendix** below) can then be employed using computer iteration to recover the effective $\mathbf{t_o}$ for this process. The answer is that $\mathbf{t_o}$ comes out to be 4.8 hours for this segment. One probably cannot use the simple Newtonian **Equation [2]** above for such problems, because it contains no provision for the conduction "off-set" delay time of ln2* $\mathbf{t_o}$ = 0.69 $\mathbf{t_o}$. As we will see in the appendix, this offset time can be thought of as the time it takes for a maximal cooling gradient to advance by conduction to the brain center, so that afterward all parts of the brain may cool with the same exponential $\mathbf{t_o}$.

For cooling times approximating or exceeding $\mathbf{t_o}$**,** such as we are dealing with here, and for a water ice bath where heat diffusion equation solution constant **C** = 2 (see the **Appendix**), it is however possible to use the approximate **Equation [5]**, also derived in the Appendix. For example, where **$\Delta T(t)$** represents the difference in temperature between the brain and cooling bath at time t:

$\Delta T(t) = \Delta T(0)$ C $e^{-t/to}$ Equation [5]

Putting in values for these variables:

12.6 ^oC = (37 ^oC) * 2 * **exp – (**8.5 hours/**t_o**)

Solving for **t_o** gives 8.5/ [ln (74/12.6)] = 4.8 hrs

Note that use of the approximate **Equation 5** has resulted in the same answer.

The figure of 4.8 hours for **t_o** is reasonable, but not great, theoretical "pure-conduction" result for the center-brain cooling of a human head in a fairly good thermal bath. We may compare it to the 7.5 hr result for **C-2150** after failure of thumper effectiveness in the middle of his field cool-down. The head of **C-2150** was also almost completely submerged in ice-water, and his brain was probably cooling at least at full ice-water conduction rates. The reason for these similar results (indeed, **C-2150** in the ice bath did *worse* in some CPR segments) is discussed qualitatively in the conclusions, and semi-quantitatively in the **Appendix.** Basically the similarity is probably due to the fact that there is a severe limit on how fast the human head can be conductively cooled by *any* means. When it comes to conduction-cooling through tissue of the head, fairly good ice-packing with no stirring can be as good as a well-stirred immersion ice-bath. The reason for this is that both ice and ice-water bath are good enough to get the skin to ice temperature, and after that, it is only (slow) heat diffusion inside the head which determines how temperatures inside the head evolve.

At the 8.5 hour post mortem point, an emergency ad hoc cryonics team had arrived at the mortuary which had finally been picked for the procedure, and patient **A-1216** underwent beginning of cephalic isolation and then direct head-only circulatory blood washout. This procedure was also carried out in the preparation room of the commercial funeral parlor. Isolated cephalic washout was not then a standard field procedure in cryonics-- and this patient was the first case in which it was done. However, the technique in this case proved useful from both a technical and legal standpoint, in as much as it allowed **A-1216**'s "legal remains" (defined by law as his torso) to remain behind in his home state over the weekend to satisfy California law, while his head, legally only a "tissue sample," went to Alcor in Scottsdale, Arizona, for rapid perfusion and cool-down.

Before the cephalic isolation and while it was being done, the patient cooled 2.2 ^oC in one hour to 10.4 ^oC, at a cooling **ΔT** averaging 11.5 ^oC. This gives a **t_o** of 5.1 hours (we use **Equation 2,** because a cooling gradient through the head has already been established, and **Equations 5** and **6** are not appropriate). The numbers show that the attempt at better ice-packing at the same time cephalic isolation which was being done, apparently didn't help thermally.

At this point, field washout at the local mortuary was began, but an absence of well-pre-cooled washout perfusate availability in this emergency case resulted in a "semi-cold" perfusion, which neither heated nor cooled the patient significantly. After perfusion was complete, 4.5 hours after cephalic separation (and now 14 hours post-mortem), the patient's nasopharyngeal temperature had changed little, and was 9.8 ^{o}C.

The isolated head of **A-1216** was then wrapped in plastic and packed in crushed ice. It then cooled conductively on the road trip from California to Arizona, which little of the ice melting on the way. We have a good series of hand-recorded temperatures for his conductive cooling from 7 ^{o}C (14.5 hrs postmortem) to 1.5 ^{o}C (20 hours postmortem) on the 5.5 hour road trip to the cryonics facility. Here, we have a "cephalon" perfectly surrounded by ≅ 0 ^{o}C air (at the neck) and ice (remainder of head). The $\mathbf{t_o}$ here (again using **Equation 2**) is a surprisingly rapid 3.6 hrs. The figure may be less accurate than the others, due to the lessening temperature gaps we are dealing with in this segment, and it may not represent a true decrease in $\mathbf{t_o}$ from previous segments. On the other hand, it may possibly be real, and represent the patient's true conduction rate to this medium, now modified by heat removal though the stump of the neck in the closed transport container-- a phenomenon something which we hadn't had the opportunity to see before, either in this patient or the previously discussed one.

Model Cooling Time-Constants in Case #3 (Patient A-1034)

This case illustrates a number of novel cooling scenarios we had not previously encountered, such as hospital personnel CPR and ice-packing, use of a highly efficient Alcor A.C.T. (Alcor Cardiopulmonary Transport) moblile heart-lung bypass field perfusion unit, and rapid cephalic isolation and private jet transport. Temperature data was collected for the later part of this process.

A-1034 was an elderly Alcor patient who died suddenly and unexpectedly (probably of pulmonary embolism or heart attack) in a Los Angeles area rehabilitation facility in December, 2002. No Alcor team was standing by, since the patient had been doing well and was not thought to be in acute danger (he had had two full Alcor standbys in the previous year after suffering heart problems and pneumonia). The rehab facility was well-briefed in what to do for a cryonic suspension, and they administered heparin, packed the patient in all the ice which was available in the facility (which was a great deal, since an ice machine was available). They also did somewhat diffident CPR for the next 3 hours, until a hastily assembled volunteer cryonics team arrived at the facility, and placed the patient in a modified ice bath (a heavy-duty plastic body bag, with many bags of crushed ice completely surrounding the patient). At this point CPR picked up (the team had a CardioPump, which is a suction device which attaches to the chest, allowing a manual operator to lift the chest wall, as well as compress it). No thumper was used and the patient did not have an airway, so may or may not have been getting any oxygen. Manual CPR was continued through the one-hour trip to a local morgue, where bypass/washout was to be performed. The patient arrived at the morgue entirely packed in ice, at 5.5 hours after clinical death. Only then were temperature probes inserted though his nose into his deep nasopharynx, and his initial central head temperature was found to be 17.6 ^{o}C. He'd lost -20 ^{o}C by scalp thermal conduction, and manual CPR alone. Calculation of half-time for this phase = roughly 7.5 hrs (Newtonian).

At the morgue, the patient was intubated by the rest of the waiting cryonics team, but the oxygen which was finally delivered to his lungs did him little good, since chest compressions soon had to be discontinued for surgical reasons. The patient was found to have a tortuous and difficult femoral vein structure. Isolating and cannulating this required too much delicacy to be disrupted by the large body movements which accompany good chest CPR with a CardioPump. Even so, it still required 1.9 hours to get the patient on bypass. Calculation of time constant during the surgical period gives a surprisingly long 12 hours, indicating perhaps slippage or inattention to head ice packing, since essentially no CPR was being done.

Washout was finally performed with ice-chilled MHP-2 solution at 6 ^{o}C. During washout, 20 L of this solution was perfused open-circuit by the A.C.T. device in about 9 minutes, giving a washout rate of 2.2 L/min at the 120 mmHg infusion pressure being maintained. During this time, patient temperature dropped from 15.1 to 10.4 ^{o}C. Using an initial cooling differential of 9 C, this gives a time constant of 0.2 hours, which is close to theory for 2 L/min perfusion (see Appendix below: the 12 minute time constant suggests that the thermal mass being cooled was equivalent to 2*12 = 24 liters of water, which is reasonable for the thermal core of a 50 kg man.

This patient's temperature additionally fell by another –1.9 ^{o}C to 8.5 ^{o}C in the next 10 minutes after the pump and perfusion was shut off, presumably as a result of internal body thermal equilibration.

Cephalic isolation was accomplished in just a couple of minutes at this temperature, and within 2.3 hours after arrival at the morgue, the patient's cephalon was on its way to a chartered Lear-jet in Long Beach, CA for transport to Alcor in Scottsdale, AZ. Transport was in a plastic bag packed in crushed ice in an ice-chest, the bags used to minimize contact with actual ice (for fear of freezing skin which would later cause ice nucleation problems). We have conductive cooling data for this phase of the transport, which lasted just 1.66 hours, and during which the patient cooled to 4.8 ^{o}C. The time constant here calculates to 2.9 hours, which is a little faster than the 3.6 hours for the previous case as an isolated cephalon.

CALCULATION OF E-HITS FOR THE THREE DISCUSSED ACTUAL CASES

We are now ready to calculate **E-HIT**s for the patients just discussed. We will do it both assuming no oxygen support (for didactic purposes), and also with adjustment for oxygen for the segments of cool-down where it was historically available for **C-2150** and **A-1034.**

.

E-HIT for Case #1 (Patient C-2150)

The total **E-HIT** for patient **C-2150**, who got immediate thumper support and field bypass, is calculated in 3 segments to match his three observed cooling rates.

1) His descent to a temperature of 22 ^{o}C during the most rapid phase of cooling on thumper and with lavage (a period of 0.9 hrs) results in a hypoxic **E-HIT** of 0.51 hrs. This would have been the figure if his lungs had not been used to oxygenate his blood during assisted CPR. If he is assumed during this time to have been supplied with oxygen sufficient to meet 50% brain metabolic demand (as discussed above), then his **E-HIT** rate drops to zero after his temperature falls below 28 ^{o}C, and thus his total **E-HIT** damage is less than 0.1 hrs, as noted in the section above on partial oxygenation during CPR (**Eq 4a**.)

2) His slower descent to 18 ^{o}C over 1.5 hours after ice lavages had been stopped, and probably after thumper support become ineffective and was probably supplying little or no oxygenated blood to his brain, resulted in **E-HIT** of 0.39 hrs. If he was getting some warm blood from a non-cooled body core (a theory discussed above) then this number would be modified in ways that we cannot calculate. So here we will keep the 0.39 hours, and remind ourselves that there are still many pitfalls in this method.

3) His very rapid descent from 18 ^{o}C to 5 ^{o}C again after field bypass and washout was instituted (1.1 hrs) would have resulted in a purely ischemic **E-HIT** of 0.14 hours (if he hadn't gotten oxygen), but no **E-HIT** in reality, since was being supplied with oxygenated blood and perfusate during this time.

Giving credit for the oxygen he got, his total **E-HIT** to here (at 3.5 hours into suspension) comes out at 0.5 hrs. This is his equivalent ischemic time at normal temperature, when his transport over about 2 hrs of road-trip to the suspension facility began.

At arrival at the facility for cryoprotective perfusion (5.5 hrs post mortem) his total **E-HIT** was about 0.65 hrs (had he gotten O2 on the trip it would still have been 0.5 hours). Had he required a no-CPR 5.5 hour road-trip into another state while packed in ice, as patient **A-1216** did, he would still have had an **E-HIT** of only 0.87 (at 9 hours post pronouncement). At 20 hours post pronouncement (for a more direct comparison to **A-1216**), the extra 11 hours at 3.25 min/hour gives an extra **E-HIT** of 0.59 hrs, for a total of 1.5 hours **E-HIT**. There are numbers typical of cooling at the limits of our ability and luck in cryonics early in the 21st century.

2. E-HIT for Case #2 (Patient A-1216)

The segmental **E-HIT**s for patient **A-1216** above, who cooled also at three different rates, are as follows:

He sustains an **E-HIT** of 4.93 hr at 9.5 hours post pronouncement (beginning of his field washout). Much of this happens during the time-delay phase of initial simple conduction cooling.

2) His field washout results in an additional **E-HIT** of 0.53 hr.

3) The 5.5 hour transport **E-HIT** (giving him the benefit of the cold temps measured) is only 0.40 hours (one sees here the result of the approximately 18 to 1 advantage of the very cold temperatures maintained during this time).

No correction for oxygen delivery needs to be done at all in this case, because cooling was totally anoxic through the whole process. The *total* **E-HIT** for the above segments is 5.9 hours at 19.5 hours post pronouncement-- the same answer one would get from a purely conductive cool-down of the same length with a $\mathbf{t_o}$ of 5 hours (which is about the same as his cooling during his early phase before head separation). This **E-HIT** is not by any means wonderful, but it does show how well one can do in emergencies, with no CPR support, no immediate standby team, and only a helpful hospital and morgue attendant to do ice packing of the head of a patient.

This patient got about 1.3 times the damage he would have gotten if he'd had immediate cephalic isolation and a very good head-ice-bath transport, assuming his real measured isolated-head $\mathbf{t_o}$ of 3.6 hours through this whole phase (which would have resulted in an **E-HIT** of 4.55 hours at 19.5 hours). The difference is the time delay in isolating his head after death, and cooling delay associated with field surgery and washout.

This patient had 5.9/ 1.83 = 3.2 times more ischemic time damage than he would have had, had he had a thumper and PIB ice-bath available for 3.5 hours at clinical death before transport, even assuming no oxygen delivery with those modalities.

With oxygen delivery by thumper/PIB to an initial transport temp of 5 ^oC (which would have taken about 2*1.8 = 3.6 hrs), he would have gotten a 16-hr-transport **E-HIT** of 0.95 hours, plus whatever **E-HIT** resulted from getting him initially cooled to 28 ^oC where his metabolic stretch factor is about 2, and CPB could presumably have then have kept up with his O_2 demands. For thumper/PIB it takes about 0.5 hours to cool 9 ^oC, and if we assume that we (no doubt unfairly) presume fully anoxic **E-HIT** rates during this entire time, we get about 0.35 hrs of **E-HIT** on this segment (a very conservative value). This gives an **E-HIT** of 0.35 hours for initial cool-down, plus a transport **E-HIT** of 0.95 hours, for a grand total of 1.3 hours. Thus, even assuming the same time from deanimation to arrival at the cryonics facility, this patient actually got 5.9/1.3 = at least 4.5 times the ischemic damage due to no standby, as he would have gotten if he'd had a standby team with thumper/PIB and O_2 at his side, at the time of deanimation.

3. E-HIT for Case #3 (Patient A-1034)

To mortuary assuming no oxygen: 2.6 hours
With oxygen (incidental ventilation during CPR; patient's ambient airway)
During 1.9 hour surgery: 0.37 hours
During 0.15 hour washout: 0.02 hours
For 1.66 hour jet transport to Arizona: 0.15 hours

Total: Assuming no oxygen during CPR: 3.14 hours
Assuming CPR from the beginning and oxygen:

V. SOME THEORETICAL COOLING TIMES FOR DIFFERENT SCENARIOS

From the information we now have, we can now make some tables of estimated cooling time-constants ($\mathbf{t_o}$'s) and **E-HIT** values at 12 hours post mortem for various cryonics situations and scenarios, some of which have yet to be actually observed or undertaken. In them, we will assume certain values of $\mathbf{t_o}$'s for the head-center temperature cooling curves. Scenarios 1 to 5 below are conductive, and **E-HITs** are estimated using **Eq 7.** Scenarios 6 to 10 are advective/Newtonian, and **Eq. 3.** has been used to tabulate **E-HIT's.**

Time-constants:

The following time-constants are used for the conductive/pure heat-diffusion case:

1) We will assume $\mathbf{t_o}$ = approx. 16 hours for air convection cooling in bed, assuming half the head insulated by pillow contact, and half of the rest by hair. Unless you die unattended from heat stroke as your air conditioning quits, this is your worst cryonics scenario in non-disaster and non brain-mechanical damage conditions. Of course, there are many conditions where you might not, or cannot, be found before 12 hours have passed. However, these are rare.

2) We will assume $\mathbf{t_o}$ = 8 hours for best air natural-convection brain cooling from 37 ^{o}C at room temperature, assumed to be 24 ^{o}C. (See **Appendix**). This is a maximal value, and it assumes absent hair (as do the other air-cooled scenarios below). This is consistent with German studies for brain cooling in room conditions, as a function of time of death.

This rate of cooling is the best that cryonicists can obtain if they cannot legally touch or move an uncovered body, and are waiting for a coroner to sign off, so a body can be cooled actively, and moved from the place of clinical death.

3) We will assume $\mathbf{t_o}$ = 6 to 8 hours for a mean of 7 hours, in a morgue at 0 ^{o}C with no forced air movement.

As in all these problems, we must remember that we have two separate factors to consider: cooling rate is determined by both $\mathbf{\Delta T}$ and $\mathbf{t_o}$. Absolute cooling *rates* will be three times faster with 3 times the cooling gradient, even at the same $\mathbf{t_o}$. Thus, cooling in 0 ^{o}C air will be *more* than 3 times as fast as at 24 ^{o}C, even for the same process with the same time-constant.

4) We assume $\mathbf{t_o}$ = 5.0 hours for careful head ice packing, or for an ice bath for whole body patients in arrest with no CPR (we have used the median value for patients **A-1216**and **C-2150** here). Because of the high heat transfer coefficients for these procedures, this figure also applies for any water bath or good water skin wash (see the **Appendix** for the justification of this).

5) We assume $\mathbf{t_o}$ = 2.9 hours (see transport of **A-1034**) for an isolated plastic wrapped cephalon packed in chipped-ice, all surfaces being cooled, including neck stump. Note that transport of **A-1216** gave a time of 3.6 hours here, so this constant may vary a little upward for other cases.

The next time-constants are for the advective/Newtonian case:

6) We assume $\mathbf{t_o}$ = 1.8 hours for thumper support in a portable water bath (using data from **C-2150)**.

7) We assume $\mathbf{t_o}$ = 0.2 hours for field cardiopulmonary bypass with a standard medical heat-exchanger, from field. washout data for **A-1034** above. Note that this assumes a very good field bypass unit, such as the Alcor A.C.T. (Alcor Cardiopulmonary Transport) device.

8) We assume $\mathbf{t_o}$ = 1.0 hours for CPR plus exotic lung lavage, before bypass. This is one theoretical cooling modality which we should at least mention. Perfluorocarbon liquid lung lavage using ice-cold perfluorocarbon has been tested in animals, but only partially, and in one single case, in cryonics. At the company **Critical Care Research**, results showing equivalent $\mathbf{t_o}$'s as low as 1.2 hours for this cooling process in living anaesthetized dogs have been obtained **[7]**. The caveat is that these are with normal cardiac outputs, and might not be as good using the lower cardiac outputs of CPR. Since little data is available in humans (see below), we can only guess that this process would augment thumper or CPR cooling support somewhat, but to an unknown degree. A constant $\mathbf{t_o}$ of 2.4 hours from lavage alone (figuring about 50% normal blood circulation in CPR) would nearly double the effectiveness of thumper/bath cooling, and bring it to within cardiac bypass cooling rates (total $\mathbf{t_o}$ about 1.0 hrs).

Note: To calculate a sum $\mathbf{t_o}$ for two different concurrent advective processes **a** and **b** with respective time-constants $\mathbf{t_o(a)}$ and $\mathbf{t_o(b)}$, then the formula for the time-constant for the whole process is $\mathbf{1/t_o(sum) = 1/t_o(a) + 1/t_o(b)}$). In what follows we will (as a first approximation) assume this number for the combination time-constants in cases where 2 or more cooling methods are being used concurrently.

[discuss tricky combo of conduction and advection at short times.]

SCENARIOS WITH THEORETICAL 12-HOUR E-HITS

Here we can now tabulate some theoretical **E-HIT**s at 12 hours for some typical cryonics scenarios in which total anoxia is assumed. Each scenario is followed by the expected/theoretical temperature at the end of 12 hours. Scenarios 1) to 6) are primarily conductive, and **E-HIT**'s are estimated with **Equation 7** (**BASIC** Program 2 in **Appendix**). Scenarios 6) to 10) are primarily advective/Newtonian and **E-HIT**s are estimated with **Equation 3** (**BASIC** Program 1 in **Appendix**).

SCENARIO:

1) Dies in bed on side, has head hair, is not discovered (30.5 ^oC at 12 hours):	**E-HIT** 9.2 hrs
2) Dies unattended at 24 ^oC on floor, face up, no hair (28 ^oC at 12 hrs).	**E-HIT** 7.8 hrs
3) Dies outdoors at 0 ^oC, or dies and is taken to morgue at 0 ^oC with poor air circulation. No hair. (7 ^oC at 12 hrs).	**E-HIT** 3.1 hrs
4) Dies attended indoors, has hair wetted and head packed in frequently changed washcloths with 10 ^oC cold tapwater, or put in bathtub with 10 ^oC tapwater run	

over the head (12.5 ^oC at 12 hours). **E-HIT** 3.8 hrs

5) Dies attended with very good head ice pack (3.4 ^oC at 12 hours) **E-HIT** 2.7 hrs

6) Good ice pack to 2 hours (25 ^oC), then cephalic isolation with good ice bath for 10 hrs (1.1 ^oC) **E-HIT** 2.4 hrs

7) Thumper/PIB 1 hr (21 ^oC) then good ice pack 11 hrs (2.3 C) **E-HIT** 1.8 hrs With O_2: x

8) Thumper 0.5 hrs (28 ^oC), then CPB to ~2 ^oC (approx. 2.5 hrs), then good icepack 9 hrs (0 ^oC). **E-HIT** 1.2 hrs

9) Thumper plus Lung Lavage 1 hour (14 ^oC), then good icepack 11 hrs (1.5 ^oC) **E-HIT** 1.3 hrs

10) Thumper/PIB/Lavage 0.5 hour (20 C) then CPB 3.5 hours (0.4 ^oC) then good icepack 8 hrs (0 ^oC). **E-HIT** 1.1 hrs

REFERENCE THREE REAL CASE E-HITS, RE-CALCULATED AT A UNIFORM 12 HOUR REFERENCE TIME:

C-2150 (thumper/bypass in living room, iced transport as whole body w/o CPR) **E-HIT** 1.1 hours

A-1216 (No CPR; ice packs in hospital and morgue, road transport as cephalon) **E-HIT** 5.4 hrs

A-1034 (Poor CPR at hospital, better CPR on road, no thumper, good bypass at morgue, transport as cephalon in private jet). **E-HIT** **-**3.2 hrs

Note that 12-hour extrapolation of this last **E-HIT** is a bit unfair, since a great deal of expense was undertaken to insure that transport time was minimal (transport time of less than 2 hours here was comparable to time taken time taken to get the patient from place of death to mortuary, or to get him washed out once he'd gotten there). The **E-HIT** figure would apply to someone having the same experience, using a chartered jet to fly 3000 miles rather than 500.

V. A FEW OBSERVATIONS ON THINGS WHICH STAND OUT:

1) It takes a thumper/PIB and the significant amount of ice (more than100 lbs) necessary to fill a PIB, in order to get into the **E-HIT** range of 1 hour, for totally anoxic suspensions.

2) One can do surprisingly well (**E-HIT** = 1.8 hrs at 12 hrs) with nothing but really careful head ice-packing. With early cephalic isolation followed by even better conduction, it might in theory be possible to get to **E-HIT**'s of less than 1.6 hours, with ice conduction-cooling alone. More data is needed on this option. One problem is that early isolation takes time, and if the head is un-packed for the procedure, this is warm ischemic time running at full rate. Thus, if it takes more than 0.2 hours = 12 "warm minutes" to isolate the head, it's not worth doing from the cooling standpoint; instead it would be better to cool the head conductively in place, with ice packs.

3) It requires extraordinary measures and very rapid femoral artery/vein access to get to the "ultimate suspension" with cool-down **E-HIT** around 30 min at 4 hours (remember that to get the first 4 hour cool-down E-HIT we need to subtract 8 hrs of transport **E-HIT** = 0.64 hrs from the total 1.1 hours given for the best scenario above).

4) Cool-down **E-HIT**s less than 30 min will require CPB cooling with heat exchangers of greater capacity than are currently available. Also, time to surgical access of femoral vessels is a severe problem to any scenario which relies on really good CPB heat exchange. Finally, since 30 minutes is 9.25 hours of transport even at maximal cool-down, it should be evident that E-HITs for cases which take more than 12 hours from clinical death to the start of cryoprotective perfusion, will result in **E-HIT**s substantially greater than 1 hour, unless some way is found of oxygenating the patient at 0 ^{o}C during transport.

Again, for reference we have real cases **C-2150** with **E-HIT** of 55 min calculated at 12 hours (the relatively poor performance here even with thumper/PIB available, is due to arterial access delay). For patient **A-1216** we have an **E-HIT** at 12 hours of 2.7 hrs. The poor performance here was due mainly to lack of standby and unskilled head-ice-packing. For **A-1034** we have an **E-HIT** of , with again poorer numbers due to unattended death, lack of skilled initial CPR, and again delay in vascular access in washout, due to difficult vessel anatomy, in many ways similar to **C-2150** (perhaps the real lesson here, is that if we want really first class cryonics, we need to have real surgeons in the field, which was not the case in either bypass discussed here).

5) For 24 hour transports, once can simply add 39 minutes (**E-HIT** of 3.24 min for every real-time hour) for those scenarios above which have reached reasonably close to 0 ^{o}C at the end of 12 hours (probably any method as good as the best ice-packing, or better).

In the above we have not taken into account the effects of early blood washout. We think blood washout this is beneficial simply from the point of removing hemolysing and clotting blood from the brain, but we have no way of knowing the tradeoffs involved.

6) Finally, note that all **E-HIT**s above are calculated at the center of the brain/head, so they over-estimate damage to the cerebral cortex and probably most memories, which will be significantly more peripherally placed in the head, where they will cool starting sooner. Thus, conductive/anoxic **E-HITs** are worst-case scenarios, with at least one conservative factor built in.

Even when looking at the center of the head (where conduction cooling will be at the worst disadvantage vs. circulation cooling) conductive cooling is more important than many people in cryonics (including the author) had previously thought.

VI. MAJOR CONCLUSIONS

VII. RECOMMENDATIONS (LESSONS TO BE LEARNED FOR PRACTICAL CRYONICS)

[1]

APPENDIX
(MATHEMATICS, EXPERIMENTS, NUMERICAL RECIPIES, NOTES)

Part I. Acknowledgements

A more mathematical treatment of the conduction head cooling problem is given below. For the three dimensional Laplacian-operator heat diffusion equation solutions, the author has followed the time-honored method of engineers, who go to textbooks for this kind of thing (even the noted physicist E. Schroedinger, faced with a very similar equation for the hydrogen atom in 1925, was forced to beg help from mathematician H. Weyl, so this practice has a long and proud tradition). Recommended texts include **[1].**

The author acknowledges an early and extensive treatise on heat and mass transfer in cryonics **[6]** published in Alcor's **CRYONICS** magazine (Sept. 1985) by cryonicist and mathematician Arthur Quaife, Ph.D. Some of the material in this essay is generally covered by Quaife's theoretical discussion, however little quantitative data is used in Quaife's work. We have taken the opposite approach. A good deal of the mathematical elegance and generality to be found in Quaife has been sacrificed in the present treatment, for the sake of both simplicity and also due to the possibility of comparison to certain data on actual cryonics cases not available in 1985. The subject here is treated more from a biological engineering viewpoint. For a fuller treatment of physical theory, the reader is referred to Quaife.

The author is greatly indebted to medical physicist Brian Wowk, Ph.D. for help in simplifying some of the more intractable mathematics of heat transfer for these practical applications, and also for his insistence that the author not ignore the oxygenation effect of correctly-done CPR or CPB. Errors which remain are those of the author, not Dr. Wowk.

Part II. Abbreviations Used in the Text

Part III. Forced circulatory (advection) cooling of the brain.

Part IV. A Simplified Mathematical Treatment of Air and Water Pure-Conduction Cooling of the Head in Circulatory Arrest.

There has been some debate about the existence of a post mortem temperature rise in muscles and the body, for metabolic reasons that are unclear. This effect, sometimes called by the formal Latin term *algor mortis*, need not concern us, however, because it affects only the body and not the head during circulatory arrest; while at the same time, during artificial circulation (CPR) in cryonics it will be expected to be swamped by whatever methods of cooling are in use at the same time.

During circulatory arrest, air-cooling of the head may happen at room temperature in still air, or at nearly 0 ^{o}C in the (usually) un-stirred air of a hospital or city morgue cooler. (Even if in stirred air, bodies in morgues are general covered by sheets, which interfere with advection). Neither situation has a really good theoretical solution, for reasons that will become clear below. In neither situation (or in any situation likely to arise in cryonics) does cooling happen slowly enough that thermal transients from the center of the head to the surface may be neglected. In other words, it takes significant time for the temperature at the center of the head to conductively follow the surface temperature, and cooling in cryonics essentially always happens at scales far less than this typical time.

The Biot Number. In such thermal problems, where one has both a surface-advection problem and an interior-conduction problem, it is routine procedure to begin by deciding which effects are going to be most important. To do this, it is traditional to start by looking at a dimensionless ratio comparing the two effects, called the "Biot number" $\mathbf{B_i}$. The Biot number is basically a ratio of two quantities: The first quantity is the total thermal resistance *within* the object, which is due to its size and the thermal resistivity of the material(s) of which it is composed (i.e., that of various different head tissues, in the case of cryonics). The second quantity is the thermal "contact-resistance" at an object's surface/thermal bath interface. For example, this would be the air-to-skin resistance to heat transfer, for a problem in which the head cools in air. For the human body, the effective contact resistance also includes that of structures under the skin, since subcutaneous fat does not conduct heat quite as well as the more watery tissues which compose most of what lies underneath.

The ratio of the two main resistance quantities above gives an idea of how the temperature gradients will be proportioned in a given object (such as a head) when it is suddenly subjected to an outside thermal stress – i.e., during the time an object is heated or cooled by putting it in an environment which as a different temperature than it has. For example, if the thermal contact of a head with surroundings is poor, so that heat flows poorly from surroundings to scalp, this effect will dominate the problem, and the heat resistance *inside* the head will be unimportant to the problem. If the reverse is the case, the scalp and tissues immediately beneath the scalp will rapidly cool to the outside bath/environmental temperature, and cooling of the inside of the head will be entirely dominated and limited by diffusive heat flow *in the deep interior* of the head. In the latter case, during the time of heat-flow and equilibration, one would expect the temperatures within the head to vary greatly with depth from the scalp.

Heat conduction transient problems, such as occur when a human head is placed in a new thermal environment, are greatly simplified by either very high, or very low, Biot numbers. The reason is that in these cases, the effects of either bath-contact resistance (surface contact resistance), *or* the internal conduction resistance may be neglected.

Specifically, if the Biot number is "high" (usually greater than 2 or so, and certainly when greater than 5 or so), it signifies that most of the system thermal resistance is within the object, and the thermal bath capacity, or power to cool or warm, is thus more than enough to keep the surface temperature at the bath temperature. In such cases involving cooling (we're always going to assume the cooling case, in what follows), one is already cooling as fast as one can at a given bath temperature, and there is nothing more than can be done by conduction at that temperature, no matter how one stirs. To put this another way, one cannot get the skin colder than the bath, and once that is done, a capability for better bath heat transfer "power" doesn't help at all. For humans, such conditions easily obtain with un-perfused skin in water baths-- even in unstirred water baths. They also occur with the rapid kinds of gas stream cooling now being developed experimentally in cryonics. However, they don't quite occur with normal unforced ("convective") air cooling. Alas, this cooling method is too slow, and lacks the power needed to keep the skin near air temperature, at least during early cooling.

By contrast, "low" Biot numbers (usually less than 1/2 or so, and certainly when less than 0.2) signify that surface heat transfer is so slow that all parts of the object have a chance to nearly "catch up" to a single uniform internal temperature—a temperature which is NOT the bath temperature. This kind of thing might happen (say) in a solid metal sphere covered with thermal insulation. As will be made clear below, this does not happen at any cooling rates which cryonicists are ever likely to see--- the thermal conductivity of tissue is simply too low to allow heat to be very evenly distributed in the un-perfused human body or head, at surface heat removal rates normally encountered in any conductive medium—even free air. It might happen to an unfortunate suffocated astronaut whose head remained insulted by the stale air in his helmet. However, just about any kind of decent convective cooling, or even radiative surface cooling in vacuum, takes heat out of a human head fast enough that we will expect always to find significant temperature gradients from surface to center, while cooling takes place.

We may now start to be more quantitative. For spheres of radius **R**, surface heat-transfer coefficient **h,** and heat conductivity **k**, the Biot number $\mathbf{B_i}$ is given by the simple formula: $\mathbf{B_i = Rh/k}$

Calculation of Biot numbers for the unperfused human head in unstirred free *air* (for examples, see below) show that in many cryonics situations we must unfortunately often deal with the problematic intermediate-value Biot numbers in the range of 1 or 2. We might have guessed this, from the ordinary everyday life observation that the normal temperature of the skin (somewhere around 91 ^{o}F or 33 ^{o}C at room temperature) is intermediate between that inside the body, and the air. This tells us that Biot numbers for the human body cooling in air cannot be very high. The uniformity of temperature inside most of the body during life suggests that the effective heat resistance inside the body might actually be effectively quite low in life, and indeed this is a good approximation for body interior, when blood circulation/advective heat transfer is operating. It is even a good approximation for the skin during flushing, in environments with heat stress above comfortable room temperature. However, after cardiac arrest, the transfer of heat from the interior to the surface of the body is by pure conduction only, and this causes the effective Biot ratio for the body to rise. Then, much larger internal body temperature gradients appear than are seen during life with normal blood circulation.

In calculating the Biot number for air-cooled circulatory arrest in cryonics, we first run into the problem of determining the surface heat transfer coefficient "**h**" for the human body. Here we must deal with three types of heat transport. The first is heat transport due to natural convection (air movement due to the buoyant rise of heated air). The second, which we will mostly ignore in this treatise, is forced convection from air (a sort of wind-chill effect due to fans in morgues, and also ambient breezes and winds, etc.) All such heat removal effects may be lumped together under the general term of *advection*, which simply means cooling or heating by means other than pure diffusion of heat without the gross movement of cooling or heating media. Note that that term *advection* applies just as readily to "forced convection" internal cooling of brain and head by blood circulation. This sort of advective cooling is set at zero in the calculations for persons with no circulation in most of the examples below. It should be noted that, due to the high thermal resistance of the head, forced air convection is as effective as a stirred water bath, at gas speeds of about 20 to 30 m/sec. However, such winds are encountered only in experimental cooling conditions in cryonics (essentially nitrogen vapor "wind-tunnel cooling"), and when they are, they can be treated with the same mathematics as for the stirred water bath.

The last type of heat loss to be discussed is loss due to radiation transport of heat from the skin. The human body's radiation of infrared at a peak wavelength of 10 microns carries away heat, just as radiant heat from a heat lamp does. The skin, whether pigmented or not, is essentially "black" when viewed in the far infrared. It is about 98% as efficient as a theoretical "black body", which is the theoretic best a surface can be, as a heat radiator. An equation called the Stefan-Botzmann law can be used to estimate the magnitude of this process. In this equation, the power in watts radiated per square meter **P** is given by $\mathbf{P = \sigma\, \varepsilon\, (T_s^4 - T_e^4)}$. Here $\boldsymbol{\sigma}$ is the Stefan-Boltzmann constant (5.67×10^{-8} watts/m^2/^{o}K^4). The constant $\boldsymbol{\varepsilon}$ is emissivity, which as has been noted, is a relatively constant 0.98 for skin at physiologic temperatures. $\mathbf{T_s}$ and $\mathbf{T_e}$ are the skin and environmental temperatures, respectively, in degrees kelvin. This equation divided by $\mathbf{T_s - T_e} = \mathbf{\Delta T}$ shows the radiative part of **h** = $\mathbf{P}/\mathbf{\Delta T}$ to be $\mathbf{\sigma\, \varepsilon\, (T_s^2 + T_e^2)\, (T_s + T_e)}$. This expression reduces to $\mathbf{4\, \sigma\, \varepsilon\, T^3}$ for cases where $\mathbf{T_s}$ and $\mathbf{T_e}$ are close in value (i.e., $\mathbf{\Delta T}$ is small with respect to either $\mathbf{T_s}$ or $\mathbf{T_e}$, so either can be used as a generic **T**). This is the case for human cryonics, where the radiation cooling gradients are always small with regard to the absolute kelvin temperatures. Thus we have:

$$\mathbf{h\ (radiative,\ small\ \Delta T) = P/\Delta T = 4\, \sigma\, \varepsilon\, T^3 = (}2.2 \times 10^{-7}\mathbf{)\ T^3}$$

Doing this calculation for a typical environmental temperature of 298 ^{o}K (77 ^{o}F) and a typical skin temperature of 306 ^{o}K (91.4 ^{o}F), i.e. for temperatures close to 300 ^{o}K, gives radiative **h** values of about 2.2e-7*300^3 = 6 watts/m^2/ ^{o}K. These are fairly close to radiative losses which have been measured for the head, but slightly overestimate the measured value, probably because real heads often have hair or are resting on surfaces (which they warm), and thus are not as efficient at infrared radiation as they could ideally be.* Thus, while the radiative loss is easily calculated from the Stefan-Botzmann equation, unfortunately the exact "view factor," or temperature of surrounding area "seen" by the skin, varies from area to area in the body, and with body position. Ultimately, the Stefan-Botzmann equation can serve as a general guide for temperature dependence in these circumstances, but the actual radiative-loss rates must also be taken from measured situations. The radiative contribution to **h** at normal room temperatures during life has been measured to be not 6 watt/m^2/^{o}K, but rather about 4.6 watt/m^2/^{o}K, (which is a little surprising given the equation above which predicts that radiative losses should not be this low until environmental temperatures around 273 ^{o}K = 0 ^{o}C are reached, but remember the problems of hair and nearby warmed surfaces already discussed).

**Footnote: If (say) stuck out on a pike.*

Natural or "free-convection" heat loss in air, which results from the air carrying off heat vertically in a plume of heated and buoyant air, can be laboriously estimated by different techniques, but is best measured directly. For the human body in still air, on average, the free-convection part of **h** is about 3.4 watt(s)/m^2/^{o}K.

Advective loss (forced convection) due to other kinds of air circulation (wind chill) can also be calculated and measured, but we will neglect them since they generally are not important in cryonics situations which involve indoor situations or corpses under sheets in morgue coolers. Unfortunately, we cannot neglect the other advective or radiative heat loss processes, since (as noted) they are comparable in magnitude for humans in still air at room temperature. We probably *can* reasonably neglect heat transport from sweating heat-loss in many cases after circulatory arrest, since sweating stops immediately at death and thus (except for cases in which the skin is unusually wet) so does this type of heat loss.

As we have said, in still air, the naked skin looses about as much energy from infrared radiation as it does by free convection, and the total heat-transfer coefficient **h** at normal skin temperature is the sum of the convective and radiative components, or empirically about 8 watt/m^2/^{o}K. Again, this is for naked skin in still room-temperature air, under conditions of low perspiration and low losses from sweating.

[Foot Note 1]: We may estimate an average whole-body **h** for room temperature considering the added effect of clothing and hair, from the knowledge that little heat is lost by breathing or sweating under such conditions, and that the total heat transfer coefficient must then be the actual metabolic power (about 135 watts for a 70 kg man) divided by the temperature gradient (9 ^{o}C for a 24 ^{o}C room and 33 ^{o}C skin) and the radiative surface area of the standing body (2.2 m^2). This gives **h** = 135/(2.2*9) = 6.8 watt/^{o}K/m^2, which is a reasonable value for a clothed person. The average value of **h** one would expect to determine the cooling of an entire human corpse under many conditions of death might be a bit more or less, depending on whether or not the surface upon which the corpse is lying is a better or poorer conductor of heat than is air. If a corpse has a heat capacity of 200,000 joules/kelvin and is cooled initially at 135 watts (the resting value in life), this gives an initial cooling rate of 2.4 ^{o}C/hr. In forensics, however, the cooling rate (again set by total convective and radiative heat transfer) soon drops off to only about a third of this value, because of rapid cooling of the skin, which is in turn allowed by a fact we've already discussed: heat diffuses from inside a dead body at only a limited rate, and is not able to keep the skin nearly as close to the internal body temperature as in life.]

How does **h** change with a change in cooling **ΔT**? Although we know the radiative contribution to **h** is not going to be linear in temperature (a relationship which might seem to be implied by using an radiation-additive figure for total **h**), nevertheless we can see that the radiative component of **h,** because dependent on the cube of absolute kelvin temperatures, changes less than 8 % going from normal skin temperature to room temperature: (298/306)^3 = 0.924. The reader will have to accept on authority at this point that the dependence of free convection **h** on absolute temperature is even weaker than is the case for radiation. Thus, for cooling from skin to room temperature we can still use "still room air" combined value of **h** = 8 watt/m^2/ ^{o}K for the naked head, over the entire temperature range we're interested in. This value which should be much the same in circulatory arrest, as in life. In life it has been observed that the supine head has up to 30% higher **h** values and therefore cooling rates than the normal upright head. However, this is probably a hair effect, and we will neglect it, assuming, except where explicitly stated, that hair is either absent, or that its insulative effect has been neutralized by wetting it with water. Indeed, a total value for **h** of 8 watt/m^2/ ^{o}K is about the value experimentally obtained for the more-or-less hairless heads of newborn infants **[8].**

For head tissue conductivity (**k**) we may will use the mean of published values for muscle (0.4 watt/m/^{o}K) and brain (0.6 watt/m/ ^{o}K): this number comes out to 0.5 watt/m/ ^{o}K.

Thus, the Biot number **B_i** for the naked head lying on a surface in still air at 25 ^{o}C is:

B_i (still air, 25 ^{o}C) = **Rh/k** = (8 watt/m^2/ ^{o}K) *(0.1 m) / (0.5 watt/m/ ^{o}K) = **1.6** (dimensionless)

This **B_i** value is near 1.0, suggesting nearly equal contributions of thermal resistance inside the head and thermal resistance at the scalp/air interface, once again reinforcing the fact that we cannot neglect either the conductivity of the head tissue itself, or the somewhat poor thermal "contact" of the head with its normal air environment. The Biot number near unity shows that these processes have effects that are comparable in magnitude, when the head cools in unstirred air.

For a human head which is cooling in 0 ^{o}C air by natural convection at a gradient of 37 ^{o}C (a morgue cooler, say, with unstirred air), available semi-empirical convection-coefficient equations (not shown) give the same convective contribution to **h** as for the smaller temperature gradient of room temperature (there is only a weak dependence of natural-convection on absolute temperature). In the morgue at around 0 ^{o}C, by contrast, the radiation part of the coefficient is expected to increase by a factor of about 2.7 (here we use the simplified form of the Stefan-Bolzmann law above). This gives a total **h** of 16 watt/m^2/^{o}K initially for a head in air at 0 ^{o}C, although this will be heavily temperature-dependent and non-linear due to the 3rd power dependence of the radiative contribution to **h** (Stefan-Boltzmann equation above), and thus will be correct only at the beginning of cooling. The implied Biot number for this phase is twice the previous one, or 3.2.

The Heat Diffusion Equation (or, “Consider a spherical cow…”)

Having now (using the **Biot** numbers) looked at what engineers called "eigen-conditions" (German for "proper" conditions, which means initial, or boundary conditions) for an advection/conduction thermal transient problem, we are finally ready to look at the main governing equation(s) for such problems. Temperatures in the interior of the head resulting from transient pure heat conduction in the head (as takes place during cardiac arrest) may be roughly calculated using the boundary conditions above, using solutions of the *heat diffusion equation* (also called the heat flow equation):

$$\nabla^2 T = -1/D * \partial T/\partial t$$

Here **T** is the function of spatial and time variables which defines the temperature "field." This field is simple the set of temperatures inside the object, as a function of place and time. Since we've postulated a uniform sphere, it takes only one variable **r (**for radius**)** to define "place" and one more **t** for time. In a uniform sphere suddenly subjected to a new uniform surface temperature bath, temperature at any point on a shell at a given radius from the center, will be the same.

The quantity "∇^2" ("del-squared", also known as "nabla" or the "Laplacian partial differential operator") is a mathematical function which will be familiar to those who have had some vector calculus. The next bit of discussion is for the benefit of those who remember some of this, but won't be very helpful for those without this kind of math background somewhere, and the remainder of this section may in that case be skipped. Nabla **T** or $\nabla^2 \mathbf{T}$ can probably best be thought of in this context as $\nabla \cdot (\nabla \mathbf{T})$**,** or the *divergence* of the *gradient of* ***T***. The gradient of **T,** or $\nabla \mathbf{T}$**,** takes a temperature field **T** in space and converts it to a set of vectors, each of which at any point lies in the direction of the maximal temperature change in space (it points in the direction of "hot"), with a length which is proportional to how rapidly over space the temperature is increasing, in the indicated direction. Very high thermal gradients in space mean that the material is being put under a high stress to make heat flow (temperature here acts something like voltage). Not surprisingly, the rate of actual heat flow is directly dependent on the gradient in a material, with the other factor being the thermal conductance of the material. This is what the Fourier equation asserts.

There is one more complication, however, and that is the fact that temperature in a material may be changing in time as well as in space. Even if heat is not being generated in a material, heat flow across closed boundaries may not be conserved because heat-energy can "disappear" by needing to heat up material as it moves through space.

First-year physics courses often deal with the familiar Fourier heat conduction equation, which is mentioned in the section on advection above. The Fourier equation applies to objects in steady state heat flow situations in which heat is passing through an object, and in which, although different parts of the object may be at different temperatures, no particular part of the object is being heated or cooled (i.e. is changing temperature). Under these conditions, the temperature field within the object is not constant in space, but it is constant in time. In *steady state* thermal conduction, thermal gradients do not change in time. In these situations we don't have to worry about the heat capacity of the material itself. By contrast, in cases where the thermal gradient is changing over time, and parts of the material are being heated or cooled, we do need to worry about the material's heat capacity.

The *divergence* is how we take care of this disappearing heat energy flux, when heat is being taken up by the material the heat is flowing through. In electrostatics where divergence is usually first encountered, it may be remembered that divergence of an electric field ends up being a measure of the amount of charge enclosed by a surface drawn tangent to the field lines.

[ ]

number which is proportional to the heat energy flowing through a bit of matter at that location. The quantity ∂**T(r,t)**/∂**t** is the partial derivative of **T(r,t)** with respect to time **t.** Finally**, D** (sometimes symbolized α) is the thermal diffusivity of the medium, which is equal to $\mathbf{k/C_v}$, the ratio of the medium's conductivity **k** and its volume-specific heat capacity $\mathbf{C_v}$ (in m.k.s. units, $\mathbf{C_v}$ is expressed in joules/m^3/kelvin degree. Note also that $\mathbf{C_v}$ = density*$\mathbf{C_m}$, where $\mathbf{C_m}$ is the mass-specific heat capacity in joules/kg/kelvin).

The heat diffusion equation above results when the Fourier "steady state" heat conduction equation is subjected to rigorous energy conservation conditions, so that all the energy which heats the substrate while proper temperature gradients are being set up, is properly accounted for. This allows actual heating or cooling of an object to be computed, as a wave of heat moves through it from a “new” temperature bath, which has been suddenly set at an object boundary at some time **t**. The "Fourier's law" equation contains only the quantity **k** (conductivity) because (again) this equation deals only with steady-state condition where the total heat energy in the material is not changing. The difficulty that the Fourier treatment cannot handle is that a material heat conductor may either absorb or give up heat, in the process of going from uniform temperature, to the profile of graded internal temperature gradients which characterizes steady-state conduction from one temperature bath to another. For problems of this type, which describe this transition (called "transient" or "unsteady" conduction problems), the heat capacity of the material $\mathbf{C_v}$ must naturally enter into the calculations. This is the origin of the ratio $\mathbf{k/C_v} = \mathbf{D}$ which we see in the full transient-heat-diffusion treatment, which is what we need for transient heat-conduction problems.

The Case of the Transiently-Cooled Sphere/Head

The “spherical cow” is an old and tired biophysics joke, but we are now about to model the human head as a uniform sphere--- a better approximation than for the cow, though still not by any means perfect. Still, this treatment will allow us to examine the mathematics of the kinds of temperature changes that go on, in the interiors of large and lumpy pieces of tissue which cool only conductively from the outside, as they are suddenly subjected to a different (colder) bath temperature.

For tissues, the value of the thermal diffusivity **D** is usually on the order of 10^{-7} m^2/sec, and for the brain it is about 1.7 x 10^{-7} m^2/sec. For the head, we may use the mean of values for muscle and brain, which gives **D** =1.4 x 10^{-7} m^2/sec. The 0.1 meter value for **r = R** for the head is a bit of an estimative stretch, since obviously the head isn't quite a sphere, but we will be conservative and use **R** = 0.1 m (meter) as very roughly the mean distance in an adult head from any part of the (scalp, face, or neck) to the center of the brain. We are also explicitly making an approximation by using a single **D**, which effectively removes any radial dependence of **k**, a situation we know isn't perfectly accurate for the head (the slightly lower conductivity skull is on the outside, with the higher conductivity brain inside, etc). So we cannot expect really accurate answers doing the problem without a more complex model. However, since the heat conduction values of bone and brain do not differ greatly, we will find that we come closer than a factor of 1.5 to the correct answer (i.e., what we empirically measure).

We mentioned that surface-convection temperature transient problems with lower Biot numbers (**B_i** < 0.1) are especially easy to solve. Because of the relatively uniform temperatures inside such objects at all times, such solutions can be done from energy balance considerations alone. The time-constant for such problems and conditions is simply the (inverse) ratio of the Biot number and a Fourier time, which is in turn defined as $\mathbf{t_F} = \mathbf{R^2/D}$ where **R** is the radius of conduction and **D** is the thermal diffusivity of the conductive media. Thus, $\mathbf{t_o} = \mathbf{t_F} / \mathbf{B_i}$. In cryonics, where $\mathbf{t_F}$ is about 20 hours, we can see that if we had enough head "insulation" to give Biot numbers of much less than 1, cooling would be so slow that the cooling time-constant $\mathbf{t_o}$ would be measured in multiples of this "20 hour" Fourier time-- which is to say, in days. Fortunately for human patients, we don't have to deal with such a slow-cooling situation, even in the worst of cryonics scenarios, for the human head in practice is never insulated well enough for this approximation to be useful.

Now we return to our air-cooling case, where we have calculated **B_i** (remember) at about 1.6. In order to solve the heat diffusion equation as a boundary value problem for radially inward transient heat conduction in a uniform sphere, it is much easier to work in spherical coordinates. It also considerably simplifies the problem if we assume a uniformly constructed sphere in a uniform bath as a boundary condition, so that our mathematical terms contain only the variables **r** (radius) and **t** (time)**.** Here is the heat diffusion equation for a sphere of uniform material, with no heat generation (which would describe a heat with no metabolic heat generation, as would be the case with no blood flow).

$$\partial^2 T/\partial r^2 - 2/r\, \partial T/\partial r = -1/D\, \partial T/\partial t$$

As with most partial differential equations, we hope it is possible to separate variables in the solution function(s), so that we can convert the problem to one of several independent ordinary differential equations. In other words, we first presume that we can write the function **T**(**r,t**) as a product of two separate functions of **r** and **t** only:

$$T(r,t) = T(r)*T(t)$$

It may be guessed from the beginning that this might be true for the problems we are considering with regular geometry and uniform spheres of uniform material, we can expect that at any given radius **r** in a sphere, the temperatures will all be the same at any given **t**, so one parameter doesn't affect the other. Those readers already familiar with similar Laplacian partial differential equations in physics (other diffusion problems, and also wave equations for spherical potential solutions in quantum mechanics) will not be surprised that the attempt to separate variables works with the heat conduction equation for simple geometric forms and boundary conditions, and does indeed yield separate solution functions dependent on **r** and **t** only. At this point we can either crank through the math or just look up these solution functions in an appropriate engineering text such as **[1].**

We elect to do the latter. The **t**-independent but **r**-dependent **T(r)** solutions are the functions (1/n***A**) *sin(n***A**) where **A** = **r/R**, the dimensionless fractional distance outward from the center of the sphere. We will temporarily ignore these solution functions, since we are interested in the present discussion only in the center of the sphere (or head) where **r** = **r/R** = 0, and thus at the places where **T**(**r** =0) = 1. In other words, at the center of the sphere, only the time-dependent part of the total solution applies, and for this reason the entire **T(r)** part of the solution, which is always equal to 1 at the sphere center, can be ignored and forgotten. With **T(r)** out of the way, the solution for **T(0,t)** = **T(t)** can now be presented (again, remember that we have simply looked this up, and did not derive it). The solution for the change in temperature at the center of a sphere at time **t**, which is **ΔT(0,t),** is given by the following infinite exponential series:

$$\mathbf{T(0,t)} = \mathbf{\Delta T(t) = \Delta T(0) * C} \sum_{\mathbf{n=1}}^{\infty} (-1)^{\mathbf{n+1}} \exp(-n^{\mathbf{2}}\,\boldsymbol{\tau})$$

Or, writing out the summation terms:

$$\mathbf{\Delta T(t) = \Delta T(0)\ \ C}\ \ [e^{-\tau} - e^{\mathbf{-4\tau}} + e^{\mathbf{-9\tau}} - e^{\mathbf{-16\tau}} \mathbf{+ ...}] \qquad \textbf{Equation [6]}$$

This still looks messy, but has actually now been considerably simplified for purposes of calculation. Note the resemblance to Newtonian **Eq. [3]**, save for the constant **C** and some extra higher order exponential terms. Here, **ΔT(t)** is the temperature difference between sphere center and bath at any time **t.** Again**,** we must remind the reader that **ΔT(0) = T(0) –** $\mathbf{T_b}$**,** or in other words, **ΔT(0)** is the initial temperature difference between **the thermal bath** temperature $\mathbf{T_b}$ (assumed constant in all these problems!) and the center of the sphere/head temperature at time **t** = 0. The ratio **τ = t/**$\mathbf{t_o}$**,** is a dimensionless ratio of the variable time **t** and a characteristic time-constant $\mathbf{t_o}$ = $\mathbf{R^2/ (D\ \theta}^2)$, which we will find recurring in the mathematics. (Note in fact that our $\mathbf{t_o}$ is simply the "Fourier time" $\mathbf{t_F}$ divided by a numeric constant quantity $\boldsymbol{\theta}^{\mathbf{2}}$). We'll define the other two new constants **C** and **θ** which first occur in **Equation [6]** above, shortly.

From the numbers we give in the preceding paragraph for the head, we can estimate that the Fourier time $\mathbf{t_F}$ for the head is $\mathbf{R^2/\ D}$ = $(0.1\text{m})^2/1.4 \times 10^{-7}\ \text{m}^2/\text{sec}$ = 71,400 sec = 20 hours—a number we have already mentioned. This 20 hour time simply means that in conduction problems involving the (un-perfused) head, temperature equilibrium will have mostly gone to completion, on roughly this time-scale, after a temperature transient change is imposed as result of sudden exposure to a new and different thermal environment. This time is roughly in accordance with cryonics experience. How much less than 20 hours is actually required for thermal equilibrium of head and bath, depends on the value of the constant $\boldsymbol{\theta}^{\mathbf{2}}$. This number may be as high as $\boldsymbol{\pi}^{\mathbf{2}}$ = 9.3 (see below) for good thermal bath contact problems. In such cases, $\mathbf{t_o}$'s will be on the order of just a few hours.

As with the Newtonian **E-HIT** derivation, the expression for **ΔT(t)** above in **Equation [6]** is related to the one which we've sought for $\mathbf{\Delta T_n(t)}$**,** which we wanted to plug into our integral in **Equation [1]** , in order to get a function $\mathbf{S(\Delta T_n(t))}$ for any **t**, and thus a grand time-dependent function with which to calculate the total ischemic **E-HIT** across a span of **t** for the tissues at, or near, the brain center**.** Again we make use of the fact that $\mathbf{\Delta T_n(t) = \Delta T(0) - \Delta T(t).}$ We can now see that the value of this temperature gap function is **zero** at time **t** = 0, as it ought to be (the brain hasn't cooled at all), and the value of the stretch function **S(t=0)** at time zero is 1, again as it ought to be.

Inserting now the expression for $\Delta T(t)$ from **Equation 6:**

$$\Delta T_n(t) = \Delta T(0) * \{ 1 - C\, [e^{-\tau} - e^{-4\tau} + e^{-9\tau} - e^{-16\tau} + \ldots] \} \qquad \text{[Eq 7]}$$

Again of course this looks like Newtonian cooling $\Delta T_n(t)$ derived above: $\Delta T_n(t) = \Delta T(0)\,[1 - e^{-t/t_o}]$. Aside from the extra terms, the main differences are the constant **C** and also the hidden constant θ (which occurs in the evaluation of the t_o in τ). The **C** and θ constants both arise in solving the heat diffusion equation for conditions involving a certain geometry and a given Biot number. We can look them up in standard engineering tables *from* the Biot number, once we know the boundary conditions and geometry we interested in. In turn, once we have these constants we can evaluate our expression **Equation 7** for $\Delta T_n(t)$ above for any time **t**. The expression for $\Delta T_n(t)$ can then be plugged into **E-HIT Equation 1** in the same way that we've already used to get **Eq 3** from **Eq 1**. We can then integrate to get the purely conductive (and obviously necessarily ischemic) **E-HIT** for the brain center. Again, this is the equation which already was graphed for "conductive **E-HIT"** in the main section above. As noted in the main section, this evaluation of **Eq. 1** for conduction (using the conductive $\Delta T_n(t)$ expression of **Eq. 7)** is a moderately more complicated integral than for Newtonian cooling:

$$\text{E-HIT (conductive)} = \int_0^t \exp\{-2.92 * [1 - C\,(e^{-\tau} - e^{-4\tau} + e^{-9\tau} - e^{-16\tau} + \ldots)]\}\, dt \qquad \text{[Eq 8]}$$

Note again that $\tau = t/t_o$ so that even conductive **E-HIT** can be evaluated in terms of an effective time constant "t_o"**,** although it is not of course the simple Newtonian time constant.

Just as in the case of **Eq 3**., a (small) computer program is required to carry out such an integration in any kind of useful time period (another illustrative program in **BASIC** for this is included in the **Appendix**). The number of terms required for higher order part of the exponential series to become insignificant, depends how small τ is. For $\tau > 1$**,** only a single term suffices. But even for a τ of 0.1 (indicating a time only 10% of t_o) a summation of the first 10 terms of this equation still gives $e^{-\tau}$ within 1 part in 100,000. A modern personal computer can calculate 100 terms just as easily, in a few seconds. For our calculation of **E-HIT**'s in this essay, for example, we've used a 100-term exponential summation and incremented our times in units of 0.01 t_o (or $n\, t_o/100$) for the entire time **t =** total time of cooling.

As we note in the main body of this paper, when we graph "conductive **E-HIT**" at the brain-center for various t_o times, in the way we did for Newtonian cooling, we find that the **E-HIT** for conduction again turns out to again be a straight fraction of t_o, so long as times are sufficiently long. However, it is a larger fraction of **t** than in the case of Newtonian cooling. As we have already noted, the long-time approximation for the **[Eq 8]** integral is:

E-HIT (conductive, brain, 37 C) = 0.97 t_o + time/18.5

We have given this formula earlier as a conduction case **Rule of Thumb.**

As usual, this equation is very accurate only for **$t/t_o > 5$.** For smaller times we need to do the exact integral. For example, the conductive **E-HIT** for a standard 2 **t_o** cooling time in cryonics, is close to half the actual time taken to cool, or closer to 1.0 **t_o** than the equation above would predict (the equation predicts 1.08 **t_o**).

Approximations of the Heat Diffusion Equation Spherical Solution, for Mathematical Insight. A computer allows us to easily numerically evaluate any complicated equation without worrying about making approximations in order to save work. However, to see how the conductive thermal behavior described by **Equation 3** above behaves *conceptually*, it's helpful to look at the first term only of the expansion. This term can be used as a good approximation for "large times" i.e., after a significant fraction (perhaps 20%) of the $t_o = t_F/\theta^2$ time has passed. For the center of the sphere, the expression for the first term of **Eq. 6** has already been given in the main section as **Eq. 5**:

$\Delta T(t) = \Delta T(0)\ C\ \exp(-t/t_o)$ **Equation [5]**

But for the constant **C**, this would be an equation for simple exponential or Newtonian cooling, with the effective time-constant given by t_F/θ^2. We can see immediately that this can't be right for small times $t \ll t_o$, for it predicts that **$\Delta T(0) = \Delta T(0) * C$** instead of merely **$\Delta T(0)$.** The value of **C** is never more than 2, but still it is the remaining neglected terms of the expansion which take care of entirely factoring out the constant **C** for small values of time **t,** so that the complete **[Eq 6]** infinite series solution for the temperature can never give numbers larger than the starting temperature difference **$\Delta T(0)$**. (For example, for very small values of **t/t_o** and with **$\theta = \pi$,** as it must be for **C = 2,** the exponential expansion sums to exp(-ln2) = ½, canceling out the **C** and giving us the **$\Delta T(0)$** we need). Thus, use of a single-term expansion equation, such as that above, causes some incorrect answers (errors up to a factor of 2) with times a small fraction of **t_o**, and this error is due to mal-approximations from using just one term of this expansion.

As noted, the constants **C** and **θ** are small dimensionless interrelated numerical constants (one determines the other, by a certain transcendental trigonometric formula), and which both depend uniquely on the value of **B_i** for any given geometry. These constants can be calculated from the appropriate formula, or simply looked up in engineering tables such as are found in reference **[5]** (see page 227). When one does this, one finds that the constant **C** varies from 1 to 2 (as we go from small to infinite Biot numbers), and the related **θ** at the same time varies from infinitesimal to **π** (again as we go from small Biot numbers, to infinite Biot numbers).

One way of viewing **[Eq 5]** is that the *later* exponential behavior of temperature decrease in the center of the head (which follows the single term expansion) behaves *as though* simple **$\exp(t/t_o)$** exponential cooling is taking place, but with **ΔT** *initially* larger (by a factor of **C**) than was actually the case. Since **C** is typically 2 for situations like ice baths, and 1.4 or so for air/radiation cooling, we see later conductive cooling-rates looking as though the brain center were being cooled against gradients from 1.4 to 2 times larger than they initially really were.

Again, for the "long time" case time where **t** is not small with regard to **t_o** (i.e., **t** is greater than about 20% of **t_o**), we may use **[Eq 5].** We can also rewrite it to subsume the constant **C** into the exponential term, as:

$$\Delta T(t) = \Delta T(0)\ \exp\ -[\ \ln C - (t/\ t_o)\ ]$$

Which can be rewritten:

$$\Delta T(t) = \Delta T(0)\ \exp\ [(t - t_o \ln C) / t_o]$$

At longer times $\mathbf{t/t_o > 0.2}$ or so, the temperature at time **t** is correctly described by the equation above, in which the cooling curve is an almost simple exponential $\mathbf{exp\ (t/\ t_o)}$ but appears modified from the simple form, by an effective "off-set" or "conduction-delay" time, which is equal to $\mathbf{t_o{*}lnC} = \mathbf{(t_F / \theta^2)\ lnC.}$ It can be seen now that this effective time delay causes central brain temperatures to decrease later than they would, in simple exponential/Newtonian cooling. The result is a (more or less) fixed delay in cooling at the center of the head over what would be seen there, if the primary thermal resistance of the system was at the scalp, instead of within the deeper tissues of the head.

Such a thermal conduction delay is indeed seen experimentally, for it has been observed in the central brain temperatures of human corpses in forensic studies **[9]**. Its theoretical value is about $[20\ \text{hrs}/(1.8)^2] * \ln 1.4 = 2.0$ hours for the somewhat lower values of **C** which results from a cooling bath of air (**C** = about 1.8; see below), and the actual measured delay, before central brain cooling becomes truly exponential/Newtonian, has indeed been measured to be about 1.x hours in humans cooling in air. **[9]**

As noted, the parameters **C** and $\boldsymbol{\theta}$ are solution parameters which depend in a complicated way on the eigenconditions—which in this case means the Biot number. For large Biot numbers (> 500) corresponding to a relatively large convection coefficient **h** (i.e., a human head in a well-stirred water bath, where **h** may easily exceed 6000 watt/$m^2/^oK$), **C** turns out to be exactly 2, and $\boldsymbol{\theta}$ is exactly pi ($\boldsymbol{\pi}$). Inserting $\boldsymbol{\pi^2}$ for "$\boldsymbol{\theta^2}$" in the temperature solution above, we get $\mathbf{t_o =}$ 2 hrs and:

$$\Delta T(t) = \Delta T(0)\ \exp -[\ (t - (\ln 2 * 2\ \text{hrs}))\ /\ (2\ \text{hrs})]$$

Thus, $\mathbf{t_o}$ in this model, where the head is in excellent thermal contact with the cold-bath, will be 2 hours, and this is the time-constant we should expect to see when we have *maximal* head surface cooling. The cooling delay at the center of the head is now $\mathbf{t_o}$ ln2 = 2 ln2 = 1.4 hours. This conductive cooling is of the type which occurs when the skin is held at exactly bath temperature, which causes maximal temperature difference at the beginning of the problem to appear across the skin surface. This solution $\mathbf{t_o}$ will also model the expected behavior for ultra-rapid gas convection cooling, as well. An example would be a forced nitrogen vapor stream at high velocity such as 20 m/sec.; such streams of cold gas have been used experimentally in cryonics during the vitrification phase of cooling in neuropreservation.

Note that the $\mathbf{t_o}$ value of 2.0 hours is not too different from our previously observed best $\mathbf{t_o}$ values of 2.9 to 3.6 hours for a disconnected human head ("cephalon") packed in ice (see actual cases detailed above). We at first posit that some of the difference between theory and measurement comes from the fact we have calculated the $\mathbf{t_o}$ for conduction to the center of the brain, whereas in the cryonics case measured, the $\mathbf{t_o}$ is from pharyngeal probe temperature data, which means we're measuring times to the center of the *head, not the brain.* Unfortunately for this argument, we've already used a value of **R** consistent with an entire head. If one assumes that the average human head has a mass of 4 kg and the density of water, then its effective radius should be on the order of **R** = $[(3/4\pi)*4000]^{1/3}$ cm = 10 cm (again implying $\mathbf{t_o}$ of $(0.1)^2/(1.7 \times 10\text{-}7)$ = 2 hrs).

Our next guess is that the head isn't really in perfect contact with the thermal bath in these situations. Cryonics transport of cephalons in both of the cases above were for plastic-wrapped heads packed in crushed ice which didn't melt much during transport. In such circumstances, there may well exist many areas of skin contact which are not held at exactly 0 ^oC. Thus, it may be that with a true liquid bath, ideal contact conditions can be achieved, and measured values for $\mathbf{t_o}$ will fall from 2.9 hours to the 2.0 hours predicted in theory.

Whatever the reason for slower cooling, it probably won't be fixed by a *stirred* bath. There is little reason to imagine that heat-conduction for a human head can be improved by stirred ice baths, for a stirred ice-bath **h** of >6000 watt/m^2/ ^oK is a huge overkill in cooling-ability for a spheroid 4 kg piece of tissue with about 80% of the specific heat of water.

An actual lowest value of $\mathbf{t_o}$ of 2.9 hours in these circumstances (i.e., a good conductive medium supplying sufficient cooling power to keep the scalp at 0 ^oC) implies that the actual Fourier time $\mathbf{t_F}$ = $\mathbf{R^2/D}$ for the human cephalon with a good conductive bath is closer to (2.9 hours) multiplied by $\boldsymbol{\pi^2}$ = 29 hours. We may call this latter value the "semi-empiric" Fourier time for the naked head in a "pretty good" contact thermal bath. As we've noted, the discrepancy between the 29 hours for $\mathbf{t_F}$ we've essentially measured, and the 20 hours we had estimated from basic theory, isn't yet resolved. If we assume the problems are for other than contact, once we have a correct empirical value, we can use it with **Equations 5** or **7** to estimate cooling for human heads in other situations than ice baths. We do this simply by plugging in other values of the Biot number for differing cooling conditions, and using the different values of the θ and **C** which are implied by these, with the empiric Fourier time of 29 hours. We will use this empiric Fourier time value (our single fudge factor to make theory agree with reality) in all of the calculations below, for conduction involving longer time constants for poorer thermal baths.

Let us take an example. Consider first the case of a head in still air at 25 ^oC, cooling by air convection and by (somewhat imperfect) infrared radiation, a case for which we have already calculated the Biot number at 1.6. We can look up **C** and θ for this Biot number in our tables, and find that **C** is about 1.4 and θ is about 1.8. This θ gives $\mathbf{t_o}$ = 20 hrs/$(1.8)^2$ = 6.2 hrs for the **D** and **R** we had been using. If the corrected or semi-empiric $\mathbf{t_F}$ time implied from our actual case **A-1034** is used, the corresponding $\mathbf{t_o}$ for air cooling is 29 hrs/$(1.8)^2$ = 9 hours *(need to compare with German literature values).* In the absence of better numbers, we may use the latter figure for expected $\mathbf{t_o}$ for death at room temperature in quiet (indoor) air, and this is the number we have used in our table of expected **E-HIT**s above for simple room-temperature air-convective cooling.

In theory, for a morgue at 0 ^oC (this temperature is probably an overestimate for morgue coldness), and again with still air such as occurs under a sheet in a body box, the relatively increased radiative loss at this temperature gradient gives a Biot number of 3.2, and a θ of 2.3. Thus we get a semi-empiric $\mathbf{t_o}$ of 29/$(2.3)^2$ = 5.5 hours.

Notably, patient **A-1216**'s implied $\mathbf{t_o}$ from his measured cooling curve (assuming a 37 ^{o}C gradient), is measured at 4.8 hr, and this is close to the temperature fall-rate we measured later with a much better ice-packing of this patient's scalp and head. Thus, we may presume from the numbers that patient **A-1216** therefore probably did get fairly good head ice-packing for the entire time between death and his delivery to the cryonics team.

At this point we need to take specific note of something which may be a little bit surprising, and which is one notable conclusion of this treatment. The time-constant for good still air-cooling at 0 ^{o}C is less than twice that for the best ice-conduction cooling at 0 ^{o}C. To be specific, the ratio of time-constants for ice-cold air vs. ice-contact is the ratio of the squares of the θ coefficients for cold air vs. ice-cold water $(\pi/2.3)^2 = 1.86$. Thus, s*tirred ice-water cools a human head roughly only twice as fast as unstirred ice-cold air*. The reason for this lies in the drastic limits set on maximal cooling rates by heat conduction resistance within the head itself. These are independent of the kind of bath used to cool, and thus limit the maximal effectiveness of the bath itself. Once the scalp skin is at the temperature of 0 ^{o}C, the head cannot be cooled any faster by conductive media (stirred water or gas) at this temperature, no matter how effective these media are.

Ratio of purely ischemic central brain E-HITs from ice-cooling, vs. air-cooling.

Part IV. Equations for Estimation of Empirical $\mathbf{t_o}$ From Cooling Curves, and for calculation of E-HIT

Part V. The Literature on Post Mortem Brain Cooling.

Part VI. EXPERIMENTAL OBSERVATIONS AND CHECKS [Conducted by Steve Harris and Sandra Russell]. Some very simple experiments to model thermal conduction in lumps of tissue can be done with ordinary ground beef. A famous cryobiologist once said that cryonics would succeed when hamburger could be turned back into the cow. Doubtless the Nanomachines of Our Friends in the Future will accomplish this eventually. In the meantime, however, hamburger may serve as a cheap tissue thermal-conduction model for our more humble purposes, here at the beginning of the 21st century.

In the following three experiments, 10 lbs of commercial raw ground beef was intermittently microwaved and then mixed by hand, to a uniform temperature between 38 and 40 ^{o}C. It was then formed into an ovoid 17 cm in height and 20 cm in diameter, in a plastic pan. Hair-thin thermocouple probes were then inserted into the mass, at distances of 4.25 and 8.5 cm from the top of the mass. Three different cooling regimens were then instituted, in three separate trials, on the heated mass:

[1] Cooling in quiet air at 19.5 ^{o}C.

[2] Cooling under icepacks made from crushed ice in plastic bags (approximately 2/3rd's of the tissue mass surface).

[3] Cooling in unstirred ice-water, with the mass covered with water except for the thermocouple exit points at the top.

EXPERIMENTAL RESULTS

N.B. Waste not, want not. After the experiment's end, all unspoiled experimental materials were offered to the facility's guard animals, which consumed them with gusto. Nanomachines were not available to turn the material into live cow, but dog nanomachines (a.k.a. dog ribosomes) were available to turn some of it into live dog.

PART VII. ILLUSTRATIVE BASIC PROGRAMS FOR E-HIT CALCULATION

=========================

NOTES AND REFERENCES

[1] To be sure, ideas in aesthetics and politics are what we've learned to call "memes," and they are subject to *some* evolutionary feedback. There are selective forces on *all* ideas, after all, which have to do with their replication-readiness or ease, and/or their objective survival utility to organizations or societies. These forces have been responsible for what progress we have been able to make in ethics and law (democracy, antislavery, universal suffrage, etc). But it's been painful. Too often, what has felt like "progress" is seen, upon closer inspection, to consist merely of the state in which people finally give up arguing and simply isolate themselves. Separatism is common in philosophical movements, which tend to fractionalize to the point that smaller and smaller groups of fanatics associate only with people who think more and more like they do.

[2] Haneda K, Thomas R, Sands MP, Breazeale DG, Dillard DH. Whole body protection during three hours of total circulatory arrest: an experimental study. Cryobiology 1986 Dec;23(6):483-94

[3] Dai, J, Swaab, DF,M Buijs, Ruud. Recovery of axonal transport in "dead neurons." Lancet 1998; 351 (9101): 499-500. See also Verwer RWH, Hermens WTJMC, Dijkhuizen PA, et al. Cells in human postmortem brain tissue slices remain alive for several weeks in culture. FASEB J 16 (1): 54-60 JAN 2002

[4] Michenfelder JD, Milde JH. The effect of profound levels of hypothermia (below 14 degrees ^{o}C) on canine cerebral metabolism. J Cereb Blood Flow Metab. 1992 Sep;12(5):877-80. This paper more or less finds a Q10 of 2.2 from 37 ^{o}C all the way down to 7 ^{o}C in dogs. It appears to differ from the authors' earlier findings that Q10 can increase to as much as 4.5 below 27 to 14 ^{o}C in dogs, but the authors had concluded in this earlier paper that the increase was due to O_2 use from continuation of EEG activity in that interval when anesthesia was inadequate (as is sometimes the case in cryonics, but need not be). The paper finding the anomalous increase in Q10 when EEG is active, at intermediate temps is: Anesthesiology 1991 Jul;75(1):130-6. Without this factor, Q10 in dogs appears fairly constant from normal to very low (7 ^{o}C) body temps. This discrepancy may be possibly a warning to use barbiturates or other drugs wherever possible in cryonics, in order to suppress EEG activity and thus brain metabolism.

[5] Incropora and Dewitt, **Fundamentals of Heat and Mass Transfer**, 4th Edition (John Wiley, and sons, 1996); see especially Chapter 5 for analytic approaches to 3-D transient conduction problems, including the special case of the sphere.

[6] CRYONICS magazine, v. 6(9) issue #62 (Sept. 1985). Published by the Alcor Life Extension Foundation.

[7] Rapid (0.5 degrees °C/min) minimally invasive induction of hypothermia using cold perfluorochemical lung lavage in dogs. Harris SB, Darwin MG, Russell SR, O'Farrell JM, Fletcher M, Wowk B. **RESUSCITATION** 2001 Aug;50(2):189-204. In this study, cooling rates of 0.5 °C/min. in 20 kg dogs were reached, at a cooling differential of about 36 °C, giving a naïve $\mathbf{t_o}$ of 36/0.5 = 72 min., or 1.2 hours.

[8] Newborn head transfer coefficient

[9] German forensic studies

Dear Hugh, Brian, et al.:

We don't have reliable values for temperature vs. metabolic/ischemic damage, but the best studies on Q10 for metabolism (oxygen uptake) have shown a Q10 of about 2 in humans, dogs, and piglets down to about 15 C, and for dogs, 2.2 down to 7 C. These later studies were done by Michenfelder and Milde, and their 1992 paper looks to be trying to correct their own earlier study in which they'd initially reported values of around 4 in deep hypothermia for dogs, which don't agree with anything. I've included abstracts of both papers.

The maximal brain ischemic duration data roughly agree with the metabolic data, so long as one uses 10 minutes as the maximal homeothermic ischemic brain time. Thus, a value of Q10 = 2.2 for dogs would give a ratio of 2.2^3.7 for 1 °C in dogs (figuring they start at 38 C), which would be 18.5. That would give a max arrest time of 1.85 hours at 6 min normothermic equivalent, and 3.1 hours at 10 min. In fact, resuscitation from 3 hrs total circulatory arrest in dogs packed in ice at 1 degree °C has been published by Haneda et al (see below), but some of the dogs had some neurological damage, and these authors were obviously unable to get to 4 hours, or they would have done so. (Had they been able to go 4 hours, that would imply Q10 of around 4. But so far, we've yet to see it).

We did go past 4 hours in Leaf's work at Alcor years ago, and even got to 5, but this was with asanquinous perfusion with an O2-containing perfusate, and doesn't count in the same category as complete ischemia. Likewise, Taylor et al have done >90 min with dogs at 7-10 C, but again this is with trickle flows and some oxygenation, so again it doesn't count the same. I think an equivalent Q10 for damage of 2.2 is probably about right. I also think the 10 min figure for maximal baseline normothermia (37-38 C) duration time is reasonable, because dogs coming off bypass from extreme hypothermia get a lot of "post-resuscitation" mild hypothermia (34 C) treatment, and we know that THAT alone can make dogs resuscitatable out to 10 minutes of equivalent warm ischemia. So brains can take at least that much. (Remember, BTW, that mild hypothermia is applied AFTER the ischemic interval, for periods typically 6 hrs. It's a resuscitation treatment, and doesn't apply to cryonics. We merely use it to show that the damage at 10 min is reversible, since this treatment reverses it).

So anyway, the quoted figures for 90 min at 10 ºC are from Taylor et al, and are not for complete circulatory arrest. If they were, that would give $x^{2.8} = 9$ at best, which implies x = Q10 = 2.7 at minimum. As Hugh notes, this seems a stretch unless Q10 changes more than we think with temperature. But I don't think we need to make that assumption yet. They don't dare run humans in 10 ºC total circ arrest for aneurism repairs past about 45 min, so far as I can tell. The conservative figure of 2.2 holds.

And yes, this does mean that there are severe difficulties getting people to 10 oC without a huge amount of equivalent ischemic time. With no oxygen but maximal thumper and circulation cooling, one gets equivalent normothermia hypoxia times around 30 min in cryonics. For the best real cases, such times would be about an hour. Presumably our actual results were better, since we had oxygenation support which would mimic asanquinous perfusion. But cryonics cases in which all cooling to ice temp was done by simple heat conduction without oxygenation have equivalent brain ischemic times of several hours even with the temperature correction, with nothing to suggest that this amount of damage wasn't actually done. Since 10 minutes (perhaps 15 with fancy drugs) is the present survivable maximum, that's not good. It doesn't mean these patients are damaged beyond repair, but why would you do this to somebody when you didn't have to?

SBH

J Cereb Blood Flow Metab 1992 Sep;12(5):877-80

The effect of profound levels of hypothermia (below 14 degrees C) on canine cerebral metabolism.

Michenfelder JD, Milde JH.

Department of Anesthesiology, Mayo Clinic, Rochester, Minnesota 55905.

The goal of this study was to determine the temperature coefficient (Q10) for canine CMRO2 at temperatures below 14 degrees C. Eight dogs were anesthetized with halothane for surgical preparation. The animals were placed on total cardiopulmonary bypass and CBF was measured by direct sagittal sinus outflow. Duplicate measurements were taken at 37, 13, and 7 degrees C. The EEG became isoelectric at a temperature of 12.0 +/- 0.8 degrees C. The Q10 between 13 and 7

degrees oC was 2.19 +/- 0.59. With rewarming to 37 degrees C, cerebral metabolic variables returned to control levels. Brain biopsies taken at the end of the study yielded normal values for brain energy stores. We conclude that the Q10 for CMRO2 at temperatures between 7 and 37 degrees oC can be profoundly affected by the state of cerebral function as reflected by the EEG. In the absence of EEG activity, an expected Q10 value of 2.2 reflects only the direct effect of temperature on the rates of biologic reactions.

PMID: 1506453 [PubMed - indexed for MEDLINE]

Anesthesiology 1991 Jul;75(1):130-6

The relationship among canine brain temperature, metabolism, and function during hypothermia.

Michenfelder JD, Milde JH.

Department of Anesthesiology, Mayo Clinic, Rochester, Minnesota 55905.

Cerebral protection by hypothermia is commonly attributed to cerebral metabolic suppression. However, at temperatures below 28 degrees C, the relationship of temperature to cerebral metabolic rate of oxygen consumption (CMRO2) has not been well characterized. Accordingly, the relationship between brain temperature and CMRO2 was determined in eight dogs during cooling from 37 to 14 degrees C while the EEG was continuously monitored. Cardiopulmonary bypass was initiated and control measurements were made at 37 degrees oC during anesthesia with nitrous oxide 50-60% inspired and morphine sulfate 2 mg.kg-1 intravenously (iv). Upon cooling to 27 degrees C, the nitrous oxide was discontinued and the morphine was antagonized with naloxone 2 mg iv. Measurements were repeated at 27, 22, 18, and 14 degrees oC and in four dogs again at 37 degrees oC after nitrous oxide 50-60% had been reestablished at 27 degrees oC along with administration of morphine sulfate 2 mg.kg-1. For each temperature interval, the temperature coefficient (Q10) for CMRO2 was calculated (Q10 = CMRO2 at x degrees C divided by CMRO2 at [x - 10] degrees C). Between 37 and 27 degrees oC the Q10 was 2.23, but between 27 and 14 degrees oC the mean Q10 was doubled to 4.53. With rewarming to 37 degrees C, CBF and CMRO2 returned to control levels, and brain biopsies revealed a normal brain energy state. During cooling, the EEG developed burst suppression at or below 22 degrees C. With further cooling, the periods of suppression increased; however, burst activity continued in seven of eight dogs even at 14 degrees C.(ABSTRACT TRUNCATED AT 250 WORDS)

PMID: 2064037 [PubMed - indexed for MEDLINE]

Cryobiology 1986 Dec;23(6):483-94

Whole body protection during three hours of total circulatory arrest: an experimental study.

Haneda K, Thomas R, Sands MP, Breazeale DG, Dillard DH.

Survival following 3 hr of total circulatory arrest under profound hypothermic conditions was explored in 19 adult mongrel dogs. Thermoregulatory management included combined surface/perfusion hypothermia and azeotrope anesthesia in 95% O2/5% CO2. All animals were resuscitated and survived for at least 12 hr. During the last seven trials (Group II) the following principles were applied: uniform whole-body cooling where differences between rectal, esophageal, and pharyngeal temperatures averaged less than 1 degree C, induction of circulatory arrest at approximately 3 degrees C, constant lung inflation (10-12 cm H2O between 20 degrees oC cooling and 20 degrees oC rewarming, including the 3-hr arrest period) and ventilation assistance with positive end-expiratory pressure (4 cm H2O) after 20 degrees oC rewarming, intraoperative maintenance of colloid osmotic pressure (COP) above 11 mm Hg, replacement of the cooling perfusate with a colloid-rich rewarming prime (COP = 15 mm Hg) and restoration of hemostasis with fresh whole blood transfusions. The application of these principles resulted in the long-term survival of five animals with four survivors displaying no clinically detectable neurological abnormalities. However, two animals developed optic impairment and one animal died from intusseption on the fourth postoperative day. Despite the improved results, it should also be noted that during pilot (Group I) studies (from which the aforementioned principles were derived) fatalities from complications attributed to systemic edema, central nervous system, or pulmonary or coagulation dysfunctions occurred in 9 out of 12 trials. We conclude that whole body protection following 3 hr of total circulatory arrest at a uniform temperature less than 5 degrees oC can be successfully accomplished.

PMID: 3802887 [PubMed - indexed for MEDLINE]

1: Resuscitation 2001 Aug;50(2):189-204

Rapid (0.5 degrees C/min) minimally invasive induction of hypothermia using cold perfluorochemical lung lavage in dogs.

Harris SB, Darwin MG, Russell SR, O'Farrell JM, Fletcher M, Wowk B.

Critical Care Research, Inc. 10743 Civic Center Drive, Rancho 91730-3806, Cucamonga, CA, USA

Objective: Demonstrate minimally invasive rapid body core and brain cooling in a

large animal model. Design: Prospective controlled animal trial. Setting: Private research laboratory. Subjects: Adult dogs, anesthetized, mechanically ventilated. Interventions: Cyclic lung lavage with FC-75 perfluorochemical (PFC) was administered through a dual-lumen endotracheal system in the new technique of 'gas/liquid ventilation' (GLV). In Trial-I, lavage volume (V-lav) was 19 ml/kg, infused and withdrawn over a cycle period (tc) of 37 s. (effective lavage rate V'-lav=31 ml/kg/min.) Five dogs received cold (approximately 4 degrees C) PFC; two controls received isothermic PFC. In Trial-II, five dogs received GLV at V-lav=8.8 ml/kg, tc=16 s, V'-lav=36 ml/kg/min. Measurements and main results: Trial-I tympanic temperature change was -3.7+/-0.6 degrees C (SD) at 7.5 min, reaching -7.3+/-0.6 degrees C at 18 min. Heat transfer efficiency was 60%. In Trial-II, efficiency fell to 40%, but heat-exchange dead space (VDtherm) remained constant. Lung/blood thermal equilibration half-time was <8 s. Isothermic GLV caused hypercapnia unless gas ventilation was increased. At necropsy after euthanasia (24 h), modest lung injury was seen. Conclusions: GLV cooling times are comparable to those for cardiopulmonary bypass. Heat and CO(2) removal can be independently controlled by changing the mix of lavage and gas ventilation. Due to VDtherm of approximately 6 ml/kg in dogs, efficient V-lav is >18 ml/kg. GLV cooling power appears more limited by PFC flows than lavage residence times. Concurrent gas ventilation may mitigate heat-diffusion limitations in liquid breathing, perhaps via bubble-induced turbulence.

PMID: 11719148 [PubMed - in process]

SBH

-----Original Message-----
From: Steve Harris <sbharris@ix.netcom.com>
To: sbharris@ix.netcom.com <sbharris@ix.netcom.com>
Date: Monday, April 01, 2002 7:24 PM
Subject: Fw: Wups,your name mutated off the mailing list for this (Matt at alcor has a copy also)

>
>I welcome Email from strangers with the minimal cleverness to fix my address
>(it's an open-book test). I strongly recommend recipients of unsolicited
>bulk Email ad spam use "http://combat.uxn.com" to get the true corporate
>name of the last ISP address on the viewsource header, then forward message
>& headers to "abuse@[offendingISP]."
>----- Original Message -----
>From: <SBHARRIS@IX.NETCOM.COM>
>To: <lemler@alcor.org>
>Sent: Friday, March 29, 2002 1:36 PM

>Subject: Wups,your name mutated off the mailing list for this (Matt at alcor
>has a copy also)
>
>
>Crew:
>
>After doing some preliminary calculations, I've decided that my theory of
>the very small volume of cooled tissue being responsbible for the fast temp
>drops after FC lung lavage on A-1867, has some real problems. The most
>suspicious thing is that when I calculate the time-constant for the 2 fast
>lavage-associated temp drops (ignoring the rebound dip and using o=
>nly the equalibrium endpoint), I get 0.9 hrs for the first one and 1.8 hrs
>for the second. The 1.8 hr constant is exactly in the range of what one
>would expect with good thumper support with patient in ice bath, and is what
>we got from JG (C-2150). The 0.9 hours is typical of full bypass cooling
>(and is what we got in JG on bypass), so *that* difference may be due to
>cooling of the PFC. If so, however, its effect is much less than I
>supposed-- certainly less than half as much, probably enough to give us the
>standard 20% of total thermal mass cooling we see for the most rapid phase
>of "cold" distribution in dogs.
>
>The main first order effect of FC-lavage (or lung fill-up) I suspect is to
>make chest compression efficient, just as Mike had hoped it would all along,
>so that we actually add advective cooling to conductive cooling when the
>lungs are full! We see this effect when it drops out as the first lavage
>ends and the temperature of the patient stays absolutely stable (!), dispite
>thumper still going and her in the bath. Mike adjusts thumper here, as well
>he should have, but the effect of doing that isn't very impressive *until*
>the second lavage goes in. THEN we go back to circulatory cooling with the
>sa
>me time-constant as JG getting good compression (ie, 1.8 hrs, which is
>comfortably faster than the 3-5 hours typical of conduction only). Finally,
>after the second lavage, cooling goes to the standard 3 hour time-constant
>you expect with not much more than conduction only-- and this is true even
>in the segment before the thumper is stopped (you see NO differen=
>ce in cooling from doing that!). In fact, for this patient I calculate 3.4
>hours for the segment *after* cephalic isolation is complete, which is also
>just about exactly what we got in A-1216 in his ride to Scottsdale as a
>celphalon on ice. So the thumper (segment from 2 to 2.5 hours) was doing
>very little with no FC in the lungs.
>
>I hope this case illustrates the value of good data collection and how much
>about the basic nuts and bolts of cryonics there is to learn from EVERY
>case, when it is done right.
>
>

>Steve Harris
>
>==============
>From: Mgdarwin@cs.comDate: Fri, 22 Mar 2002 18:20:12 EST
>To: sbharris@ix.netcom.com, david@uswo.net, davshu@sunline.net,
>SLubais@cadence.com, jlemler@alcor.org, David.Shipman@alu=
>m.mit.edu, mathew@alcor.org, djt@ihot.com, wowk@21cm.com
>Subject: Re: Logger data graphedSteve,
>Thanks so much for the graphing and the interpretation. I think its
>important
>to try to balance the thermal equation in this case, but I'm not sure it can
>be done. The data collected is automated, the probes were stapled in place,
>and nasopharynx was empty of ice water contamination. So, I take it the data
>are accurate. I've some thoughts about how the heat exchange took place, but
>only you can really tell if they are reasonable.
>In a message dated 3/22/02 9:30:10 AM Pacific Standard Time,
>sbharris@ix.netcom.com writes:
>> I've faxed graphs to Dave Shumaker. Basically they don't make sense
>unless
>> one deletes the very first point (the 27 C pharyngeal), and all the rectal
>> temp points that bounce around from 24 to 15 C (occasionally going back up
>to
>> 33 or so even at the end to show that the 15 C points aren't real).
>Yes, the DuaLogger was behaving erratically and that's why I switched the
>probes. I didn't know what else to do. She had very short external auditory
>canals and I couldn't get the probes in place there, and I'm an expert!
>> The rectals very suddenly go back up to track the pharnyngials at about
>100
>> minutes into the procedure, and I think this is when the switch must have
>> been made.Yes, that is correct.
>> Otherwise it's pretty interesting. Looks like the first lavage
>permanently
>> cooled her brain from about 33 C to 24 C, and the second from maybe 20 C
>to
>> 13 C. A 1500 mL PFC lavage at 0 C has about 1620 cal relative to a
>person
>> at 24 C, suggesting the mass cooled is very small here (something like
>(1620/[
>> (.7)*11 C]=3D 2 kg.) This is less than lungs blood and brain. For the
>second
>> lavage it's 13*1500*.45/.7*7 =3D 1.8 kg. Pretty much the same amount of
>tissue,
>> but I haven't a clue as to what. Brain is 1.3 kg, lungs perhaps .2 kg,
>and
>> blood 3 kg. There must have been almost no blood, and you're only cooling
>a

>> small fraction of that.
>Is the following analysis reasonable, and does it all add up?
>1) She most certainly had very little blood. When I walked into the room
>with
>Dave Shipman she was completely blanched. Not your typical post arrest
>"corpse" but blanched like she had had a TBW. It was no feat of clinical
>insight to see that she was clinically dead! The amazing thing was the nurse
>and sitter who were oblivious. I believe as you speculated too, that she
>bled
>out into a viscus is a massive way. This would also explain her "chaotic"
>failure mode: her vitals had just been take 45 minutes earlier and were not
>inconsistent with the last 72 hours and, most importantly, she had pink
>extremities and good capillary refill.
>2) She got, per kg of circulating tissue, an enormous dose of vasopressin
>and
>epinephrine. Furthermore, this vasopressin was NOT going to be metabolized
>since there was little if any peripheral circulation, tissues were hypoxic,
>ischemic and going to stay that way and hypothermia was being rapidly
>induced.
>3) She had experienced 3 days of death rattle with absent breath sounds
>except at the apices. I've never in my entire experience seen pulmonary
>edema
>so bad so long. This, not to mention a fulminating infection with
>pseudomonas
>aureginosa developing from day 3 or so. I am as certain as I can be without
>autopsy that almost her entire lungs were consolidated (liver lungs) and
>that
>PFC was inaccessible to the consolidated areas. Clearly, she corrected her
>V/Q mismatch to the extent possible during the agonal period. Indeed, to the
>maximum extent possible as her last SpO2 was 74% (pretty good for the usual
>agonal cryopatient. Please note this SpO2 was obtained with a low saturation
>monitor, not the Nonin Onyx.
>As all who saw her can attest, her tidal volumes were minute the last few
>days of her life; just gasping, baby breaths for baby lungs a la Gattinoni.
>In fact, she switched from 4 deep breaths a minute when we arrived to mostly
>10 to 12 shallow ones about the time her breath sounds started to diminish,
>and then consistently was breathing 10-12 a minute once the gurgling began.
>I
>expect she had maybe 10% or less of her pulmonary volume available for gas
>exchange and a similarly small amount available for PFC contact.
>While I suctioned out 1.5 liters acutely, she refilled immediately during
>CPS. Some of what I suctioned appeared to be jejunal/ileal contents from her
>esophagus and which she aspirated immediately upon the start of CPS. I
>therefore posit that the PFC accessible amount of pulmonary tissue was very
>small.
>4) As you and I both note she could not have had much blood. What a

>testament
>to the pharmacology of ultraprofound vasoconstriction and efficacy of ACD-HI
>CPR under such conditions!
>5) The SCD was on most of the time while in hospital starting at 0804. This
>is where your expertise is relevant and critical to making sense out of the
>data. Her entire head was essentially immersed in well circulated ice water,
>certainly meeting your criterion of 100cc/min of external 0 C water for
>optimal head heat removal. I presume that heat will be removed relatively
>rapidly from the superficial tissues? Not only was her head irrigated, but
>so
>was her neck: I remember having to cover the cric wound to stop water from
>getting in it.
>6) While the SCD was off during transit something else was happening. The
>PIB
>had been "overfilled" with water by my criteria. I remember being very
>concerned that we would be unable to pick it up and put it in the van. As we
>went down the hall to the elevator I could hear ice water sloshing under the
>sheet (cover). Once in the van as I struggled to give another PFC load (the
>500 cc one) and switch over to the Dextran-THAM infusion there was
>tremendous
>sloshing in the PIB, with water washing back and forth and side to side
>loaded with ice. I remember worrying that it would swamp the cric wound, but
>mostly it was pooled around her head in fairly dynamic motion as we
>navigated
>the streets of SF at a pretty good clip. So, she probably still had enough
>water flow over the exterior of her head to meet the 100 cc/min. criterion.
>7) She had a fairly small head and there was no edema there; it was the only
>spot on the poor woman's body that wasn't edematous!
>8) ~340 cc of the meds she was given were chilled to near 0 C and 500 cc of
>mannitol was infused which as about 18 C as it had been left out on the
>balcony in SF's night air and amazingly had not crystallized. This probably
>dropped her temp a little.
>Conclusion: she probably had extremely small pulmonary and vascular
>compartments due to pathology and pharmacologic intervention. External
>cooling of skin and bone also probably contributed significantly to her
>cooling and the lack of thermal rebound. Administered medication chilled to
>well below body temperature may have comprised as much as 15% to 25% of her
>circulating volume resulting in a further decrease in temperature.
>FYI her post 1340 cc infusion of meds blood chemistries drawn before TBW at
>0945 were as follows:BUN 70Creatinine 2.8NA++ 127
>K+ 18.0 (KCL had been given)Cl- 120CO2 7
>Anion Gap 0Total Protein 3.2Albumin 1.1Globulin 2.1
>Ca++ 8.1ALK Phos 265ALT 75AST 425
>T. Bilirubin 0.2Glucose 68Post washout:BUN 42
>Creatinine 1.3NA++ 94K+ 20.2 Cl- 80
>CO2 9Anion Gap 5Total Protein 0.2Albumin 0.2

>Globulin 2.1Ca++ 4.0ALK Phos 15ALT 7
>AST 26T. Bilirubin 0.1
>Glucose 115 (NOTE: Glucose is higher post washout than pre despite MHP-2
>Hugh prepared not having any glucose! Go figure?)
>I could not get a baseline arrest blood sample during manual CardioPump CPS
>because of catheter trapping on the caudal caval wall due to (presumably)
>hypovolemia. If I had wanted to delay meds administration I could probably
>have milked out a sample using very gentle suction on the syringe, but this
>would have taken minutes. When I loosened the Syringe momentarily there was
>a
>surge of blood back to almost the hub of the tubing tail on the dialysis
>needle in the Portal catheter attesting to the preloading capacity of
>ACD-CPR! So, extreme caution needs to be exerted to prevent air entry and
>subsequent air embolism via any central line (glad I anticipated this in my
>manual 10 years ago!).
>The blood chemistry above numbers will give you some idea of the initial
>hemodilution if you make a lot of assumptions! She was on D5 half normal
>saline from Sunday till the time she arrested, mostly at 30 cc/HR. I'll be
>doing a daily I summary, but for all intents and purposes she was making 70%
>to 80% of that volume in urine until the last 24-48 hours which appeared
>normal yellow to amber. Of course, I have no way t know if she was
>concentrating or what the SG was. This is where a urinometer or dipsticks
>would have been invaluable. We called all over but couldn't get any
>Multistix
>and the nurse never brought any up to the floor despite two requests from
>me.
>In the future remind me to get urine samples for later analysis, even if
>dipsticks are available. This would have been easy to do. And, we need to
>make sure we do have dipsticks and urinometers on hand!
>I will try to get her medical records, but I can tell you that no
>chemistries
>or CBCs were done during the last week of her life. Still, it would be
>interesting to know what her last Albumin was as a rough index to
>hemodilution from meds and infused fluids.CRITICAL TAKE HOMES MESSAGES:
>1) There is no substitute for good clinical assessment and understanding.
>This patient has taught me that when I see a blanched, bloodless appearing
>patient who was formerly perfusing her extremities well (~45 minutes prior),
>I probably have a massive bleed with profound hypovolemia.
>2) The take home message from #1 above is that medications which may be
>toxic
>must be given with extreme caution in such patients.
>3) Dye markers for blood, interstitial, and cellular water volumes being
>reached should be given in the meds.
>4) The effect of vasopressin (and epinephrine) in reducing perfused tissue
>volume likely allows for far greater efficacy of brain cooling. This may be
>used to reduce the number of PFC lavages (duration of GLV) necessary, thus

>decreasing the time and complexity of field equipment for cryonics use and
>allow for other cooling methods to be brought to bear during transport such
>as external cooling, viscus lavage, CPB, or a combination of these
>modalities
>as appropriate.
>The ability to selectively cool the brain has not been considered in patents
>relating to GLV. Pharmacological mediation of tissues perfused which results
>in superior rates and degrees of CNS cooling may be very important in making
>GLV workable for cryopatients and allow for more profound, as well as more
>rapid cooling of the brain. This single patient, with very adverse
>hemodynamics (profound hypovolemia) demonstrates that GLV is likely to be
>very effective under such circumstances in achieving clinically valuable
>reductions in brain temperature which could increase tolerance to ischemia
>by
>at least 4 fold and possibly by as much as 6 to 10 fold.
>Steve, please give me your frank commentary on this analysis.
>Finally, Thank You! Thank you very much for your prompt and incisive
>analysis.
>Mike
>Darwin---
>
>
>--
>mail2web - Check your email from the web at
>http://mail2web.com/ .
>
>
>