# The S-MIX: A Measure of Ischemic Exposure*

By R. Michael Perry and Aschwin de Wolf

**Abstract**

The S-MIX is a quantitative cryonics cases outcome metric to calculate the total ischemic exposure of a patient. In this brief exposition, R. Michael Perry and Aschwin De Wolf introduce this metric and the issues involved in calculating it for a cryonics case involving several distinct procedures.

**Introduction**

An ever-present unknown in cryonics is evaluating the quality of a cryonics case. Until more is known, in fact, we will have no good assessment of case quality in terms of what we would really like to know: how well memory and other identity-critical elements are preserved in cryopreserved patients. Meanwhile we are interested in whatever reasonable indicators of cryopreservation quality it may be feasible to compute, while acknowledging these are imperfect.

One such possible indicator would be a "measure of ischemic exposure" intended to assess the amount of normal body temperature ischemic exposure a patient experiences, mainly in the early stages of a cryonics procedure before the start of cryogenic cooling. Basically, this measure would tally up how long a patient has been at a given temperature, with a heavier weighting used for higher temperatures, since more damage is occurring at these temperatures. According to a rule of thumb in wide use (the so-called $Q_{10}$ rule), each decrease of 10°C is supposed to halve the amount of damaging activity per unit time. More generally, we can assume that each drop of 10° reduces (divides) the activity by a factor $Q_{10}$. At least it is considered roughly accurate for $Q_{10} \approx 2$, though it must not be pressed very far. Here we adopt this "exponential rule," with the understanding that it is only a starting point.

In 2003, Dr. Steve Harris also developed a measure aimed at estimating the total duration of normothermic ischemia during initial cooling named the E-HIT. In this article we present a closely related measure called the S-MIX (**S**tandardized **M**easure of **I**schemic E**x**posure) to express the total ischemic exposure prior to the start of cryogenic cooling as the equivalent duration of normothermic ischemia. Two special cases are considered in detail: (1) where the rate of temperature descent is constant with time. For this case we obtain the "linear" S-MIX or $\text{S-MIX}_L$, which, it turns out, is proportional to the total exposure time. (2) A second case considered is Newtonian cooling, $\text{S-MIX}_N$, in which the rate of cooling is proportional to the difference between a starting temperature and a final temperature $T_\infty$ which is never reached but approached more and more closely with increasing time. For the Newtonian case one must also know a "characteristic time" $t_C$ which is the amount of time it takes to cool the subject by (1-1/*e*) or about 63% of the difference between the starting and the final temperature. It turns out that $\text{S-MIX}_L$ is a limiting case of $\text{S-MIX}_N$ in which the final temperature $T_\infty$ is very low and the characteristic time $t_C$ is very large. S-MIX can also be attenuated to express a lower ischemic exposure when the patient is oxygenated.

**S-MIX; General Case**

We normalize our measure so that 1 corresponds to 1 hour at body temperature $B$ ($B$ = 37°C for a human). With this assumption and the $Q_{10}$ rule, with $Q_{10} = 2$, 1 hour at $B$-10°C or 27°C would be 0.5 hours by S-MIX, and for 1 hour at 17°C, 0.25 hours, etc. The measure for a fixed temperature would also scale linearly with time – twice as much exposure at a given temperature would give twice as much expected damage, consequently, twice as big a contribution. 2 hours at 37°C, then, would yield a measure of 2. At 27°C, however, in view of the exponential rule, 1-hour exposure would give a result of 0.5, and 2 hours a result of 1. Mathematically, at temperature $T$, by the $Q_{10}$ rule, the rate of ischemic damage for the general case of $Q_{10}$ is given by

$$\text{Rate of damage} = Q_{10}^{-(B-T)/10} = \exp(qT\text{-}qB), \quad (1)$$

where

$$q = (\ln Q_{10})/10 \quad (2)$$

The total ischemic damage the patient experiences, at a fixed temperature, equals the rate of damage at that temperature times the amount of time spent at that temperature, assuming the temperature is constant over the time interval. For the general case, however, the temperature varies with time, so we divide the time interval into small subintervals, for each of which we can assume the temperature is constant, and add up all the small contributions to obtain the total estimate of ischemic injury. Mathematically, the temperature is now a non-constant function $T(u)$ of time parameter $u$, and we must integrate the rate of ischemic damage between two time limits, $t_0$ and $t_1$, to obtain the total estimate of ischemic injury:

$$\text{S-MIX}(t_0, t_1) = \int_{t_0}^{t_1} \exp(qT(u) - qB)du. \quad (3)$$

In most of what follows it simplifies the treatment to normalize the start time $t_0$ to 0 and designate the finish time $t_1$ as $t$. We further simplify S-MIX(0, $t$) to S-MIX($t$). Eq. (3) then becomes

$$\text{S-MIX}(t) = \int_0^t \exp(qT(u) - qB)du. \quad (4)$$

**S-MIX linear case (S-MIX$_L$)**

For this case we start at time 0 with temperature $T_0$ and end at time $t$ with temperature $T_1$. For intermediate times $0 < u < t$ the temperature $T(u)$ varies linearly with the time according to

$$T(u) = T_0(1\text{-}u/t) + T_1(u/t) \quad (5)$$

Applying eq. (4) then gives

$$\text{S-MIX}_L(t) = t\exp(-qB)[\exp(qT_0) - \exp(qT_1)]/[qT_0 - qT_1]. \quad (6)$$

So, we see, in particular, that S-MIX$_L(t)$ is just proportional to time $t$, the proportionality constant depending on the starting and ending temperatures $T_0$ and $T_1$. The assumption of a linear cooling rate has only limited applicability, however. For example, during the final stages of cardiopulmonary support (CPS) and blood washout the cooling generally slows considerably as the target temperature is approached. A more accurate approximation of the cooling profile is Newtonian cooling which we now consider.

**S-MIX$_N$ (NEWTONIAN)**

In its "pure" or idealized form the basic assumption about Newtonian cooling is that we start at temperature $T_0$ as before, but the final temperature $T_\infty$ is never reached but only approached in the limit of infinite time. Instead, the temperature $T(u)$ at time $u$ is given by

$$T(u) = T_0\exp(-u/t_C) + T_\infty(1 - \exp(-u/t_C))$$
$$= T_\infty + (T_0 - T_\infty)\exp(-u/t_C), \quad (7)$$

where $t_C$ in this case is the time needed to cool to $1 - 1/e = 1 - \exp(-1)$ of the distance between $T_0$ and $T_\infty$. (For a human body, a good rough estimate of $t_C$ is about 7 hours. This means, for example, that if a postmortem body initially at 37°C is placed in a 0° cooler, so $T_\infty = 0°$, and left for 7 hours it will cool to a temperature of 63.2% = 1-1/$e$ of the way from 37° to 0°, or 13.6°C.) The measure in this case is determined by substituting the expression for temperature $T(u)$, eq. (7), into eq. (4).

In practice we start as before with temperature $T_0$ and reach temperature $T_1$ at time $t$. We can then determine $T_\infty$ as needed for the calculations from eq. (7):

$$T(t) = T_1 = T_\infty + (T_0 - T_\infty)\exp(-t/t_C), \quad (8)$$

from which it follows that

$$T_\infty = (T_1 - T_0\exp(-t/t_C))/(1 - T_0\exp(-t/t_C)). \quad (9)$$

To obtain an expression for the integral, eq. (4), for the Newtonian case, two additional quantities need to be defined:

$$s = q(T_0 - T_\infty), \quad (10)$$

and the "mainsum function" ms given by

$$\text{ms}(x) = \sum_{k=1}^{\infty} \frac{x^k}{k\,k!} = x\,{}_2F_2(1,1;2,2;x) = \text{Ei}(x) - \ln(|x|) - \gamma, \quad (11)$$

where Ei is the exponential integral function given (for real-valued, nonzero $x$) by

$$\text{Ei}(x) = \int_{-\infty}^{x} \frac{\exp(u)}{u} du, \quad (12)$$

and $\gamma$ is the Euler-Mascheroni constant, 0.5772156649…. With these conventions, then, we can express the Newtonian S-MIX$_N$ by

$$\text{S-MIX}_N(t) = \exp(qT_\infty - qB)[t + t_C(\text{ms}(s) - \text{ms}(s\exp(-t/t_C))]. \quad (13)$$

Using eqs. 10-13 it is straightforward to show that S-MIX$_N$ reduces to S-MIX$_L$ in the limiting case that $t_C$ is large and the ratio $t_C/T_\infty$ is fixed ($|T_\infty|$ is also large), so effectively the cooling rate does not change with time but is still appreciable. (In practice, of course, $T_\infty$ cannot be colder than absolute zero but this physical limit is not important for the mathematical properties considered here.)

**Lessening the S-MIX through metabolic support**

So far, in our consideration of possible variants of S-MIX (linear, Newtonian) we have not recognized the benefits of providing metabolic support to the tissues during CPS and blood washout. To remedy this, we propose that we decrease the ischemic "hit" when the patient is ventilated during CPS. Since the cerebral blood flow during artificial chest compressions (manual or mechanical) falls short of what is observed during normal circulation we only allow a 50% reduction of ischemic exposure. During blood washout, when physiological perfusion pressure is possible, the ischemic hit can be allowed to be non-existent for the duration of the blood washout, *provided that ventilation was present during CPS as well*. The presence or absence of oxygen is reflected in an ischemia weight function that can have 0 (physiological oxygenation), 0.5 (oxygenation during CPS), or 1 (no oxygenation). In this way the original S-MIX, of whatever form, linear, Newtonian or more general, is transformed in a simple way to a weighted form, S-MIX$_W$ according to:

$$\text{S-MIX}_W(t) = w\text{S-MIX}(t), \quad (14)$$

where

$$w = \begin{cases} 0, \text{physiological oxygenation} \\ 0.5, \text{oxygenation during CPS} \\ 1, \text{no oxygenation.} \end{cases} \quad (15)$$

We have assumed that weighting parameter $w$ is constant during the time interval of the cooling (from start time 0 to end time $t$). It is expected that otherwise Newtonian rather than linear (or more general) cooling will be assumed, in absence of frequent temperature measurements. So from eqs. (13-15) we obtain an explicit expression for a weighted, Newtonian version of S-MIX,

$$\text{S-MIX}_{W,N}(t) = w\text{SMIX}_N(t). \quad (16)$$

There will also be a succession of time intervals each with its own weighting $w$, along with start time (normalized to 0) and end time $t$, and different values of both $T_0$ and $T_\infty$ (and possibly $t_C$). The total S-MIX will be the sum of all the values obtained for the different time intervals; see discussion below.

**Cryonics case S-MIX calculation**

The $\text{S-MIX}_{W,N}$ formula is easy to apply for a time interval in which conditions are stable (presence or absence of oxygenation, parameters for Newtonian cooling). However, we run into a major practical problem when we consider that a cryonics case consists of several procedures. A typical cryonics procedure employs several distinct cooling methods to induce hypothermia. In ideal cryonics cases a patient is immediately placed in a portable ice bath for vigorous external cooling. Then, at 20°C, external cooling is followed by *internal* cooling with an organ preservation solution until a temperature is reached that is safe for cryoprotective perfusion (between 5°C and 0°C). In non-remote cases there is additional complication that a patient spends a considerable period at a *fixed* temperature (~ 0°C) before the start of cryoprotection. A typical case also shows different kinds of oxygenation modalities (or the absence thereof).

An accurate calculation that incorporates those elements entails that we calculate the measure from a comprehensive set of cooling data. If such comprehensive data is not available (or can only be estimated or inferred), a more accurate measure can be obtained by breaking down the cooling data in distinct segments that correspond to typical cryonics procedures. For example, we can calculate the S-MIX for a total case by adding up the S-MIX scores for:

1. The time between circulatory arrest and completion of cardiopulmonary support (37°C to 20°C)
2. The time between the start and completion of internal cooling (20°C to 5°C)
3. The time between the start of cryoprotection and the start of cryogenic cooling (5°C to 0°C) [local]

*OR*

The time between the start of cold transport and the start of cryogenic cooling (5°C to 0°C) [non-local]

In practice, the difference for segment 3 for a local or non-local case is relatively minor for the purpose of calculating the S-MIX because the cold transport temperature approximates the (ideal) temperature for conduct of cryoprotectant perfusion. In both scenarios the temperature of the patient is in the 5°C to 0°C range but with additional S-MIX time for a patient transported on water ice.

Calculating the S-MIX by adding up the segments for these distinct cryonics procedures renders a more accurate equivalent normothermic ischemia exposure time and also allows for scenarios in which a patient spends a considerable period at a fixed temperature (in the case of cold transport or a mortuary cooler). In principle, the number of segments that is chosen for calculating the total S-MIX depends on the specifics of a case and how much precision one wants to see in the calculations. To make comparison of S-MIX values between cases meaningful, it is important to describe the segments along with the calculations.

**Conclusion**

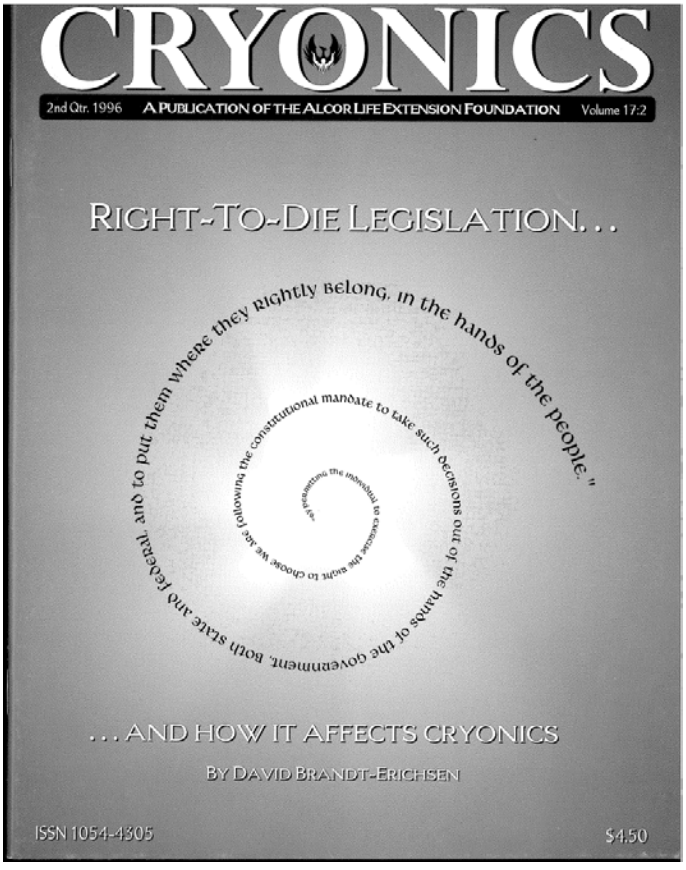
In this article we present a quantitative measure to calculate the equivalent normothermic ischemic time for a cryonics case. We assume a $Q_{10}$ rule with a cooling factor of 2 throughout. (So reaction rates, including ischemic damage, are halved by a 10°C drop in temperature.) The $\text{S-MIX}_L$ (linear case) assumes additionally that there is a constant cooling rate, or in effect, identical time spent at each small, fixed-width temperature interval, until the start of deep cooling. The $\text{S-MIX}_N$ (Newtonian) measure is then derived by allowing Newtonian cooling. Degrees of oxygenation are modeled by weighting the version of S-MIX that is assumed (in particular, $\text{S-MIX}_N$) by quantities ranging between 0 (perfect oxygenation) and 1 (no oxygenation). Guidelines are provided to calculate an overall S-MIX by summing the total contributions from distinct segments to reflect typical cryonics procedures.

It is hardly necessary to add that these ideas can be further refined. As stated before, in an ideal case the S-MIX would be derived from detailed temperature data instead of adding up distinct segments. In fact, the lack of such temperature data is itself indicative of compromised case work. The assumption that cryogenic cooling starts at 0°C is not always realistic and may over- or understate the situation. It may not be known exactly when the patient reaches a temperature of 0°C and this will need to be estimated.

There can also be cases where the temperature rises again due to poor compliance with cold transport protocol or compromises during perfusion. Is it realistic to assume that a patient did not suffer some degree of cerebral ischemia prior to circulatory arrest? Should a more sophisticated measure incorporate the administration of neuroprotective medications? Are there circumstances in which oxygenation aggravates ischemic injury?

It is inevitable that calculating an ischemic exposure measure for some cases (i.e. missing data) may entail educated inferring of times and temperatures. However, we think the above could be a starting point to *one* useful indicator of cryopreservation quality as it allows us to identify trends and correlate duration of ischemia to case outcomes. ■

*This article is a revision of R. Michael Perry's "Toward a Measure of Ischemic Exposure" (*Cryonics* Magazine, 2nd Quarter, 1996). The most fundamental change is to calculate the S-MIX$_L$ as the duration of equivalent normothermic ischemia and to present a measure that incorporates Newtonian cooling and metabolic support. We thank Hugh Hixon and Steve Harris for their contribution to developing these outcome metrics.



# Implementing the S-MIX

By Aschwin de Wolf

In the 4th quarter issue of *Cryonics* magazine Michael Perry and Aschwin de Wolf wrote the first exposition of a measure to calculate the estimated total time of equivalent normal body temperature ischemic exposure for a cryonics patient. Because it weights time spent at higher body temperature more than time spent at a lower temperature, this measure provides a more precise measure of ischemic exposure than just calculating the total time between circulatory arrest and the start of cryogenic cooling. This measure also allows for a "discount" when metabolic support is provided through ventilation. In an ideal scenario metabolic support would be provided throughout all parts of the procedure, producing an S-MIX value of zero (or close to it). In the metrics provided here the S-MIX is calculated by dividing the total ischemic time in segments, ideally corresponding to distinct procedures (cardiopulmonary support, surgery, blood washout etc.) which allows applying discounts to parts of the case where metabolic support was available. In practice, this approach can only be an approximation because there can be (brief) interruptions of metabolic support and the efficiency of ventilation can vary. To simplify matters we assumed a metabolic discount of 50% when ventilation was performed during CPS.

In the segmental approach we calculate the S-MIX for a given temperature decrease between a start and end time of a procedure (for example, cardiopulmonary support). It should be noted that this approach is a simplification because the cooling rate from the start to the end of a segment is not identical. To remedy this, we calculate a segment under the assumption of Newtonian cooling in which the cooling rate decreases as the difference between the cooling medium and patient temperature decreases. An even more precise calculation would use all the actual measured temperature data available for a case. This is an approach we aim to implement later in the meta-analysis project, which will allow us to compare both approaches. One of the challenges with this approach is that comprehensive temperature data is only available for a few select cases.

How to incorporate metabolic support in the S-MIX is a complicated issue. In our first exposition we allow for a 50% discount in the S-MIX if ventilation is provided during cardiopulmonary support. If this is followed by oxygenation during washout we give a 100% discount. This approach is open to several objections. Giving a 50% discount for ventilation is somewhat of an arbitrary number meant to reflect the lower cerebral perfusion pressure that can be obtained by (mechanical) chest compressions. Whether this number is reasonable is difficult to determine without doing cerebral oxygenation measurements in the patient, or at least modelling various scenarios in a research model. Another complication arises when a higher metabolic discount is allowed for oxygenation during washout (and cryoprotectant perfusion). One might argue that the dissolved oxygen in washout solutions and cryoprotectants will provide adequate oxygenation of the brain, even in the absence of actual oxygenation. So far we have assumed that oxygenation is always beneficial for the patient without considering the possibility that for some patients oxygenation will actually be detrimental. This topic is mostly unexplored in a typical cryonics context and requires more experimental investigation as well.

The typical cryonics patient may have accumulated (regional) metabolic deficits during the agonal phase as well. This is not taken into account in the way the S-MIX is currently calculated. The most obvious reason for this is because we know so little of the metabolic state of the brain in the typical cryopatient.

In principle, the S-MIX can be calculated for any temperature. At this point, we calculate the S-MIX for all procedures up to the point that cryogenic cooling starts (typically around 0 °C). In principle, the S-MIX can be calculated for sub-zero temperatures but in practice this adds little additional value because the time spent at subzero temperatures before solidification is so short that very little equivalent normothermic exposure time is incurred. The only relevant exception to this concerns storage at dry ice temperature, which can occur as a temporary low-temperature storage measure (for example, when cryonics arrangements still need to be finalized) or after field cryoprotection. The table below shows the S-MIX for storage at dry ice temperature (-78°C), based on $Q_{10}$=2.

| Exposure, in days | S-MIX in minutes |
|---|---|
| 1 | 0.50 |
| 2 | 0.99 |
| 3 | 1.49 |
| 7 | 3.48 |
| 14 | 6.96 |
| 31 | 15.41 |
| 62 | 30.83 |
| 186 | 92.49 |

As can be seen, even storing a patient at dry ice temperature for half a year "only" generates an equivalent normothermic ischemic exposure of about 1.5 hours. This estimate is likely to be on the conservative side given that the patient is either frozen or has a highly viscous vitrification solution in his system, which

inhibits most or all diffusion-based biochemistry. One positive consequence of these calculations is that it can support the practice of holding a patient on dry ice for extensive periods when long-term cryogenic storage arrangements are being arranged.

Unlike a straightforward task like calculating the duration of a procedure (for example, cryoprotectant perfusion) the S-MIX is a good-effort *approximation* of the degree of ischemia in a patient's brain. One thing we hope to do in the later stages of the Alcor meta-analysis project is to experimentally model and validate some of the assumptions made in the S-MIX calculations. We will also seek to correlate the S-MIX of a patient with CT scan results to further understand and quantify the relationship between ischemic exposure and the quality of cryoprotection. Like the meta-analysis project itself, the development, validation, and refinement of a quantitative ischemia measure is a work-in-progress that evolves as we learn more. ■