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Rationalization of thermal injury quantification methods: Application to skin burns

Benjamin L. Viglianti [a], *Mark W. Dewhirst* [b], *John P. Abraham* [c,*], *John M. Gorman* [c], *Eph M. Sparrow* [d]

[a] *Department of Radiology, University of Michigan, Ann Arbor, MI 48108, United States*
[b] *Department of Radiation Oncology, Duke University Medical Center, Durham, NC 27710, United States*
[c] *School of Engineering, University of St. Thomas, St. Paul, MN 55105, United States*
[d] *Department of Mechanical Engineering, University of Minnesota, Minneapolis, MN 55455, United States*

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ABSTRACT

Classification of thermal injury is typically accomplished either through the use of an equivalent dosimetry method (equivalent minutes at 43 °C, CEM43 °C) or through a thermal-injury-damage metric (the Arrhenius method). For lower-temperature levels, the equivalent dosimetry approach is typically employed while higher-temperature applications are most often categorized by injury-damage calculations. The two methods derive from common thermodynamic/physical chemistry origins. To facilitate the development of the interrelationships between the two metrics, application is made to the case of skin burns. This thermal insult has been quantified by numerical simulation, and the extracted time-temperature results served for the evaluation of the respective characterizations. The simulations were performed for skin-surface exposure temperatures ranging from 60 to 90 °C, where each surface temperature was held constant for durations extending from 10 to 110 s. It was demonstrated that values of CEM43 at the basal layer of the skin were highly correlated with the depth of injury calculated from a thermal injury integral. Local values of CEM43 were connected to the local cell survival rate, and a correlating equation was developed relating CEM43 with the decrease in cell survival from 90% to 10%. Finally, it was shown that the cell survival/CEM43 relationship for the cases investigated here most closely aligns with isothermal exposure of tissue to temperatures of ~50 °C.

1. Introduction

Quantification of thermal injury to tissue is important for a wide variety of intentional and unintentional thermal exposures. Unintentional exposures lead to burns to skin or internal body regions and the extent of injury must be properly quantified in order for adequate therapy to be applied. On the other hand, many modern medical applications involve the intentional increase of tissue temperature. Elevating tissue temperature for the purpose of providing therapy for pathological diseases and malfunctions has been practiced for thousands of years [1]. In the oncological environment, for example, hyperthermia is used either as a direct treatment modality or as an adjuvant to enhance other therapies. Direct treatment relies on thermal energy to cause denaturation of the targeted cells. Indirect methods utilize thermal energy as an adjunct to improve the efficacy of the direct cytotoxic therapy [1], such as radiation or chemotherapy [2–5].

* *Corresponding author*. Tel.: +1 612 963 2169.
E-mail addresses: benjamin.viglianti@alumni.duke.edu (B.L. Viglianti), jpabraham@stthomas.edu (J.P. Abraham).
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Generally, thermal-based treatments are subdivided into two groups with respect to the targeted tissue temperature. Generally, as well as for discussion here, tissue temperatures above 50 °C are reserved for direct treatment, and the therapy is termed *ablation*. When the target temperatures are between 40 and 45 °C, the term *hyperthermia* is used to describe the therapy [1,6].

Ablation therapy relies on the direct cytotoxic effect of temperature elevation. This mechanism of cell death is related to denaturing both functional and structural proteins (intra and extra cellular) [6]. The major extracellular structural protein constituent is collagen of various types, all with similar sensitivities to thermal injury [7,8]. Thermal denaturation of collagen is a high-temperature metric of severe thermal damage and represents an upper-bound target process in ablation treatments that, when reached, is a sure sign of cellular death and severe vascular disruption.

Hyperthermia-based therapies rely on elevating the tissue temperature to relatively non-cytotoxic levels to alter the local physiological environment and/or cellular functions in a way that enhances other treatments. The details of these changes are extensive and have been reviewed elsewhere [1,6,9,10]. The dominant physiological changes involve improved blood flow and oxygenation, stimulation of immune cell migration, and increased vascular permeability.

Independent of the heating method used, standardized metrics are needed to quantify the relationship between thermal exposure and damage. This is particularly important when comparing results from different studies, quantifying tissue-dependent sensitivities to heat, or attempting to repeat studies for the purpose therapeutic implementation. Two methods have come into general use for quantifying the deposited thermal energy. The ablation community often uses the *damage index* or the 50 °C isothermal contour, whereas the hyperthermia community typically uses cumulative equivalent minutes at 43 °C, or the CEM43 method [6,10,11]. Both the damage index and CEM43 methods are based on the underlying premise that tissue damage follows an irreversible first-order chemical reaction with the rate constant following the Arrhenius relationship. Despite this commonality, the two methods are used differently: one to predict the degree of necrosis and the other to guide treatment duration.

These methods have been used for the last quarter century, with some rationalizations between them reported in the published literature [11–16]. Here, the two methods are reconciled in what is believed to be a definitive manner. In particular, a specific case study is carried out to facilitate a highly detailed rationalization. Furthermore, for the seemingly the first time, the CEM43 method is used to predict the depth of skin burns. It will also be shown how cell survival results for disparate thermal histories can be brought together and correlated.

The application used here for the demonstration has particular importance for the treatment of burns and the results will be compared with literature information on scald wounds. On the other hand, it is expected that the method can also be applied for other situations, such as the intentional application of heat in medical treatments.

2. Injury quantification methods

2.1. CEM43 °C method

Cumulative equivalent minutes of thermal treatment at 43 °C (CEM43 °C) (first proposed by Sapareto and Dewey [11]) is commonly used as a standard in the hyperthermia literature to compare different thermal treatment histories to an equivalent heating time at 43 °C. This procedure is discussed in depth in [6,10]. Although the analysis is based on the assumption that thermal damage follows an irreversible first-order chemical reaction, experimental data have demonstrated that observed damage is approximately linear with temperature over a narrow range. Additionally, the dose response curve has inflection points ("breaks"); the break is related to increased tolerance to thermal injury that is developed during heating [6,10]. There is insufficient data for human tissue to accurately define the breakpoint; most data show that it varies from 43.5 to 47 °C [6,10]. However, Lepock et al. [16] concluded that 43 °C in cell culture likely represents the upper limit at which thermal tolerance can be induced in human cells.

For intentional thermal treatments, tissues are often heated to the lower end of the injury-causing temperature range so that the breakpoint has particular importance. On the other hand, for scald wounds where temperatures usually greatly exceed the breakpoint values, its consideration is much less important. In those circumstances, the bulk of the injury occurs well above 43 °C.

Because of the presence of a breakpoint, the calculation of CEM43 has to occur in two steps using Eq. (1) separately above and below the breakpoint.

$$\mathrm{CEM43°C} = t[R_{\mathrm{CEM}}]^{(43-T)} \tag{1}$$

The symbol t is the time of thermal exposure. The time-scaling ratio R_{CEM} is the number of minutes needed to compensate for a 1 °C change in the applied therapeutic temperature, either above or below the breakpoint, and T is temperature in degrees Celsius. The breakpoint of 43.5 °C is chosen here, with an R_{CEM} below the breakpoint of 0.233 and above the breakpoint of 0.428.

Eq. (1) can also be used in a differential and/or a discretized form if the thermal history is dynamic and known.

$$\mathrm{CEM43°C} = \int_0^{\tau} [R_{\mathrm{CEM}}]^{(43-T(t))}\,dt = \sum_{i=1}^{N} [R_{\mathrm{CEM}}]^{(43-T_i)}\Delta t_i \tag{2}$$

However, the process of integration/summation has to account for temperatures that occur both above and below the breakpoint.

2.2. Damage index/injury integral method

The second metric used to quantify thermal exposure and cell injury is the damage index Ω. This metric has been widely adopted by tissue ablation practitioners. Thermal ablation generally occurs at higher temperatures than does hyperthermia. Collagen is in high abundance and is, therefore, assumed to be one of the main proteins that are involved with thermal damage at these higher temperatures. The typical thermal