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Commentary on classic paper in Hyperthermic Oncology “Tumour oxygenation is increased by hyperthermia at mild temperatures” Song, CW et al. 1996

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The paper by Song et al. entitled “Tumour oxygenation is increased by hyperthermia at mild temperatures” [1] from the radiation biology laboratory at the University of Minnesota was one of the first basic science studies to support the hypothesis that the clinical gains being seen with thermoradiotherapy in the clinic may be due to reoxygenation of the tumour and not exclusively due to inhibition of DNA repair or direct heat-induced cytotoxicity [2]. Dr. Song and others such as Vaupel, Bicher and Tanaka had previously characterized in detail much of the thermal dose and tumor blood flow relationships in multiple rodent tumor lines and even patients both in thermotolerant and non-thermotolerant situations [3-8]. However, the focus of the prior studies was much less on the benefits of mild temperatures and instead on how we might overcome the physiological reactions of the tumor to increase heat-induced cytotoxicity. By the late 1980s and early 1990s the puzzling realization occurred that clinical hyperthermia was NOT typically achieving cytotoxic levels and yet was improving treatment outcomes when combined with radiotherapy. This strongly suggested that an augmented blood flow response to non-vascular damaging thermal treatment was a major influence in these encouraging clinical results.

The blood flow response to heating is typically biphasic, increasing as temperature increases until a breaking point of vascular damage is reached. It is also well proven that increased blood flow leads to increased tissue oxygenation in most situations. An interesting additional factor that has a role to play in increasing the available oxygenation in tissue is the degree to which hyperthermia reduces the ability of the tumor to consume oxygen (by disabling respiration in sublethally heated cells in addition to reducing overall cell viability). The degree to which oxygen consumption contributes to the improved oxygenation observed in experimental and clinical studies employing mild hyperthermia will vary due to heterogeneous cell killing that may occur when various forms of thermal treatment are applied to the tumor. The general consensus is that changes in consumption in combination with improved distribution and volume of blood flow are at play at extended times after heating where the measured increase in perfusion alone has not always account for the degree of oxygenation improvement observed [9-11]. In total, a multitude of studies have generally painted the picture that in both research and clinical environments, the areas of the tumor that were heated to non-vascular damaging levels were likely becoming reoxygenated and thus more radiosensitive after heating alone [11] and especially when combined with other oxygenating strategies [12,13].

It was in 1995 during a visit from one of us (PMC) to the radiation biology laboratory at the University of Minnesota (while RJG was a graduate student there) that some of the first data on oxygenation in rodent tumour models after mild heating was being obtained and it's potential importance discussed [14,15]. We all remember well the data coming out of the Eppendorf pO₂ histograph machine to all of our amazement. We began to realize that these results had uncovered one of the most effective, if not the most effective, means to approach

the now age-old dilemma of reoxygenation of hypoxic tumors and subsequent improvement in radiation response. In the following years, Song et al. and others did indeed report significant increases in tumour radiation response when the tumour was heated with mild or moderate temperature hyperthermia [13,16-19] (coined 'MTH' by Song et al. and now commonly abbreviated as such by those in thermal medicine [20,21]). In addition, exciting new avenues for improved chemotherapy, immunotherapy and gene therapy became apparent.

This initial work and data collected in the years since by numerous groups have re-written much of how we think of thermal medicine and its potential utility in the adjuvant setting [22]. The discovery that the oxygenation levels may change transiently and at timepoints up to several days after a single hyperthermia session have suggested many new treatment strategies. Even thermotolerance, especially vascular thermotolerance, as a positive or negative factor in thermoradiotherapy has reason to be revisited. Exciting new results continue to emerge with new and improved imaging technology to study perfusion and oxygen transport during and after thermal therapy. An elegant example of present work that is squarely based on the original hypotheses about MTH comes from Lüdemann et al. using PET imaging to demonstrate that oxygen availability in tumor tissue increases after regional mild heating of pelvic tumors [23]. Their data suggests that regional heating may improve clinical tumor oxygenation for significant amounts of time between hyperthermia sessions much like Song et al. observed with local heating of tumors in earlier work. Without doubt, the results and conclusions from 'Tumour oxygenation is increased by hyperthermia at mild temperatures' have been a point of reference to help interpret much of the positive clinical data that has been obtained thus far by hyperthermia centers around the world [24-27].

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