2026 JULY 19–22 VANCOUVER, BC
JOINT AAPM | COMP MEETING

FLASH Radiotherapy is faster than a heartbeat: A model to illustrate the interplay between tissue oxygen perfusion and ultra-high dose rate effects

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ABSTRACT

Purpose: Ultra-high dose-rate (FLASH) radiotherapy has been reported to reduce normal tissue toxicity while preserving tumor control, but the mechanisms underlying this effect remain unclear. We investigated whether temporal tissue oxygen dynamics during irradiation could contribute to dose-rate-dependent changes in oxygen-mediated radiochemical reactions.
Methods: A compartmental mathematical model describing oxygen transport and radiation-induced oxygen depletion was developed. The model includes three compartments representing the heart and arterial circulation, irradiated brain vasculature, and irradiated brain tissue. Model parameters were fitted to dynamic in vivo mouse brain oxygen measurements acquired during irradiation. Simulations were performed to evaluate the influence of dose rate, oxygen consumption, oxygen replenishment, and baseline oxygenation on oxygen-dependent lipid hydroperoxide (LOOH) production.
Results: The model predicts dose-rate-dependent differences in LOOH formation between conventional and FLASH irradiation that depend strongly on physiological parameters, including tissue oxygenation, oxygen consumption, and perfusion. Simulations suggest that tissue-specific oxygen dynamics can substantially influence oxygen-mediated radiochemical reactions.
Conclusions: This work provides a quantitative framework linking oxygen transport with radiation-induced oxygen depletion and predicts how temporal oxygen dynamics may contribute to dose-rate-dependent radiochemical processes. The model generates testable hypotheses that may help explain tissue- and experiment-dependent variability reported in FLASH radiotherapy.

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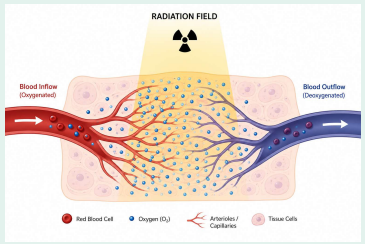
INTRODUCTION

FLASH-RT improves normal tissue protection and reduces side effects while maintaining tumor control [1]. Several hypotheses have been proposed to explain how [2]. Since FLASH-RT involves radiation exposure of microseconds to milliseconds, we hypothesize that fewer heartbeats occur during the beam-on-time and, subsequently, a lower volume of blood is irradiated, leading to less exposure of circulating oxygen in the blood and reduced oxygen resupply to the tissues.
To investigate this hypothesis and the role of oxygen resupply, we chose mouse brain irradiation and proposed a compartmental mathematical model to simulate the impact of the blood perfusion when changing the dose rate.



METHODS AND MATERIALS

This model uses a system of differential equations to describe oxygen transfer between three main compartments: 1. heart and arteries; 2. irradiated blood vessels and capillaries in the brain; 3. irradiated brain. Published data and in-vivo oxygen measurements were used to implement the model's parameters. Data from adult nude Swiss mice during FLASH-RT whole brain irradiation after local injection of Oxyphor probe in the brain (2ul, 1.2mM) [3] allowed us to fit the depletion and reperfusion rates after irradiation. With this model, computational analysis can assess how dose rate and blood perfusion could modify the total oxygen exposure during irradiation and whether this could trigger a differential effect in radiochemical reactions like lipid peroxidation at an ultra-high dose rate

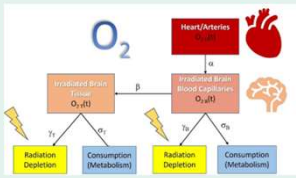


Figure 1. Compartmental model

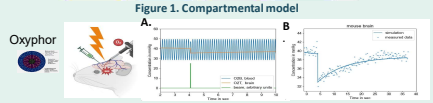


Figure 2.Model fitting with oxygen in vivo measurements.

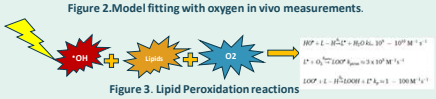


Figure 3. Lipid Peroxidation reactions

RESULTS

The model predicts dose-rate-dependent differences in LOOH formation between conventional and FLASH irradiation that depend strongly on physiological parameters, including tissue oxygenation, oxygen consumption, and perfusion.

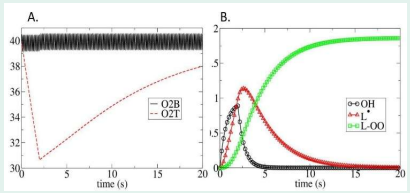


Figure 4. Numerical solutions of the rate equations for one pulse with a dose of 10 Gy in the brain at a dose rate of 5Gy/s, showing A. Oxygen oscillations in blood vessels (O2B - black) are superimposed with a drop in oxygen level in the tissue (O2T- red) due to radiation-induced oxygen depletion. B. Time evolution of •OH, •L, and •LOO radicals created after irradiation.

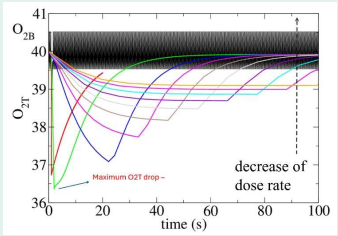


Figure 5. Time evolution of oxygen in blood and tissue, O2B (black) and O2T (colors), in the brain as a function of time and dose rates for a given continuous dose of 10 Gy. The average dose rate ranges from 500 Gy/s to 0.1 Gy/s. The first dose rate (red) is 500 Gy/s, the second dose rate (green) is 10 Gy/s, and the third one is 0.45. 0.30, 0.22, 0.18, 0.15, 0.13, 0.11, 0.1 Gy/s. That is for 10 curves

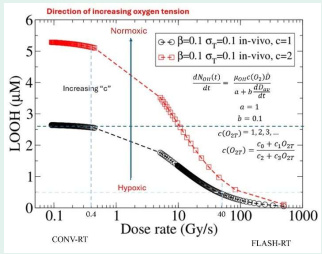


Figure 6. Numerical solutions of the rate equations (Eq. 9-16) for one pulse with a dose of 10 Gy in the brain at different dose rates, showing LOOH production in the brain dependence of dose rate for two different yields of •OH

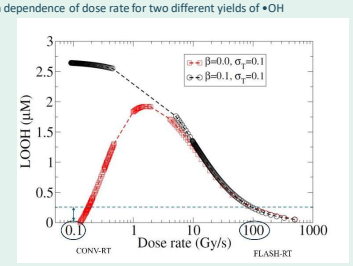


Figure 7. . Dose rate dependence of LOOH calculated by the time integration over LOOH for different perfusion β values. Circles mark representative dose-rate conditions from Leavitt et al. used for clamping experiments. (Leavitt et al 2024). We tested several intermediate values for β (0.08,0.05, 0.025) and they overlapped with the corresponding graph for β= 0.1)

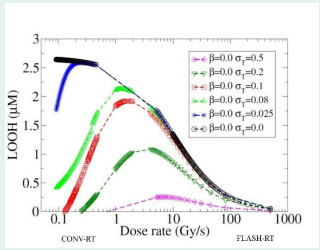


Figure 8. Dose rate dependence of LOOH calculated by the time integration over LOOH for no oxygen perfusion, β= 0, and different oxygen consumption σT values with initial PO2 40mmHg.

DISCUSSION

These results suggest that temporal oxygen dynamics may influence dose-rate-dependent oxygen-mediated radiochemical processes. This framework provides a testable hypothesis to investigate how differences in tissue oxygen dynamics could contribute to the variability reported across FLASH experimental conditions and tissues. Further experimental validation is required to determine how these early oxygen-dependent reactions translate into biological outcomes

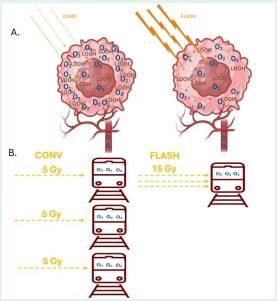


Figure 9. Scheme showing how differences in tissue oxygenation dynamics can influence dose rate dependence in lipid peroxidation. A. The scheme shows that differences in oxygenation between tumor tissues at the center and well-perfused normal tissues would lead to differences in lipid peroxidation, and how the dose rate would affect only the well-perfused tissues. B. The scheme shows subway trains representing oxygen delivery via perfusion and how the same radiation dose interacts with more oxygen at CONV-RT than at FLASH-RT

CONCLUSIONS

This compartmental model, informed by dynamic in vivo oxygen measurements, highlights the importance of considering the interplay between irradiation time and physiological oxygen replenishment kinetics as a potential contributor to dose-rate-dependent oxygen-mediated reactions. While LOOH formation represents a simplified surrogate of oxygen-dependent radiochemical processes, these findings support the hypothesis that tissue oxygen dynamics may contribute to oxygen-dependent mechanisms involved in the differential effects reported after FLASH irradiation

REFERENCES

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3. Grilj V, Leavitt RJ, El Khatib M, et al. In vivo measurements of change in tissue oxygen level during irradiation reveal novel dose rate dependence. Radiother Oncol. 2024;201:110539.