



A Pre-Clinical Study of Hyperbaric Oxygen Therapy to Enhance Radiosensitization of Glioblastoma

D. Hunter¹, A. Tavakkoli^{1,2}, B. Allen¹, D. Gladstone^{1,2}, J. Buckey^{1,2}, K. Pointer², J. Hoopes^{1,2}

¹Thayer School of Engineering

²Geisel School of Medicine at Dartmouth College



PURPOSE / OBJECTIVES

Solid tumors are often hypoxic. This is thought to contribute to radiation resistance, due to the absence of peroxide formation promoting oxygen (indirect radiation effects). **Hyperbaric oxygen (HBO) therapy consists of delivering oxygen at super-atmospheric pressures, typically > 2 atm.** Here we investigate the utility of HBO therapy in enhancing radiosensitivity of an orthotopic murine glioma model. We hypothesize that HBO therapy improves radiosensitization through oxygenation of the hypoxic glioma tumors. Additionally, tumor oxygenation dynamics prior to, during, and post HBO were measured and evaluated across a range of tumor volumes.

MATERIAL & METHODS

Tumor Radiosensitization Cohort:

Mice (N=40) were injected with SB28 glioblastoma cells in their left flank to induce tumor growth. Prior to irradiation on a Varian Trilogy Linear Accelerator, HBO group mice received treatment at 2.3 atm for 90 minutes with an 8-minute depressurization. Following HBO treatment, mice were transported from the HBO chamber to the linear accelerator and irradiated with 25 Gy at SRS dose rates (10 Gy/min) within 7 minutes of HBO therapy. Tumor volumes were monitored 3x/week for 4 weeks, with mice being removed from study once tumor volume surpassed 500mm³.

Tumor Oxygenation Cohort:

A separate cohort of mice (N=10) were injected with SB28 cells, and tumors were allowed to grow to various sizes. An air-tight fiber optic passthrough was made to enable continuous oxygen measurements before, during and after HBO therapy. 50 μL of 200 μmol Oxyphor PdG4 was injected intra-tumor 5 minutes prior to HBO therapy. Mice were anesthetized using ketamine and xylazine (inhaled anesthetics were not used due to the intra-chamber pressure). pO₂ was recorded throughout HBO therapy and for >7 minutes post depressurization.

RESULTS

No statistically significant difference was observed in tumor size at any timepoint following treatment between HBO + irradiation and irradiation-only treated mice or between HBO-only and untreated control mice. As expected, irradiated mice (with or without HBO) showed significantly smaller tumor sizes compared to non-irradiated groups (p < 0.01) at one week post treatment (Figure 1). Tumor oxygenation post-HBOT (11.13 mmHg) was not significantly different from baseline (8.11 mmHg, p = 0.91). A significant change in pO₂ during HBOT (HBOT pO₂: 25.96 mmHg, p = 0.046) was observed, though the extent of pO₂ elevation varied largely between mice. We observed a large variation in the extent of tumor oxygenation between mice, which we have attributed to variations in tumor sizes.

Hyperbaric oxygen therapy immediately prior to irradiation did not improve the radiosensitivity of the murine glioblastoma model.

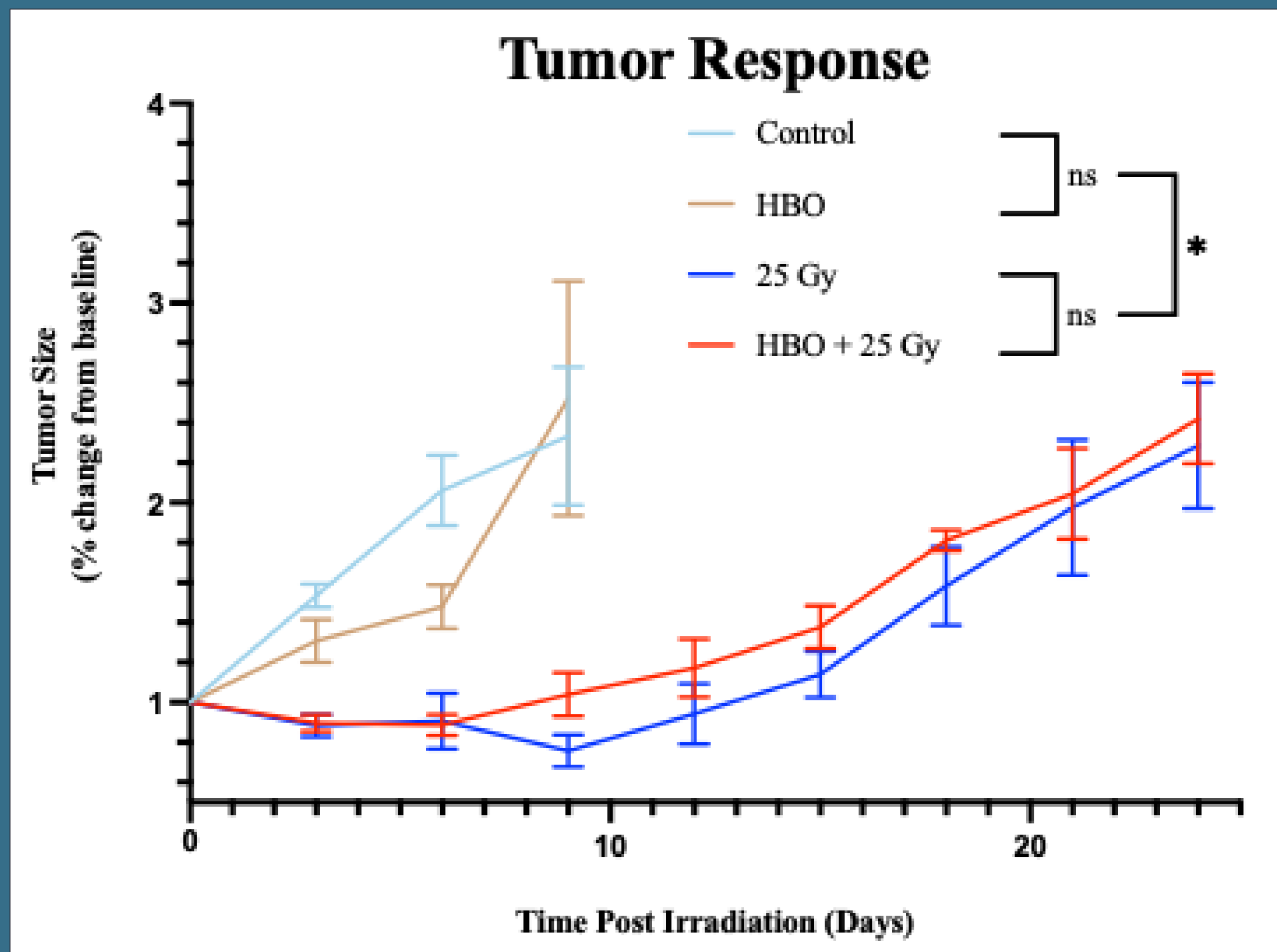


Figure 1: Tumor change in baseline volume against time post irradiation. No statistically significant differences were observed between HBO +25 Gy and 25 Gy only groups (p =0.76), and between HBO and Control groups (p=0.964). Irradiated (25 Gy containing) groups showed a significant difference from non-irradiated groups (p < 0.001).

RESULTS

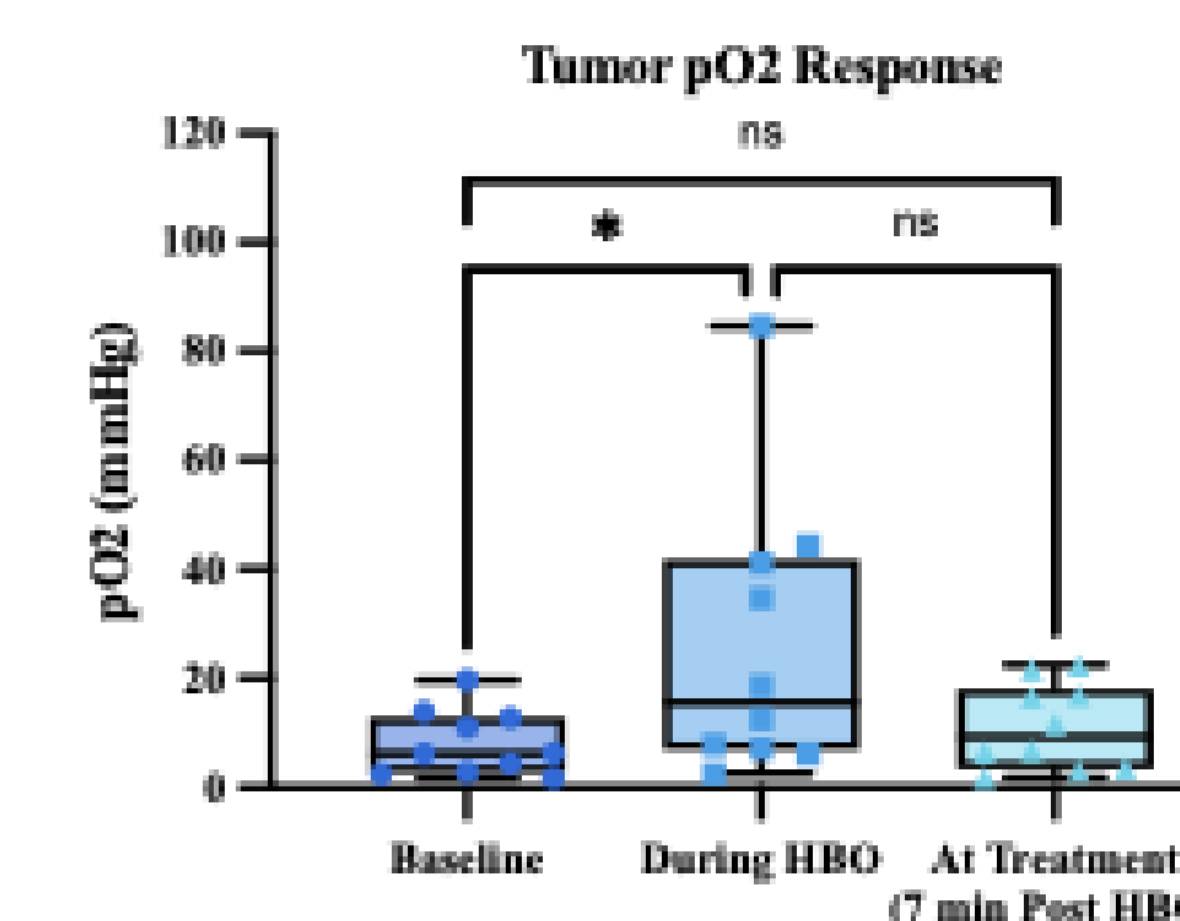


Figure 2: Comparison of tumor pO₂ at baseline, during HBO, and 7 minutes following HBO. Tumor oxygenation is statistically different between baseline and during HBO (p = 0.046) conditions, and not statistically significantly different between baseline and 7 minutes post HBO (p = 0.91).

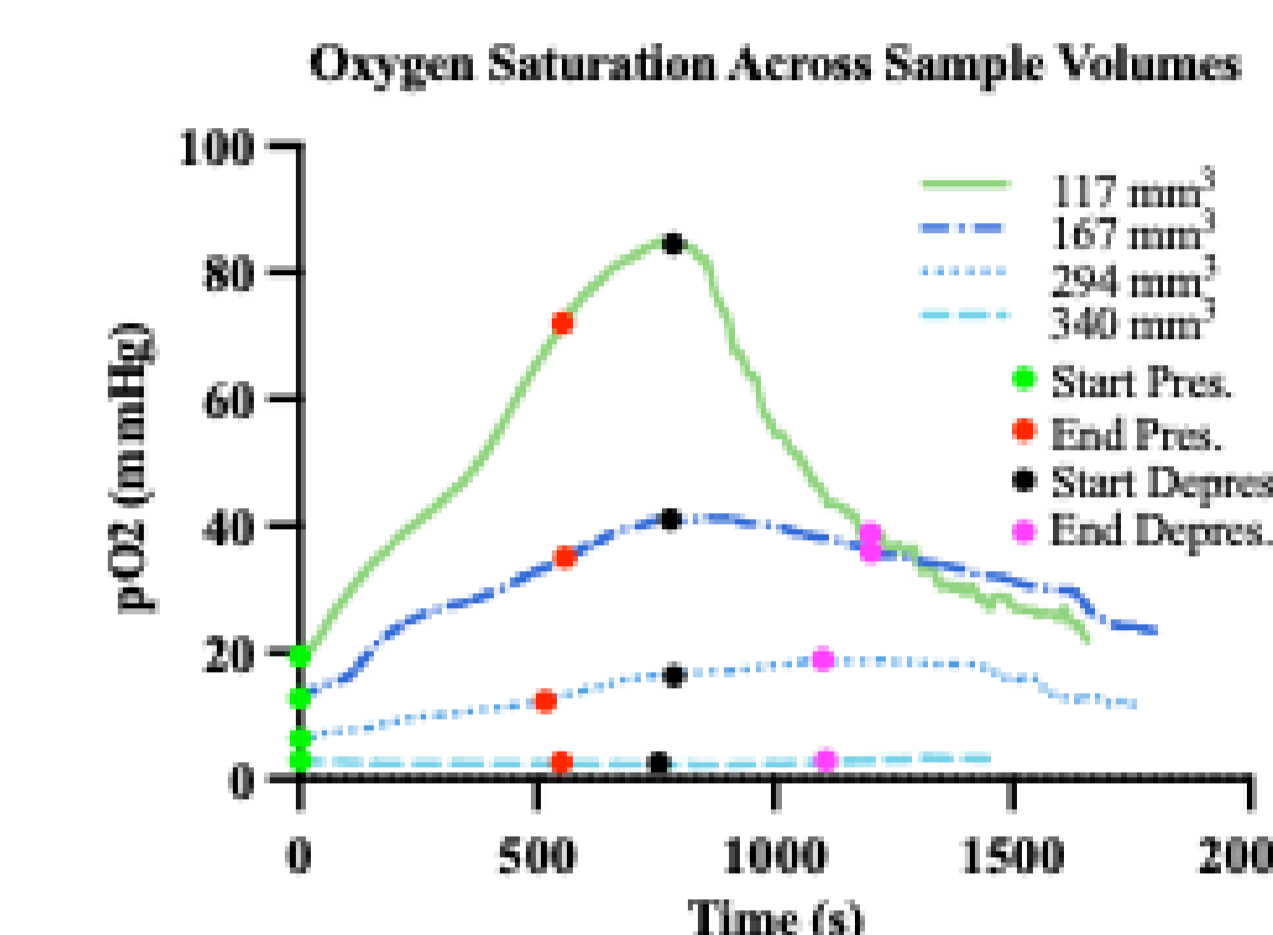


Figure 3: Oxygenation over time across four tumor sizes, 117 mm³(green, solid line), 167 mm³ (dark blue, dash-dot line), 294 mm³ (light blue, dotted line), and 340 mm³ (teal, dashed line). Start of pressurization (green dot), end of pressurization (red dot), start of depressurization (black dot) and end of depressurization (pink dot) points are marked for the four sample tumor sizes.

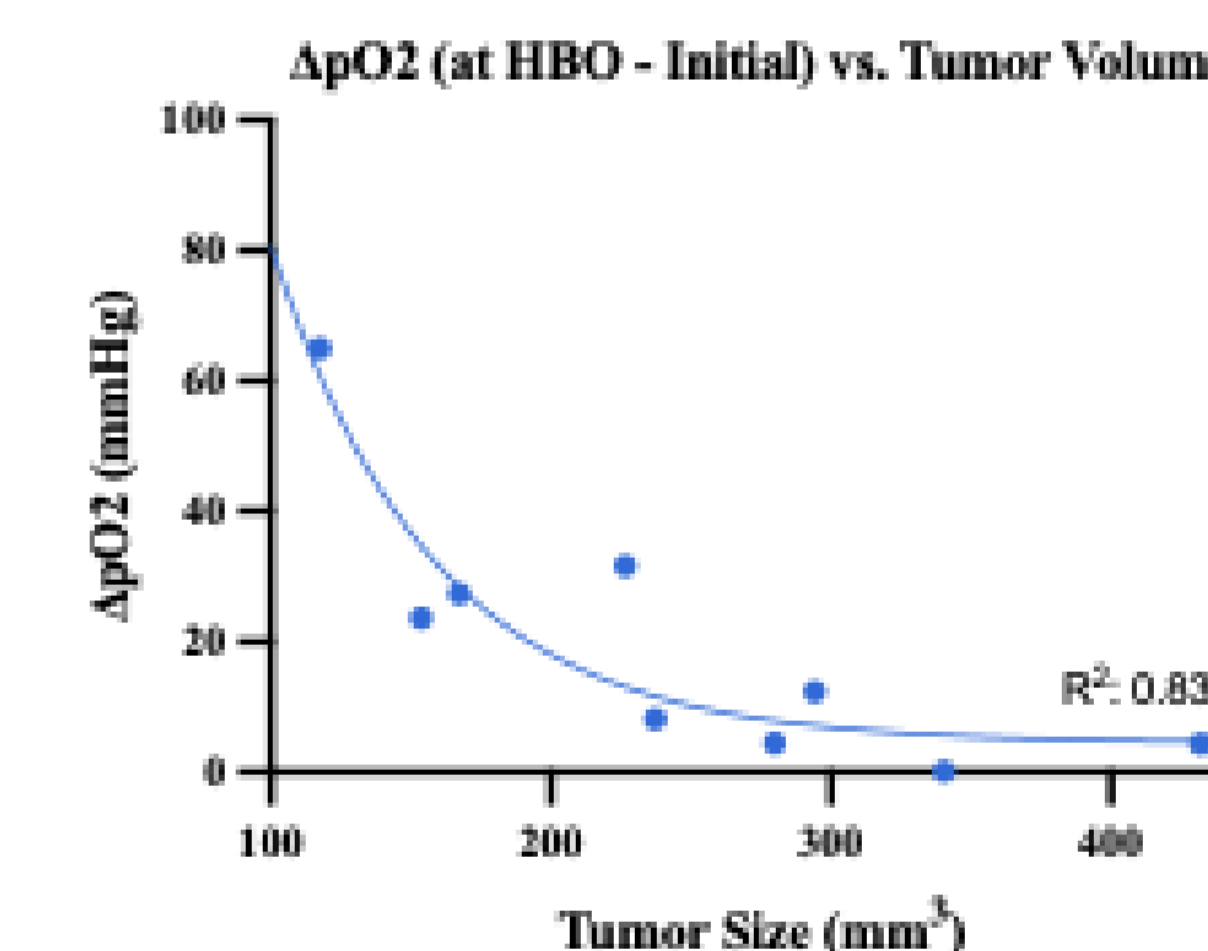


Figure 4: Maximum observed pO₂ during HBO plotted against tumor volume. A decaying exponential fit yielded an R² value of 0.83

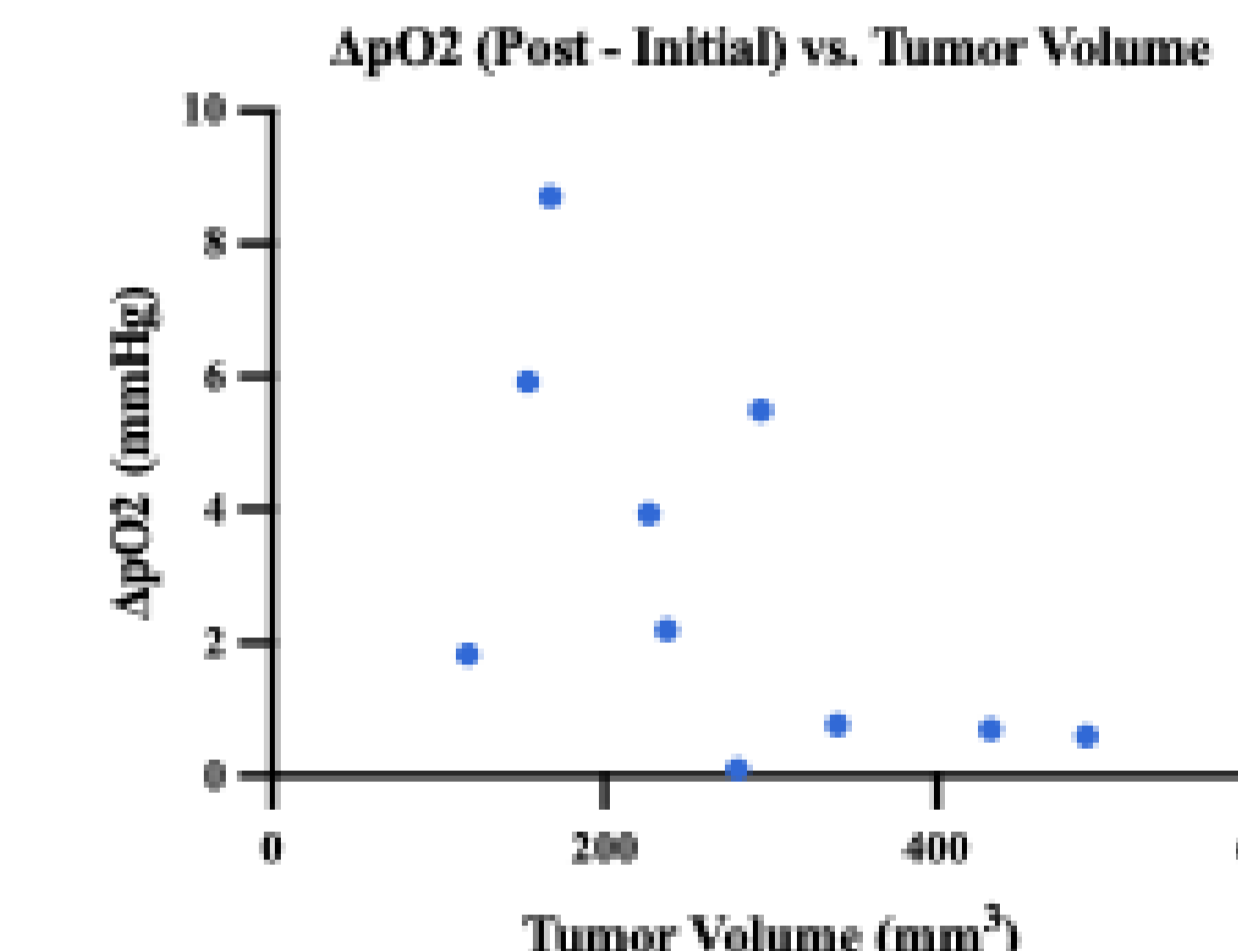


Figure 5: 7 minutes post HBO tumor pO₂ plotted against tumor volume

SUMMARY / CONCLUSION

We utilized an orthotopic murine glioblastoma model to evaluate whether pre-irradiation HBOT influences the radiosensitivity of these typically hypoxic tumors. **We saw no difference in tumor growth kinetics between mice receiving HBO + irradiation compared to irradiation alone.** This contrasts with previously published studies demonstrating improved tumor control in mice when radiation therapy is delivered during HBOT. Notable pO₂ elevations were only observed in relatively small tumors, with increasing tumor size decreasing the pO₂ elevation effects of HBO therapy. We observed that higher initial tumor pO₂ led to an increase in both HBO therapy pO₂ and pO₂ at the time of treatment. It was additionally observed that, during depressurization, tumor pO₂ decreasing closely followed the decrease in chamber pressure, returning tumors to near normoxic conditions upon full chamber depressurization. **Mouse tumors returned to normoxic conditions prior to the 7-minute mark.**

Acknowledgements:

This work was supported by a grant from the Dartmouth Cancer Center Prouty Pilot Developmental Fund, as well as the irradiation resources of the Department of Radiation Oncology and Applied Sciences (DROAS).