Inadequate tumor oxygenation strongly contributes to the failure to cure some cancers by radiotherapy. One approach to overcome this problem is the development of methods aimed at increasing the quantity of oxygen delivered to tumor. As an illustration based on this hypothesis, several studies have shown that nicotinamide with carbogen breathing can lead to enhancements of the tumor response to radiotherapy. Currently, due to the lack of adequate methodology able to measure accurately, sensitively, and non invasively the partial pressure of oxygen (pO₂) in tissues, only few compounds have been investigated for their effect on tumor blood flow or partial pressure of oxygen. Further, there has been no comparison between different classes of effective drugs. In order to improve this therapeutic approach, it could be very helpful to have access to a larger number of vasoactive agents able to modulate the partial pressure of oxygen (pO₂) in tumors. Equally important, there is a need to investigate the time course of the increase of the tumor oxygenation as well as to compare their efficacy.

Recently there has been a very significant progress using Electron Paramagnetic Resonance (EPR) oximetry. These advancements include both improvements in instrumentation and paramagnetic materials capable of measuring tissue pO₂ with an accuracy and sensitivity comparable or greater to any other method. The method's principle relies on the broadening of the EPR linewidth of a paramagnetic material by oxygen. The linewidth can be calibrated as a function of pO₂. In early applications, it was demonstrated that EPR oximetry is a convenient tool for measuring the pO₂ in murine tumors as well as for understanding the time course of reoxygenation after irradiation. We have recently discovered a new paramagnetic material which is able to report very subtle changes of pO₂ in tissues. This material is sensitive to variations of pO₂ of less than one mm Hg and possess a high spin density providing a high signal-to-noise ratio in the in vivo EPR measurements, giving the possibility to monitor rapid changes of tissue pO₂. This technological development has allowed us to design experiments in which we can predict the time course and efficacy of potential substances which elevate tumor pO₂. We used EPR oximetry to quantify the pO₂ in a transplantable mouse liver tumor model (TLT) possessing a low pO₂ after administration of 34 different compounds: angiotensin-converting enzyme inhibitors (n=3), calcium antagonists (n=5), alpha antagonists (n=5), potassium channel openers (n=3), beta-blockers (n=4), NO donors (n=4), and peripheral vasoactive agents (n=10). These drugs are routinely used in human for their vasoactive effect, i.e. in the treatment of hypertension or other blood circulation diseases such as Raynaud syndrome or intermittent claudication. The doses of the vasoactive compounds administered to mice were previously shown to be effective in changing hemodynamics (i.e. arterial pressure) in rodents. In our study, a tumor was considered as responsive when pO₂ is elevated by an additional 3 mm Hg. The absence of response was considered as an increase of less than 1 mm Hg. We observed that all NO donors (4/4), all beta-blockers (4/4), all angiotensin-converting enzymes (3/3), most peripheral vasodilators (8/10) produced a statistically significant increase of the tumor oxygenation (p<0.05) thirty minutes post-treatment in a majority of tumors. Two potassium channel openers significantly elevate pO₂ (2/3). In the class of calcium antagonists, nimodipine and bepridil were active; in the class of alpha antagonists, naftopidil also elevate tumor pO₂. Oxygen breathing was the most effective treatment for increasing the tumor pO₂ although this effect was not observed in all tumors. Further studies should be carried out in order to evaluate the combined effect of oxygen breathing associated with vasodilators which were found very effective in elevating the tumor pO₂. Indeed, several peripheral vasodilators or NO donors elevate the tumor pO₂ to a higher level than nicotinamide, compound for which the association with carbogen breathing was shown to increase the tumor response to radiotherapy.

In conclusion, we present here the first comprehensive study comparing the efficacy of vasodilators in their ability to increase the tumor pO₂. Additionally, we have identified several new compounds or new classes of drugs which enhance O₂ delivery. Further, we have confirmed the effect of other drugs for which the kinetics of action had been identified. This study should be a starting point for further experiments: dose/effect relationship for active compounds, evaluation of the radiosensitization effect with comparison to the pO₂ measured in vivo, effect of combined treatments. These results should be helpful in rationalizing treatments aimed at increasing the tumor pO₂ prior to radiotherapy. Finally, this study illustrates the power of the EPR oximetry technique as a unique tool for measuring the pO₂ in tumors and its temporal dynamics. The study emphasized the interest of several groups to advance this technology for use in human where tumor oxygenation may prove important in treatment and management of this disease.

REFERENCES