IVYSPRING INTERNATIONAL PUBLISHER

Theranostics

2017; 7(16): 3873-3875. doi: 10.7150/thno.20655

Editorial

Oxygen breathing challenge- the simplest theranostic

Ralph P. Mason ✉

Prognostic Imaging Research Laboratory, Department of Radiology, The University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, Texas 75390-9058

✉ Corresponding author: Tel: 214-648-8926; Email: Ralph.Mason@UTSouthwestern.edu

Received: 2017.04.19; Accepted: 2017.04.19; Published: 2017.08.31

Abstract

Multispectral optoacoustic tomography provides insights into tumor vascular oxygenation with high temporal and spatial resolution non-invasively. New work indicates that a simple oxygen breathing challenge can reveal differences in tumor, potentially as a prognostic biomarker.

Key words: photoacoustic tomography; prostate cancer; pathophysiology; oxygen

Optoacoustic tomography (OT), often referred to as photoacoustic tomography (PAT), promises significant new insights into tissue physiology and notably pathophysiology of tumor development. While the principles behind OT were discovered over a hundred years ago by Alexander Graham Bell, it largely remained an esoteric technology in the realm of dedicated biomedical engineering (BME) laboratories until recently. Briefly, OT involves pulsed light inducing local thermal expansion in a material, which generates acoustic perturbations detectable as ultrasound. At its crudest, this could be considered to be analogous to thunder induced by lightning. Pioneering achievements may be attributed to the laboratories of Beard, Wang, and Emelianov [1-3]. With the turn of the current millennium, commercial instruments have become available. These user friendly, turnkey instruments open opportunities for applications in many diverse labs.

As with any new technology, benchmarking and validation are important. In the current issue of Theranostics, Bohndiek *et al*. [4] present a rigorous demonstration of monitoring oxygenation in human tumor xenografts growing subcutaneously in nude mice. They specifically chose two human tumor prostate cancer lines known to exhibit different growth characteristics and aggressiveness. The study is thorough and robust including assessment of various practical constraints. Significantly, they include test-retest examples revealing reproducibility/ consistency of measurements. Historical photoacoustic tomography examined a single wavelength and differential local tissue excitation can give some anatomical contrast, potentially visualizing organs such as kidney, spine and large blood vessels. Multispectral optoacoustic tomography is applied to allow assessment of specific chromophores. Specific wavelengths can interrogate local molecular species and the spectral differences of oxy- and deoxyhemoglobin reveal vascular oxygenation based on spectral unmixing.

Bohndiek *et al*. [4] utilize the iThera MSOT system, which is particularly suited to examining mouse pathophysiology based on excitation of a single plane of tissue using optical excitation with 10 light sources and detection in a 270º toroid with 256 ultrasound detectors. Images were acquired at 15 wavelengths between 700 and 880 nm averaging data from 7 pulses per wavelength and providing 11.5 s temporal resolution for each multi spectral image, *viz*. potential oxygen saturation map. This study examined single slices, but adjoining slices could be acquired to reveal three dimensional features. Spectral unmixing provided maps of oxy- and deoxyhemoglobin, which are ideally suited as contrast agents, being endogenous and occurring at relatively high concentration with strong absorption in the near infrared optical window.

At baseline, when anesthetized mice inhaled air, imaging indicated high total hemoglobin in the LNCaP tumors, but the investigators show that the static measurement of SO_2^{MSOT}(Air), commonly used in the literature, suggested that both tumor types had similar average vascular oxygenation and repeat measurements after 24 hrs showed wide variability. However, in response to an oxygen breathing challenge, the magnitude and extent of response was significantly different for the two tumor types. Indeed, the mean $SO_2^{MSOT}(O_2)$, responding fraction of tumor (RF), and ΔSO_2^{MSOT} were all significantly lower for PC3 than LNCaP tumors. This suggests the possibility for a non-invasive prognostic imaging biomarker.

PC3 tumors have been evaluated by photoacoustic imaging previously; notably, levels of total hemoglobin and oxygen saturation were evaluated with respect to irradiation in conjunction with microbubble stimulated vascular destruction [5]. That study used in–house developed instruments and it is encouraging to see that a commercial instrument now allows similar vascular measurements. Both studies indicate considerable heterogeneity in the vascular perfusion and oxygenation of PC3 tumor vasculature, confirmed by immunohistochemistry.

Oximetry to identify hypoxia and dynamic tumor response to intervention is a major goal in biomedicine. Indeed, blood oxygenation level dependent (BOLD) contrast (R_2*) MRI is the basis of the so-called fMRI used extensively in neurological examination [6]. Meanwhile, tissue oxygen level dependent (TOLD) contrast (R_1) MRI provides insights into tissue pO_2 [7]. Tumor vascular oxygenation has been a focus of investigation in MRI and indeed some of the current authors are pioneers in development of oxygen sensitive MRI, where they have previously shown that R_1 responses were more useful than R_2* for charactering tumors [8].

Specific comparisons of different prostate tumor types in pre-clinical studies have previously been undertaken using oxygen sensitive MRI. Mason *et al*. used combined BOLD and TOLD MRI to reveal distinct differences in oxygen dynamics between anaplastic fast growing Dunning prostate R3327-AT1 tumors and those of a moderately well differentiated slower growing, but highly vascularized subline HI [9]. As in the Bohndiek *et al*. study [4], an oxygen breathing challenge provided the vital contrast. Meanwhile, quantitative oximetry using the hexafluorobenzene reporter molecule revealed that prostate tumors may appear very similar while animals breathe air, but respond very differently to an intervention [10,11]. Clearly, the current study shows that MSOT can provide similar insights.

OE-OT adds to the armamentarium of the imaging scientist and promises new opportunities for assessing pathophysiology. In terms of new techniques it will likely not be as transformative as bioluminescent imaging, since it is considerably more complicated and expensive, but it has the great advantage of not requiring gene transfected cells. Technical considerations for OE-OT include the need for nude or well shaved skin, the art of degassing the gels required for optical and acoustic contact, effective use of data processing algorithms and choice of wavelengths. Nonetheless, the current study validates the profound new opportunities for theranostics.

Optoacoustic tomography (OT) is an emerging modality that reveals hemoglobin concentration and oxygenation with high spatial resolution, temporal resolution and sensitivity. Beyond imaging vascular oxygenation, MSOT is also sensitive to exogenous contrast agents ranging from fluorescent labels such as 800CW to near infrared gene reporters and highly absorbing materials such as gold nanoparticles and carbon nanotubes [12].

The authors conclude that the ability to differentiate prostate tumor types with different aggressiveness holds promise for translation to man, with the important goal of identifying indolent versus aggressive tumors. This is indeed a vital aspiration for current oncology in the age of personalized medicine and would be highly significant. It may be some time before practical OT is routinely feasible in the human prostate, but as the authors note, recent investigations are promising.

References

1. Weber J, Beard PC, and Bohndiek SE. Contrast agents for molecular photoacoustic imaging. Nat Methods. 2016; 13: 639-650.
2. Xia J, and Wang LHV. Small-animal whole-body photoacoustic tomography: a review. IEEE Trans Biomed Eng. 2014; 61: 1380-1389.
3. Yeager D, Chen YS, Litovsky S, and Emelianov S. Intravascular photoacoustics for image-guidance and temperature monitoring during plasmonic photothermal therapy of atherosclerotic plaques: a feasibility study. Theranostics. 2014; 4: 36-46.
4. Tomaszewski MR, Gonzalez IQ, O'Connor JP, Abeyakoon O, Parker GJ, Williams KJ, Gilbert FJ, Bohndiek SE. Oxygen Enhanced Optoacoustic Tomography (OE-OT) Reveals Vascular Dynamics in Murine Models of Prostate Cancer. Theranostics 2017; 7(11):2900-2913. doi:10.7150/thno.19841.
5. Briggs K, Al Mahrouki A, Nofiele J, El-Falou A, Stanisz M, Kim HC, et al. Non-invasive monitoring of ultrasound-stimulated microbubble radiation enhancement using photoacoustic imaging. Technol Cancer Res Treat. 2014; 13: 435-444.
6. Logothetis NK. What we can do and what we cannot do with fMRI. Nature. 2008; 453: 869-878.
7. Matsumoto K, Bernardo M, Subramanian S, Choyke P, Mitchell JB, Krishna MC, et al. MR assessment of changes of tumor in response to hyperbaric oxygen treatment. Magn Reson Med. 2006; 56: 240-246.
8. O'Connor JPB, Boult JKR, Jamin Y, Babur M, Finegan KG, Williams KJ, et al. Oxygen-enhanced MRI accurately identifies, quantifies, and maps tumor hypoxia in preclinical cancer models. Cancer Res. 2016; 76: 787-795.
9. Zhao D, Pacheco-Torres J, Hallac RR, White D, Peschke P, Cerdán S, et al. Dynamic oxygen challenge evaluated by NMR T_1 and T_2* – insights into tumor oxygenation. NMR Biomed. 2015; 28: 937–947.
10. Zhao D, Constantinescu C, Hahn EW, and Mason RP. Differential oxygen dynamics in two diverse Dunning prostate R3327 rat tumor sublines (MAT-Lu and HI) with respect to growth and respiratory challenge. Int J Radiat Oncol Biol Phys. 2002; 53: 744-756.

11. Mason RP, Zhao D, Pacheco-Torres J, Cui W, Kodibagkar VD, Gulaka PK, et al. Multimodality imaging of hypoxia in preclinical settings. Q J Nucl Med Mol Imaging. 2010; 54: 259-280.
12. McNally LR, Mezera M, Morgan DE, Frederick PJ, Yang ES, Eltoum IE, et al. Current and emerging clinical applications of multispectral optoacoustic tomography (MSOT) in oncology. Clin Cancer Res. 2016; 22: 3432-3439.