Interstitial Fluid Pressure and Hydraulic Conductivity in Solid Tumors: Introducing an In-Vitro Method for Measuring the Hydraulic Conductivity of Tumor Tissue

Hooman Salavati (1,2,3), Charlotte Debbaut (2,3), Pim Pullens (4,5,6), Wim Ceelen (1,3)

(1) Department of Human Structure and Repair, Ghent University, Ghent, Belgium
(2) IBitech–Biommeda, Ghent University, Ghent, Belgium
(3) Cancer Research Institute Ghent (CRIG), Ghent, Belgium
(4) Department of Radiology, University Hospital Ghent, Ghent, Belgium
(5) Ghent Institute of Functional and Metabolic Imaging (GIFMI), Ghent University, Ghent, Belgium
(6) IBitech–Medisip, Ghent University, Ghent, Belgium

Introduction
Resistance against drug delivery is a challenge in oncology, preventing the development of optimal therapeutic outcomes. This has been related to a group of hostile biophysical characteristics in the tumor microenvironment. Among them, the elevated interstitial fluid pressure (IFP) in solid tumors has been identified as a barrier for drug transport. Also, the hydraulic conductivity (K) of tumor stroma strongly correlates with the IFP. However, values of K in human cancer tissues are quite limited. Here, we developed a novel in vitro setup that allows to measure K in clinical samples. Moreover, the dependency of IFP over K was investigated via a numerical method.

Methods
We developed an apparatus based on modified Ussing diffusion chambers. The setup comprises the diffusion chambers along with a bubble tracker device as an index for quantifying the amount of fluid exchange through the tissue due to a hydrostatic pressure gradient in a closed system. The rate of bubble movements was converted into K values by accounting for several parameters such as the sample thickness, buffer solution viscosity, and the pressure magnitude. Also, a 2D computational fluid dynamics (CFD) model was used to simulate the sensitivity of the IFP profile to the magnitude of K.

Results
The measured values (K ranging between 6.8E-16 and 4.1E-14 m²/Pa⋅s) demonstrated a good agreement with previously published values, which were either measured in animal studies or estimated indirectly. The results indicated heterogeneity of hydraulic conductivity values in a single tumor up to a factor of 4.3. Moreover, results demonstrated that K values for the same tumor type can vary significantly. The CFD model showed that changes in K may significantly affect the tumor IFP depending on the tumor size and shape.

Conclusion
We successfully built a setup that allows to measure the hydraulic conductivity of human cancer tissue samples. Regarding the relatively high sensitivity of IFP to K values, these results can inform novel therapeutic approaches that target the biomechanical tumor environment.