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Cover story

A new look at ultrasound-mediated extravasation

Specific targeting is one of the holy grails in drug delivery. It is especially important for tumor sites and to penetrate the blood–brain barrier. Drug delivery systems have been engineered to respond to external factors, such as changes in temperature, pH, and magnetic field. Ultrasound (US) is also one of the external factors that can be used for targeted drug delivery.

Soon after the first industrial application of US for locating icebergs and ships in the early 20th century, the biological effects of US exposure were soon noted and triggered investigations. In their seminal work, Wood and Loomis laid the foundation to therapeutic applications of US, which predates today's mainstream diagnostic imaging applications [1]. Ultrasound is a pressure wave characterized by a certain acoustic pressure, wavelength and duration, which can be delivered with high spatial and temporal resolution. Energy dissipation during interaction with tissue can lead to heating as well as mechanical (non-thermal) effects, which both find therapeutic applications in thermal therapies (e.g., ablation or hyperthermia), or pressure-mediated applications like lithotripsy, bone growth stimulation or possibly drug delivery. For the latter, the combination of US with microbubbles (MBs), commonly used as diagnostic US contrast agents, is of special importance. When exposed to US, MBs are driven into a forced oscillation state generating diverse mechanical forces. When interacting with cells *in vitro*, a transient permeabilization of cellular membranes is induced, termed sonoporation, which can be exploited for drug delivery of compounds that do not cross cellular membranes [2].

The *in vivo* application of US for drug delivery is fairly complicated. The transient permeabilization of the endothelium creates pores allowing extravasation of drugs that would otherwise remain confined within the vasculature. Much of the ongoing *in vivo* research exploits this effect for site directed delivery of genes or drugs, e.g., in the brain after US-induced opening of the blood–brain barrier [3]. The US-induced drug delivery *in vivo* depends on various factors, such as the specific US treatment protocol, the exact nature of MBs, perfusion, drug, as well as fenestration of the vascular system. Yet, a recently introduced model points at a simple mechanical explanation of US-induced transient pores that close with a certain speed. These transient pores create a time window for the injection of drugs after US treatment that can be exploited for local delivery [4].

In this issue, Prof. Grüll and his group present their study on US-induced extravasation of bovine serum albumin (BSA) as a model drug [5]. Interesting in their approach is the use of nuclear imaging for quantitative tracing of the uptake amount and kinetics and the spatial distribution of radiolabeled BSA with respect to the treated tissue volume. In the study, MBs were injected while treating a well-defined area with focused US (fUS). The fUS-driven oscillation of MBs caused a local but transient increase in permeability of the vascular system, allowing enhanced extravasation of BSA into the interstitial space. The transient nature of this increase in permeability was probed by varying the waiting time between fUS treatment and the injection of BSA. The subsequent kinetics of extravasation was followed *in vivo* using SPECT imaging exploiting the full potential of three-dimensional image-based quantification. The SPECT results show that the extravasation of BSA decreases with a half-life of approximately 21 min consistent with the prediction of the transient pore model [4].

It appears that there is a universal repair mechanism of blood vessels to restore biological integrity after being exposed to mechanical stress, which may be independent of the specific tissue. Fundamental insights gained with fUS experiments may help scientists develop better approaches of US-mediated targeted drug delivery. The approach of using fUS may appear similar to that of using thermo-sensitive liposomes or magnetic field-sensitive nanoparticles, all of which have been shown to be not as effective in human patients as expected. But there is one important difference between fUS and the other previous approaches. The fUS treatment is designed to alter the biological barriers resulting in transient pore formation for efficient drug transport. The fUS approach may become an invaluable tool for achieving site-directed drug delivery.

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