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In situ measurements of magnetic nanoparticles after placenta perfusion

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ABSTRACT

Nanoparticles (NP) present promising tools for medical applications. However, the investigation of their spatial and temporal distribution is hampered by missing in-situ particle detection and quantification technologies. The placenta perfusion experiment represents an interesting model for the study of the particle distribution at a biological barrier. It allows the ex-vivo investigation of the permeability of the placenta for materials of interest. We introduce an approach based on a magnetic system for an in situ measurement of the concentration of magnetic NPs in such an experiment. A previously off-line utilized magnetic readout device (sensitivity of $\approx 10^{-8}$ Am^2) was used for long term measurements of magnetic NP of 100–150 nm size range in a closed circuit of a placenta perfusion. It represents a semiquantitative approach. The behavior of particles in the placenta and in the measurement system was studied, as well as the influence of particle surface modifications. The results suggest a transfer of a low amount of particles from the maternal to the fetal blood circuit.

1. Introduction

Nanoparticles (NP) play an increasing role in our current society – both in daily life (toothpaste, cleaning agents, deodorant) [1] and biomedicine (cancer treatment, medical imaging) [2,3]. The different NP can be composed of a diversity of materials and can show quite different shapes and characteristics. The only given similarity of all these nanomaterials is their size, with one dimension not exceeding 100 nm [3]. NPs can serve to improve the application of medicals by increasing their half-life period or their specificity [4]. Particularly in medical imaging their use is very beneficial. Especially magnetic NPs are worth to be applied as a contrast agent in magnetic resonance tomography (MRT). Nevertheless the current lack of knowledge about their potential toxicity and the chance of spatial distribution in the human body require an excessive risk assessment before bringing these particles into broad use. For this purpose, the *ex vivo* placenta perfusion constitutes an approved method to illustrate the behavior and possible alterations of placental tissue due to a certain treatment [5]. It allows investigating the behavior of agents of interest, like NPs, at the feto-maternal interface, the placental barrier, supplying helpful hints concerning a potential use during pregnancy [6]. Furthermore the human placenta represents a very suitable model of a humane organ that offers the option of the investigation of the behavior of interesting NPs without constituting ethical problems [7]. It allows analyzing the passage of NPs through human tissue as well as their retention at/inside the tissue [8] and their influence concerning different biological parameters like energy usage or the protein biosynthesis. To date, no simple standardized methods are available for quantification of NP in human tissue. Until now, the quantification of NPs in such experiments usually is performed in static samples [9], bringing up the problem of a delayed analysis period, the need of suitable sample treatment and the lack of possibilities to interact directly with the analysis system. We developed a setup to follow the magnetic signal in a floating fluid in-line by improving a given magnetic system that was designed for measuring the magnetic moment in static samples.

Aim of the investigations was to verify a potential transfer of magnetic particles across the placental barrier by means of a semi-quantitative magnetic in-line measurement in an *ex vivo* placenta perfusion experiment. To our knowledge, it is the first study of this kind.

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2. Materials and methods

2.1. Detection principle of the magnetic system

A measuring system for quantification of static magnetic beads (batch samples) was modified in order to measure particle concentrations in a flowing suspension. The original system, the Magnet Reader [10], is based on frequency composition and field strength at the non-linear magnetization curve of superparamagnetic samples (non-hysteretic). For details of the detection principle see [11,12]. The response signal generated at a frequency representing a linear combination of the two distinct excitation frequencies $f_1=49.4$ kHz ($H_{max}=1.5$ mT) and $f_2=61$ Hz ($H_{max}=4.5$ mT) is detected. In addition to the coaxial excitation coils two similar pick-up coils are mounted in one gauging head. These are used for measuring the difference between the magnetic field in the measuring coil (contains the sample) and in an empty coil. A linear measuring range is given for particle concentrations between 0.12 and 1300 µg(Fe)/mL [10] determined on superparamagnetic iron oxide particles. This lower limit corresponds with a magnetic moment of about 10^{-8} Am^2 and a particle concentration of about 1.7 µg/mL in the cuvettes for static measurements. Theoretically the minimum detectable magnetic moment is 5×10^{-14} Am^2, calculated with an integration time of 10 s [10]. There is an offset in the signal coming from a non-perfect compensation/ adjustment of the coils of about 360 mV that has to be considered. After certain time intervals during the perfusion experiments the background was measured by removing the cuvette and this signal (a function calculated by fitting a polynomial to these datapoints) was subtracted from the data measured with cuvette.

For measurements of flowing samples (integration time: ≤ 1 s) a lower sensitivity, i.e. a higher upper limit of the linear range, is expected. The noise of the measurement decreases with the square root of the increasing integration time. Since the sample cuvettes have to be modified, the change in the sample volume inside the measuring coil and a change of the exposure time of particles (in the order of 0.1 s maternal and 0.5 s fetal) caused by the flow rate (see Section 2.2) will alter the limits. In the case that a fraction of NPs is non-superparamagnetic only a semiquantitative result can be given.

2.2. Ex vivo placenta perfusion model

The employed system of *ex vivo* placenta perfusion was adopted from the setup established by Panigel et al. in 1967 [13] and further optimized by Schneider et al. in 1972 [14] (Fig. 1). Apart from the installation of the MagnetReader and non-magnetic stirrers, the setup was not modified for the magnetic measurements.

In the perfusion experiments, the placenta was connected with the pumping and measuring system by cannulae. Before the measurement the placenta was rinsed and reoxygenated for 30 min with perfusion fluid to remove remaining blood and further perfused for 2 h as a control phase without nanoparticles, to detect possible leaks and check stability of the system. Perfusion

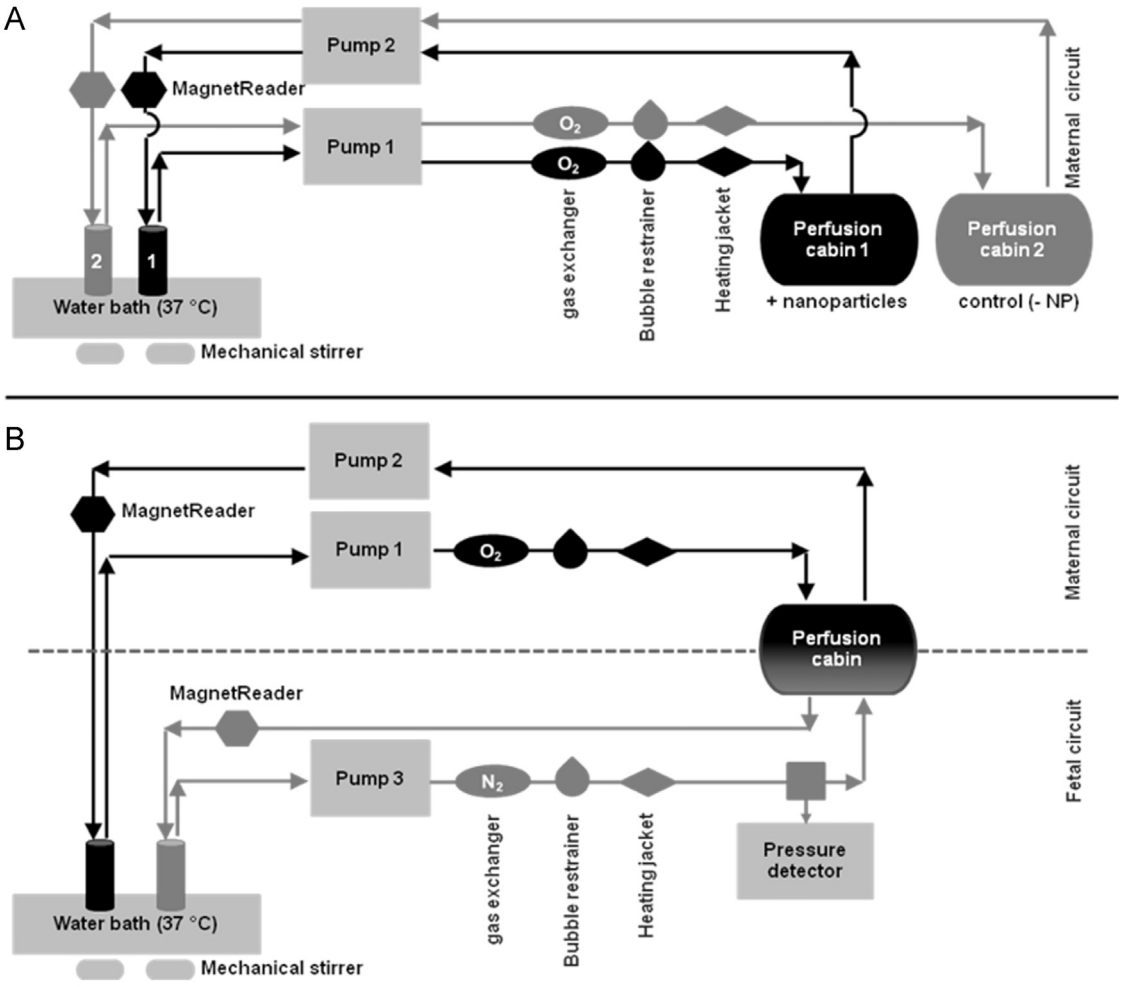

Fig. 1. The setup of the experiment. A: for evaluation of the measuring system B: for the double sided perfusion experiments.