Potential Applications of Untethered Microdevices in the Blood Vessels within the Constraints of an MRI System

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Abstract—**This paper presents potential medical applications that an untethered microdevice in the cardiovascular system could perform within an MRI system. Recent developments and continuing evolution in micro/nano fabrication and design techniques will enable the development of functional microdevices able to explore the cardiovascular system. The Magnetic Resonance Submarine (MR-Sub) project is a first step towards this goal. Magnetic force generated by the gradient coils of an MRI system provides a propulsion mechanism that simplifies miniaturization and bypasses energetic challenges. Untethered microdevices may play an important complementary role in the next generation of minimally invasive tools. A better efficiency and targetability of the treatments will be achieved when microsystems such as the MR-Sub will allow a more extensive access to smaller blood vessels.**

Keywords—**Microdevice, therapeutical applications, magnetic resonance, magnetic gradient, blood circulatory system, propulsion, minimally invasive surgery**

I. Introduction

The MR-Sub project has proved the feasibility of the concept of magnetic propulsion based on MRI system's gradient coils[1-5]. Moreover it has defined the constraints and technical challenges to overcome to control microdevices in the blood vessels within an MRI [6]. The first step before injecting an MR-Sub in a blood vessel is to digitize the unique cardiovascular system of the patient and determine a best path to a given target as presented in the same proceedings. A system that allows the tracking of the MR-Sub with the best possible spatial and temporal resolution has to be developed. The results presented last year in [2] have been refined and the tracking methodology will be presented in the next months. Then, an ECG synchronized real time control loop must be embedded within the constraints of the MRI system's computer architecture as presented in the same proceedings. The human blood circulatory system being made of arteries, veins and capillaries which diameter varies from 2.5 cm to less than 10 microns, the overall size of a particular device is dependent upon the pathways being considered. A microdevice must be dimensioned in order to reach an optimum between magnetic force, drag force, blood vessel diameter and available gradient strength [5]. Hence, it is not possible to use a single size microdevice to be actively controlled in the whole cardiovascular system. In order to reach the target area it has been designed to reach, a microdevice has to be released in the blood stream using a catheter. This allows for example a microdevice designed to navigate through an arteriole to avoid high arterial flows it cannot withstand. Linear MRI gradients are applied over the whole homogeneous region of the MRI bore. Hence, they affect every magnetic body that would be located within the navigated region. Therefore, it is mandatory to securely anchor a first magnetic microdevice before inserting and controlling a second one.

II. Environment

A. Magnetic Targeting

According to its definition in [7], magnetic targeting relies on a magnetic compound injected in the patient's body and then stopped with a powerful magnetic field in the target area. This definition needs broadening to take into account the fact that an MRI system can be used to control a magnetized body in three dimensions [3,4]. This paper presents the opportunities an MRI system can bring to magnetic targeting by the means of Magnetic Resonance Propulsion (MRP). MRP applications rely on an MRI system's gradient coils, imaging sequences and real time computer architecture to bring a magnetized microdevice in a precise location and perform targeted Minimally Invasive Surgery (MIS) applications. Applications for a first generation MR-Sub are being explored. This application must be relatively simple and bring clinical benefits with the use of a passive microdevice. Active microdevices are the next step in the evolution of this project and will be developed when MRP technology is mature enough. A passive microdevice can be used in several manners such as a drug carrier, a seed for hyperthermia, an embolizing body or as a magnetic beacon to attract smaller magnetic microparticles. MRP can be used to drive precisely magnetic beacons from a catheter tip to a selected artery. The target artery's lumen has the same size than the magnetic beacon to allow anchoring. In [8,9] the authors study the capture of magnetic microparticles by a magnetized body inside a flow. Based on this principle, inside the MRI magnetic field, magnetized microparticles could be released afterwards from the same catheter and circulate in the cardiovascular system until they are captured by the magnetic beacons as shown in Fig.1. These microparticles could carry drugs,

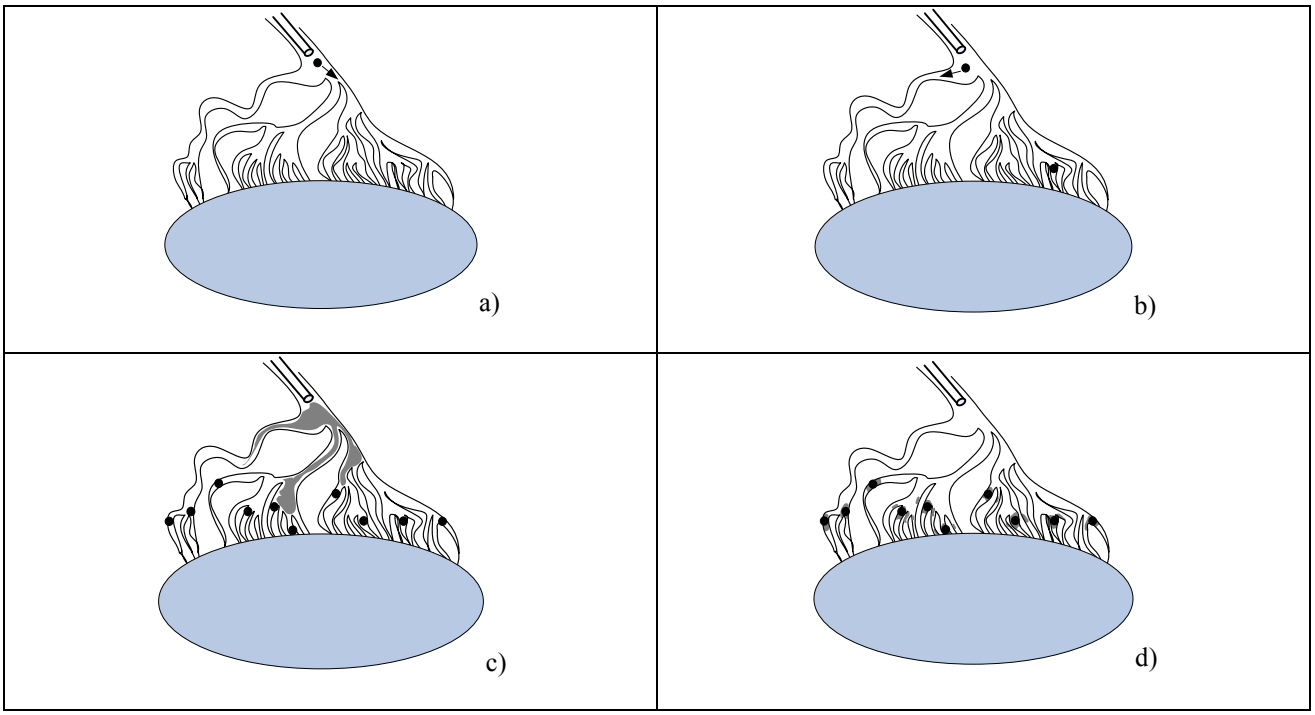

Fig. 1: Capture of magnetic microparticle by sequentially targeted magnetic beacons. a) A first magnetic beacon is inserted through a catheter in an artery upstream from the target area (here a tumor is symbolized). It is then magnetically brought to a smaller artery where it can wedge. b) After the first magnetic beacon has been anchored a second one is inserted and magnetically brought towards its target. This process is repeated until there are enough beacons to cover the whole targeted zone. c) A fluid containing magnetic microparticles small enough to go through the capillary bed is injected through the same catheter. d) It circulates within the patient's cardiovascular system until it is captured by the magnetic beacons. It can now be used to deliver hyperthermia, release drugs or induce thrombosis leading to ischemia.

deliver hyperthermia and induce coagulation. The main advantage of this approach is its flexibility. As a matter of fact, it allows tailoring of medical applications by combining the diverse properties of the MRI system, microdevice and magnetic microparticles.

B. Magnetic Particles

Magnetic particles are made of ferromagnetic materials such as iron, magnetite, nickel, cobalt, neodymium, samarium and alloys of these components. In MRI systems, where the magnetic field is very intense (≈1.5 Tesla), the most important property of ferromagnetic bodies is their saturation magnetization. As a matter of fact, saturation magnetization determines the intensity of the magnetic force acting on a magnetic particle per unit volume. Soft magnetic materials (Iron or Permendur) usually have higher saturation magnetization than hard magnetic materials (NeFeB, SmCo) and are therefore the best candidates to be used for the beacons and magnetic microparticles.

III. Review of potential applications

Many therapeutic applications of magnetic particles have been described. Their main limitation was the use of external magnets that limited the target area to organs close to the skin. Some approaches rely on magnetically tipped catheters to reach deeper organs [10,11]. Nevertheless, they cannot reach the microcirculation because of the size and limited curvature radius of catheters. We will present a survey of magnetic particles applications that could benefit from untethered magnetic microdevices such as the MR-Sub.

A. Metallic Particle Embolization

Metallic particle embolization by definition is the induction of a thrombus by the presence of metallic particles in the blood. Magnetic concentration of the metallic embolization material has been thoroughly studied in the past decades [10,12,13], in the context of aneurism treatment. This approach was not as efficient and safe than Guglielmi's [14,15]. Nevertheless, it was proved in [10] that Iron particles stimulated blood clotting and fibrosis and that the resultant metallic thrombus permanently obliterates the aneurism.

B. Magnetically Mediated Hyperthermia

An abnormal body temperature increase is referred to as hyperthermia [16]. Localized hyperthermia can be used as a tumor treatment. It has fewer negative side effects than

chemotherapy or radiotherapy in the treatment on cancers. Besides, it can be performed in combination with these techniques in order to enhance the overall treatment efficiency and reduce drug/radiation doses. Moreover, the temperature increase induces arterial thrombosis which deprives the tumor of its blood supply. In order to be efficient, hyperthermia has to be selective enough not to injure healthy tissues but it must act on a wide enough volume to affect the whole tumor. One way to induce hyperthermia is the *in vivo* injection of metallic particles which can be heated using AC-magnetic fields. Magnetically mediated hyperthermia (MMH) as described in [17] has the potential to address these shortcomings. The use of magnetic particles, in addition to concentrate the energy provided by the AC-magnetic fields allows control over the position and volume of the heated area. Among magnetic materials, superparamagnetic particles are the best candidates for hyperthermia. These subdomain nanometric particles, due to Brownian relaxation and Néel effect, are able to produce substantially more heat per unit mass than microparticles of same composition under AC-magnetic fields [18].

C. Magnetic Drug Targeting

Drug delivery is the use of whatever means possible to regulate a drug's access rate to the body's central compartment or in some case directly to the involved tissues [19]. Even though catheters can be guided in blood vessels with lumens as small as 1mm, all the microcirculation remains out of reach. When catheters are used for drug delivery, the active principle is released upstream from the targeted organ and is carried away in the microcirculation in an uncontrolled manner. Magnetic drug targeting is a way to control microparticles after they are released from a catheter. The first step is usually to inject magnetic microparticles bound with an active principle upstream from an external magnet [20]. Once the microparticles are confined within the magnet's field, the drug is released from its carrier. Magnetic carriers such as liposomes, magnetic granule, magnetic emulsions, albumin and starch microspheres or poly-(alkyl-cyanoacrilate)-nanoparticles have been used in previous studies [20]. Drug release can either be diffusion, chemically or thermally controlled [19]. In the first case, the properties of the drug and the polymeric carrier govern the release rate in the blood stream. In the second case, the active principle can be chemically linked to the backbone of a polymer and is released under the action of enzymes or biological fluids (pendant chain systems). It can also be slowly released from a bioerodible polymer. In the third case, a temperature increase that can be caused by energy sources such as an AC-magnetic field [21] or a laser exposure [22] can trigger the release from a liposome or from a hydrogel matrix [23]. Besides tumoral damages caused by a magnetically concentrated chemotherapeutic agent, the release of heated superparamagnetic particles in tumor vasculature could lead to embolization, hyperthermal treatment and enhance necrosis [24]. Selective targeting of magnetic albumin microspheres containing doxorubicin in Yoshida sarcoma-bearing rats was achieved in [25]. This application of magnetic drug targeting showed that this approach is able to greatly enhance the therapeutic index of an efficacious but toxic antineoplasic agent (doxorubicin). Complete tumor remission was drastically improved and toxicity was reduced by using lower dosages. Even though release mechanism described in [24] proved to be successful and complete tumor remission can be achieved as shown in [25], magnetic drug targeting is still limited by the use of external magnets as explained in [26].

IV. Discussion

Magnetic therapeutical applications (MTA) allow the quantity and spatial distribution of the treated area to be controlled. Nevertheless, the use of external magnets restricts the targeting possibilities to organs that are close to the skin and do not allows precise control over the spread of the magnetic microparticles. These drawbacks are addressed by the use of MRP that could allow the positioning of several magnetic beacons around the targeted area. These beacons would act as anchoring points for the microparticles (Fig.1). The method allows a much more precise and controlled manner to pinpoint the application target.

Dependent on the nature of the microparticles used several combinations of localized treatments can be envisioned. For example, once the microparticles are confined by the magnetic beacons, the release of an active principle can be achieved either by diffusion, bioerosion or, if it is thermally triggered, by inducing magnetic hyperthermia using an AC-magnetic field generated by the MRI system. If the magnetic beacons are made of a hard magnetic material, sustained release or repeated treatments could be achieved even when the patient is outside of the MRI system. As a matter of fact, hard ferromagnetic beacons retain their magnetization and maintain attraction over the microparticles in a zero magnetic field. In the case of diffusion or bioerosion driven targeted release, drug can be delivered continuously. If the release relies on a pendant chain system, several drug releases could be performed by injecting a small amount of chemical hydrolysis agent repeatedly in the same catheter that was used to inject the beacons and microparticles. In the case of a pendant chain system that is not temperature dependent, AC-magnetic field hyperthermia and chemical hydrolysis drug release could be performed independently and at will until the beacons and magnetic particles are either removed from the body or biodegraded.

V. Conclusion

The applications of MRP are numerous even though this technique is still in its infancy. First generation passive

microdevices can be regarded as complementary MIS tools that could substantially increase classical endovascular treatment efficiency. In the case of tumor treatment, the possibility to allow concentration of chemotherapeutic agent for a sustained period of time or for repeated releases combined with hyperthermia and thermal embolization that could be triggered at will is a major improvement. Next generation MR-Sub prototypes will follow the tremendous evolution in micro/nano fabrication design techniques to become mature active microsystems that will open the whole human body to medical instruments.

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