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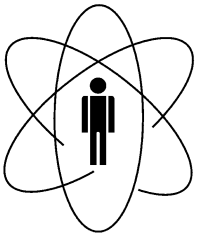

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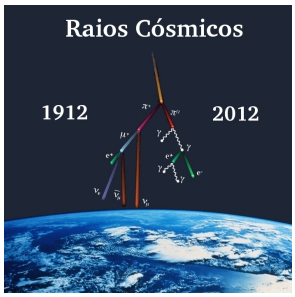

Ministério da
Ciência, Tecnologia e Inovação

MAGNETIC NANOPARTICLES-BASED THERMOTERAPIA FOR HYPERTROPHIC CARDIOMYOPATHY

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Alcohol septal ablation (ASA, TASH, *Sigwart* procedure) is a percutaneous, minimally-invasive treatment performed by an interventional cardiologist to relieve symptoms and improve functional status in severely symptomatic patients with hypertrophic cardiomyopathy (HCM) who meet strict clinical, anatomic and physiologic selection criteria [1]. Notably, mutations in two genes—MYH7 and MYBPC3 (encoding myosin-7 and cMyBPC, respectively)—account for up to three-quarters of all clinical cases of HCM in which the underlying mutation has been defined. Mutations in nonsarcomeric proteins, such as vinculin, can also result in HCM [2]. In carefully selected patients, when performed by an experienced interventional cardiologist, the procedure is successful in relieving symptoms in over 90% of patients. Hypertrophic cardiomyopathy is a condition of the heart muscle which grows abnormally thick, in the absence of a physiologic cause such as hypertension (high blood pressure) or aortic valve disease. In a subset of patients with hypertrophic obstructive cardiomyopathy, thickening of the heart muscle in a particular part of the interventricular septum causes obstruction to blood being ejected from the left ventricle [3]. Alcohol septal ablation is a technique designed to reduce the obstruction to blood being ejected from the heart; the technique creates a small controlled heart attack, killing the area of heart muscle responsible for the obstruction, and eventually causing it to become less thick [4].

Alcohol septal ablation is performed in the cardiac catheterization laboratory, and should only be performed by interventional cardiologists with specific training in the procedure. As such, it is only available in a few institutions. The technique is similar to coronary angioplasty, and utilizes similar equipment. Using wires and balloons to localize the septal artery feeding the diseased muscle, a small amount of absolute alcohol is infused into the artery to produce a small heart attack. Patients typically experience mild chest discomfort during the procedure, which takes approximately 30

minutes to complete. Analgesics and mild sedatives are administered as needed. Patients typically are maintained in the hospital for three to four days to monitor for any complications, including need for permanent pacemaker in 5-10% [5]. The problem of alcohol septal ablation method is that the alcohol can react in healthy areas of myocardium, damaging it irreversibly. In this work, we show a new method of septal ablation by hyperthermia using coating silica on iron oxide nanoparticles and magnetoliposomes. In this method, we use magnetic delivery systems based on the competition between forces exerted on the particles by blood compartment, and magnetic forces generated from the magnet, i.e., applied field. When the magnetic forces exceed the linear blood flow rates in arteries (10 $cm.s^{-1}$) or capillaries (0.05 $cm.s^{-1}$), the magnetic particles are retained at the target site and maybe internalized by the endothelial cells of the target tissue. For this application the use of nanoparticles favour the transport through the capillary systems of organs and tissues avoiding vessel embolism.

Magnetic particles ranging from the nanometer to micrometer scale are being used in an increasing number of medical applications [6]. Ferrous or ferric oxide is the main constituent of magnetic particles, although metals such as cobalt and nickel are used in other fields of application. Magnetic particles are attracted to high magnetic flux density; this feature is used for drug targeting and bioseparation including cell sorting. Currently, magnetic nanoparticles are attracting attention because of their potential use as contrast agents for magnetic resonance imaging (MRI) and heating mediators for cancer thermotherapy (hyperthermia)[7-8]. Magnetoliposomes consist of magnetic nanoparticles wrapped in a phospholipid bilayer (liposome). On the other hand, liposomes have structural and biokinetic advantages such as their ability to encapsulate therapeutic drugs or genes. The important properties of magnetic particles for inducing hyperthermia are nontoxicity, biocompatibility, injectability, high-level accumulation in the target and effective absorption of the energy of alternating magnetic field (AMF) [9]. Fig. 1 shows the thermotherapy for HCM (Schematic representation).

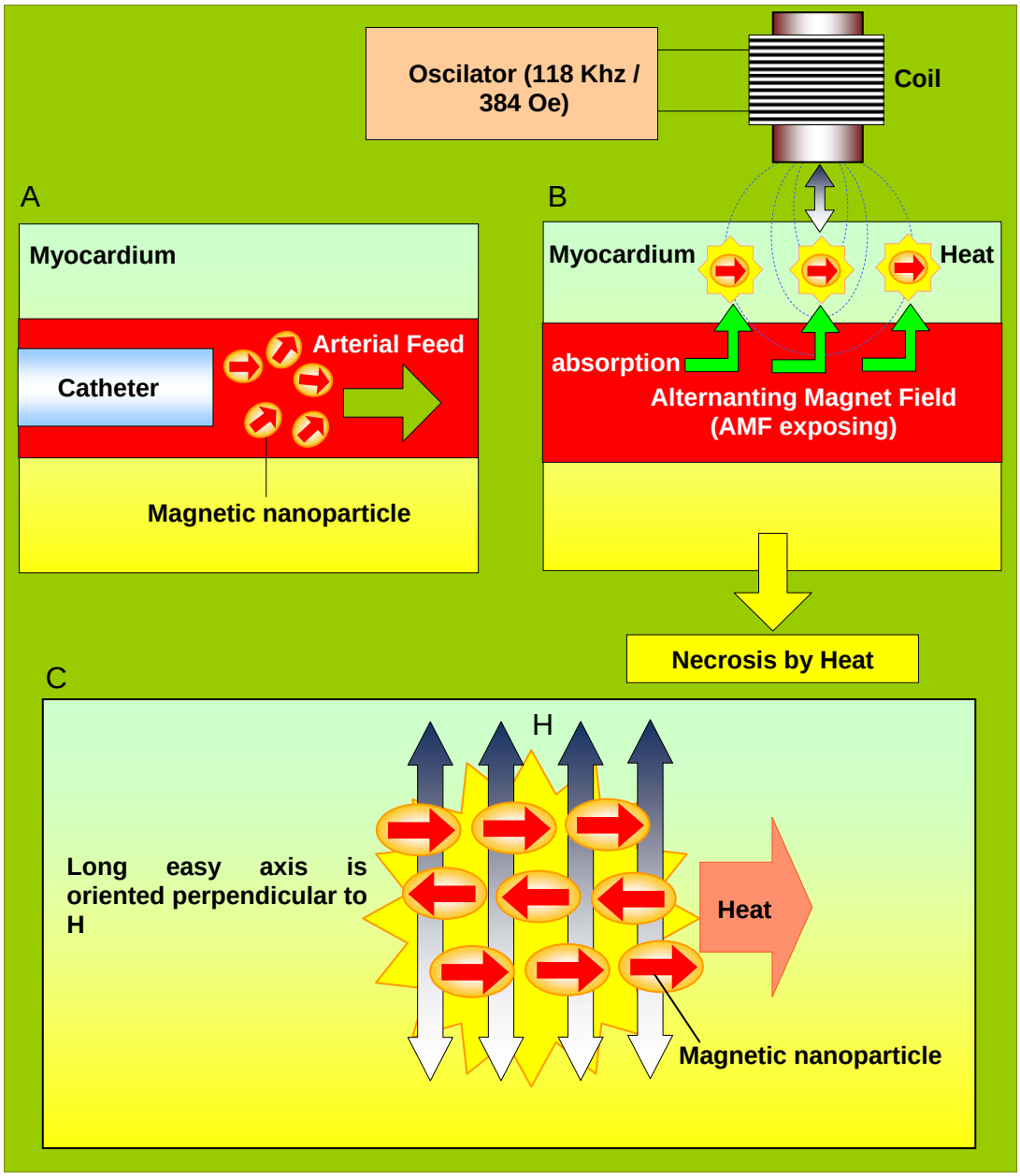

FIG. 1. Magnetic nanoparticles-based thermotherapy for hypertrophic cardiomyopathy: (**A**) A catheter is inserted into an arterial feed to heart and magnetic stands is positioned over the targed site. (**B**) The magnetic nanoparticles are retained at the target site and maybe internalized by the endothelial cells of the target tissue. An alternating magnetic field (AMF, 118 kHz and 384 Oe) is applied on endothelial cells of the target tissue. Temperature of the outer covering of the myocardium increases (~ 46 ^{o}C) producing necrosis by heat. (**C**) An oriented structure of magnetic nanoparticles in hyperthermia treatment. The schematic illustrations show ferromagnetic nanoparticles under irradiation with a high frequency magnetic field of weaker intensity than the anisotropic magnetic field, in which the nanoparticles align in planes perpendicular to the external magnetic field (H).

Coating silica (a biocompatible coating) on iron oxide particles can be difficult as its amorphous structure prohibits silica from forming a homogeneous layer on the surface of the iron oxide. It normally results in the formation of silica spherical particles on the iron oxide surface with size comparable to the iron oxide nanoparticles. Hence, the overall particle size and shape are hard to control without structural directing agents such as surfactants. In general, silica coating is carried out as the hydrolysis of tetraethyl orthosilicate (TEOS, also known as tetraethoxysilane) at a certain pH (8–10) or the neutralization of silic acid [10]. Tartaj et al. [11] have synthesized submicronic silica coated maghemite hollow and dense spheres with a high loading of magnetic material by aerosol pyrolysis. Silicacoated γ -Fe_2O_3 hollow spherical particles with an average size of 150 nm were prepared by theaerosol pyrolysis of methanol solutions containing iron ammonium citrate and tetraethoxysilane (TEOS) at a total salt concentration of 0.25M.

Thus, our method suggests that therapeutic magnetite nanoparticles are potentially effective tools for hyperthermic treatment of HCM, because in addition to the killing of cells by heat, the precision of treatment is a important factor. Magnetic nanoparticles can be used as a tool for hypertrophic cardiomyopathy diagnosis by magnetic resonance imaging (MRI) or for magnetoimpedance (MI) sensor. Hyperthermia can then be induced by alternating magnetic field exposure. Thus, magnetic nanoparticles can be used for HCM treatment at the same time as diagnosis.

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