31st Annual International Conference of the IEEE EMBS
Minneapolis, Minnesota, USA, September 2-6, 2009

Respiration Triggered Magnetic Drug Targeting in the Lungs

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Abstract— **Lung cancer kills per year 1.3 million people worldwide. It is the most fatal cancer type as far as men are concerned and the second deadliest for women.**

One of the recent technologies to treat carcinomas in the lungs consists in delivering drugs through the pulmonary pathways directly to the tumor cells over actively loaded superparamagnetic nanoparticles that are encapsulated in aerosols and guided by external magnetic fields.

However, first implementations of this technique assumed a continuous application of the magnetic field all through the inspiration and expiration phases of the artificial respiratory act that supplies the patient.

We observed that applying the field this way forced the magnetic aerosols to sediment at regions far from the target, mainly in the trachea and main bronchioles, because of the force inducing magnetic field gradients that are present over the whole field application area.

We developed an approach to avoid this effect by punctually generating the aerosol cloud exactly at the beginning of the inspiration phase, which would propel the particles to the deepest parts of the lung and therefore to the targeted cells as well, and by synchronizing the magnetic field activation with the breathing process. Our developed system analyzes the relevant respiration parameters such as pressure and flow and detects the end of the inspiration phase to trigger the magnet exactly at that point in time, when particles have reached the deepest alveoli, including the targeted zones, and do not experience forces due to the streaming any more.

The magnetic field is then held on during the expiration phase to assure the retention of the aerosols at the targeted sites, which increases the efficiency and focality of the treatment. This way, only target cells are subjected to the deposition of the drug carrying aerosols, while the other healthy regions of the lungs remain unaltered by side effects.

Keywords— **magnetic drug targeting, superparamagnetic nanoparticles, aerosols, deposition, breath triggering.**

I. Introduction

Aerosol application is considered to be established since many years in the medical treatment of many diseases such as asthma, COPD or mucoviscidose (i.e. cystic fibrosis) [1], [2], and this therapy method is nowadays intensively studied and researched for tumour healing [3], [4].

Due to the strong dependence on the respiration flow, the exact reproduction of a given drug distribution in the lungs remains a principal issue [5].

The idea of lung drug targeting came therefore as an application of the experiences gained from magnetic drug targeting in the blood vessels to assure a local treatment of pulmonary diseases [6]. This new technique is considered to have a great potential, especially for cancer therapy.

Hereby, a drug solution is nebulised and mixed with biocompatibly coated magnetic nanoparticles to form aerosol droplets that can become magnetized and therefore be steered through external magnetic sources, obeying to the following rule:

$$\vec{F} = (\vec{\mu}\nabla)\,\vec{B} \qquad (1)$$

Where μ is the magnetic moment of the aerosol and B is the flux density of the magnetic field.

Thus, the presence of a field gradient is decisive for the magnetic force F. But the application of this gradient is still dependent on many other factors.

II. Materials and Methods

A. Necessity of a time dependent magnet application

The classical approach in lung drug targeting consists in a continuous inhaling of magnetic aerosols by a patient, whereas a permanent magnetic field applied at a given location of the body increases the concentration of the deposited active agents in that area. But this way of applying a time continuous force presents many drawbacks and limitations.

A permanent field is actually inappropriate to dynamically control the inhaled aerosol flow. That is already given by the physical laws of classical mechanics and electrodynamics that automatically imply a local functional relation between the force giving source and the characteristic parameters of the respiration on which it acts.

Therefore, velocity, pressure, compressibility, density and viscosity of the medium, as well as the velocity of the particles relatively to the air should be considered as time

variable and taken into account in the conception of the whole system.

To dynamically react on these parameters, the magnet must show a very fine and accurate time dependency.

Moreover, the permanently activated magnetic field creates field gradients that cause particles to sediment far from the targeted cells in the interior of the lungs, namely in the trachea and in the bronchioles. In fact, even a slight deviation on their way to the target area would lead the particles to get in contact with the mucus layer on the inner walls of the respiratory pathways. This layer is a trap for foreign bodies entering the lungs and will automatically eliminate any caught element not intended to be in the inhalation volume.

Therefore, applying the magnetic field at the end of the inspiration phase will assure avoiding unwanted particle deposition far from the tumour region, as the injected aerosols will, undisturbed, reach the targeted cells, then be attracted by the magnet. The field is then kept on to assure the retention of the particles and their concentration in the tumour region. The figure below shows the conceived application plan.

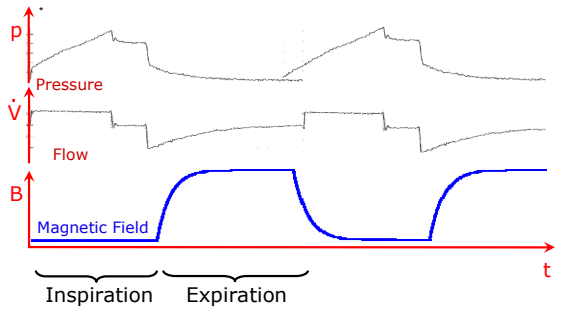

Fig. 1 Time schedule for magnet application

B. Necessity of a punctual aerosol injection

A further aspect that has to be considered in this new therapy method are the anatomy and physiology of the lungs. These have a tree structure in which the number of bifurcations increases almost exponentially with the reached depth [7]. The peripheral parts though show a high concentration of bronchioles and alveoli [8]. In order to assure drug application at any given area in the lungs, the system should allow the aerosols to reach the deepest levels of the bronchial tree.

In actual research works [9], [10], it has been experimentally validated, that the time accurate injection of particles has a big impact on the reachable depth in the bronchial tree. As a matter of fact, only the front of the inhaled air volume is most likely to reach the deepest alveoli, so that it is recommendable that it includes the aerosol cloud. Particles that are injected later will mostly remain in the upper respiratory ways, in worst cases even in the dead volume of the lungs.

Therefore, the system conceived in this work generates the aerosol cloud exactly after the end of the expiration phase, to insure its transport by the front of the next inhaled air volume.

C. Technical realization

The developed system includes, as shown in Fig. 2, three interfaces to the used experimental setup.

The control unit provides the magnet and the aerosol nebulizer with the needed signals that are synchronous with the breathing cycle. This can be assured by sensors that survey the respiration.

In a first phase of the experiments, the breath of the patient will be dictated by an artificial respiration system, so that all needed parameters will be directly delivered by it.

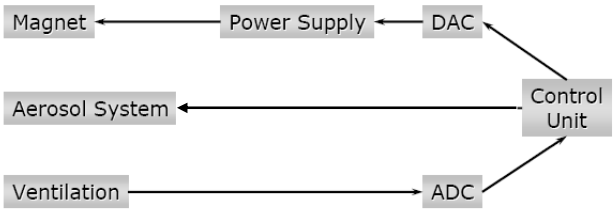

Fig. 2 Overview of the control system

The magnet control was performed using the DC power supply unit DLM-E 4kW (Elgar; San Diego).

The output of this unit can be continuously varied through an analog-input. The reaction time is 50 ms, which is irrelevant for our application and makes the system an almost real time solution.

The power supply unit has been electronically set to the remote control mode over TTL technology. This way, we could control all output values through digital and analog signals.

The delivered DC current, ranging from 0 A to 75 A, has then been matched with an input voltage interval of [0 V, 5 V]. The control of the output voltage has also been implemented the same way.

The control of the whole system is assured by the laboratory interface system USB 6009 (National Instruments; Austin, Texas). It permits tuning the output current over a DA converter with a 12 bit resolution. This leads to an accurate step of 18 mA in the magnet current.

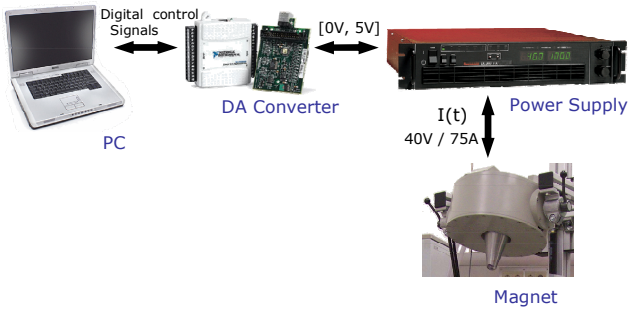

Fig. 3 Control of magnet current over DA converter

As the ventilation system determines the breathing pattern of the patient, the surveillance sensors attached to it would detect the end of the expiration phase through pressure and flow data and send an actuation signal to the inline nebulizer ("eflow"; PARI Pharma; Munich) to trigger the generating of the aerosol cloud.

Fig. 4 shows a signal flow diagram between all the components of the developed system.

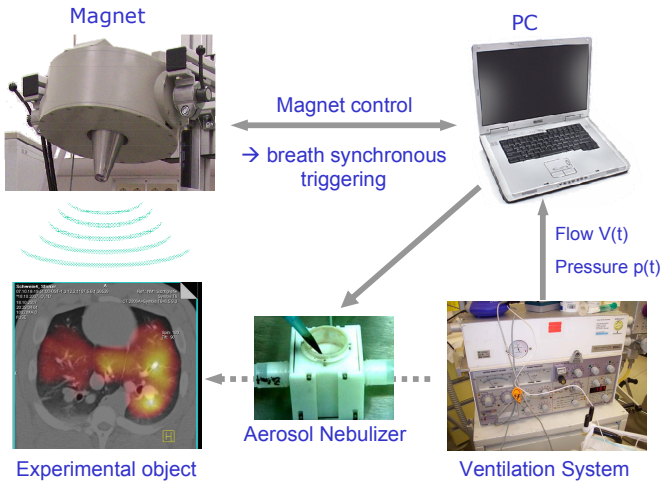

Fig. 4 Signal flow diagram of the breath synchronous control system

III. RESULTS

To insure a breath synchronous application of the magnet in lung drug targeting, a system that triggers the magnet as well as the aerosol nebulizer has been developed. It uses periodic curves continuously sent to the interface by embedded sensors to detect the different phases of the breathing pattern and control the aerosol injection and the magnet activation correspondingly.

The system can therefore perform the delivery of the aerosols to the deepest areas of the lungs, namely the alveoli, which makes it usable for diseases affecting these regions too.

The system has been successfully tested on a phantom model and assures its functions even in the presence of noise or other transient disturbances. It is suited for direct reception of trigger signals from ventilation systems and can also be used for spontaneous patient respiration, through the included sensing circuits.

At last, the conceived unit assures a very high time and amplitude precision with irrelevant reaction delays of 50 ms and output current steps of 18 mA.

The developed system is now being used in experiments on animals, mainly pigs, and results will soon be reported.

IV. DISCUSSION

Breath synchronization is one of the important issues of lung drug targeting as a therapy method for pulmonary diseases, especially lung carcinomas. Though this difficulty can be solved by accessible technical solutions, there are still other issues that can not be addressed in the same way. In fact the aerosol size, usually over 2 µm, the involved intubation techniques and the necessity of radioactive marking of the nanoparticles for visualization purposes are other serious limitations of this new method that need to be addressed and intensively studied before moving to an eventual human application. Nevertheless, lung drug targeting remains a promising approach, for it greatly contributes to the optimization of chemotherapy by localizing drug delivery and avoiding damaging healthy tissue by systemic agent application.

ACKNOWLEDGMENT

We want to thank the company PARI for providing us with their nebulizer system “eflow”.

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