Combined optical imaging and ultrasound focusing for hand-held, non-invasive cleaning of implanted cerebrospinal fluid shunting devices in patients of hydrocephalus: initial design and proof-of-concept (Project FUSCLEAN).

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ABSTRACT
This project addresses the prevention and management of the most common complication in neurosurgical patients of hydrocephalus through the design and development of a proof of concept of a hand-held device for preventive, non-invasive, easy-to-implement, and cost-effective acoustic cleaning of implanted shunts. It is based on optical and thermal image-guided ultrasound focusing for removal of accumulated debris, clearing obstructions and improving cerebrospinal fluid flow through implanted catheters and valves. Initial prototype was optimized using computational simulations on 3D models. Experimental tests showed how focused ultrasound effectively detached debris from the walls of conduits in laboratory environment.

Keywords: Hydrocephalus, cerebrospinal fluid, focused ultrasound; acoustic cleaning, optical imaging, thermal imaging, applied physics, neurosurgery, personalized medicine.

1. INTRODUCTION

Hydrocephalus is a relevant neurosurgical pathology [1], [2], both in children and in the aging population. It comprises a wide set of ailments associated with alterations of the cerebrospinal fluid (CSF) hydrodynamics and the biomechanical properties of the nervous central system structures. In many cases, these pathologies are characterized by an enlargement of the lateral ventricles of the brain (due to accumulation of fluid) and by the physiological and cognitive consequences of compression of adjacent structures, damages in surrounding tissue and other effects of increased intracranial pressure.

Treatment mostly relies on implanting subcutaneous shunt systems to drain CSF from brain ventricles to a distal cavity. However, complications are frequent and the most common are obstructions of flow through implanted catheters and valves (**Fig. 1**). They are difficult to anticipate and require immediate surgical removal because of risks of serious neurological damage and even death. Such complications have a deep social impact in the quality of life of patients, their families and caregivers, and a high economic cost. Early diagnosis and treatment of an obstructed catheter or shunt malfunction remains as a defying area and there is no preventive technology or protocol to avoid them.

This project presents the design and development of a proof of concept of a hand-held device for the application of image-guided, focused ultrasound for preventive, non-invasive, easy-to-implement, and cost-effective acoustic cleaning of implanted shunts in patients of hydrocephalus.

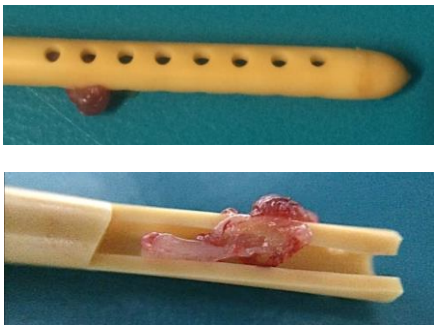

Fig. 1. Top: Explanted catheter (outer diameter of 2.7 mm) showing external deposit of about 2 mm in length. It also obstructs one of the draining holes of the tip. Bottom: Detail of the (sliced) tip showing accumulated debris (inside) that blocks CSF flow. Inner length of the deposit is about 10 mm.

Proposed approach hypothesized that mechanical effects of cavitation and acoustic streaming produced by focusing ultrasound beams on a small "sonication volume" could be used for removal of accumulated debris, clearing obstructions and improving CSF flow through implanted catheters and valves. This is a novel application of the underlying ideas of the acoustic (ultrasonic and megasonic) cleaners that are commonly used in many industrial applications to remove contaminants without damaging the surfaces of

substrates. This approach is based on physical, optical, and neurosurgical tools that already exist and are commonly used in their corresponding applications. The technical approach has been validated both through simulations and experiments in a physical laboratory environment.

2. STATE OF THE ART

Certain types of hydrocephalus are relatively common both in children and in the aging population and have a deep impact in the quality of life of patients, their families and caregivers. In adults, the most common is the idiopathic normal-pressure form [3], [4], [5]. It has an estimated incidence range of 1.8-2.2 cases/100.000 adult individuals (0.41% of the population over 65 years-old). In children, prevalence of congenital and paediatric hydrocephalus ranges to 0.5-0.8 cases/1.000 new-borns. In the majority of cases (70%), treatment usually requires neurosurgical placement of a shunt to drain CSF from brain ventricles (proximal segment, 14-20 cm), through a small hole in the skull, to a valve under the skin (cranial vault) and an outflow catheter (up to 1 m) to a distal cavity (peritoneal, heart, pleura).

Complications of shunting are frequent -and their clinical consequences define a life-threatening medical condition-. They range to a 50% failure rate 2 years after implantation in paediatric patients or to 84.5% of patients requiring 1 or more shunt revisions and 4.7% requiring 10 or more in a 20-year follow-up. The most common complication is occlusion (particularly of proximal catheter, 27%) due to build-up of excess proteins, clots and infection. However, symptoms of occlusion are initially similar to common diseases and early diagnosis and treatment of an obstructed catheter or shunt malfunction is a defying area.

There is no current preventive technology or protocol to avoid the complications of shunting. When a patient experiments a CSF drainage blockage, standard (emergency) treatment is based on the neurosurgical replacement of the shunting system.

The proposed approach should not be confused with the existing technology of “focused ultrasound surgery”. This is based on the concentration of ultrasound energy to produce an intended temperature increase and requires large, heavy and costly surgical and medical imaging equipment.

3. BREAKTHROUGH CHARACTER OF THE PROJECT

This project presents an innovative approach to a relevant, unsolved problem in neurosurgery and healthcare: the prevention and management of a very common complication –shunt obstruction– in patients of hydrocephalus along their life. It proposes a non-invasive, easy-to-implement, and cost-effective method and technology for preventive or therapeutic cleaning of implanted devices (valves and catheters). If operational, it will imply a significant change in the management of this pathology, with a substantial impact in the quality of life of the patients and a strong reduction of costs.

This project is truly multidisciplinary, combining applied physics and optics, 3D modelling and computational simulation, engineering and neurosurgery. It combines three existing technologies (optical and thermal imaging and focused ultrasound) in one hand-held device to allow for the preventive –even potentially therapeutic– “acoustic cleaning” of the implanted shunt system (valve and catheter). The application (sonication) parameters can be adjusted to the specific features and clinical status of individual patients and their shunting systems, in the current paradigm of Personalized Medicine. The proposed combination of commonly available components allows a socially responsible design of a cost-effective technology, definitely aligned with the European Union efforts to promote access to value-based healthcare.

The proposed solution would allow for the establishment of a new clinical, innocuous, procedure that could be performed on a routine basis in any patient to reduce the number and frequency of shunt revisions in (emergency) neurosurgical procedures. A scheduled “cleaning” treatment could be particularly useful in the first months after shunt placement, when risks of obstruction are considerably higher. This procedure could also be adapted to remove clots or other products in shunts of patients presented at emergency department with acute malfunction.

In addition, proposed technology could be extended for similar cleaning and maintenance protocols of other types of implanted devices (catheters, valves, pumps) in different clinical areas such as systems for pain control and medication delivery or fluid drainage in neurosurgery and neurology, oncology (chemotherapy), cardiology, lung and possible others.

4. PROJECT RESULTS

The underlying hypotheses have been validated and an initial prototype has been developed. The theoretical analysis of the problem has been completed and a thorough set of 3D computational simulations has been carried out using the finite element method. They have been successfully validated in a physical laboratory environment. Experiments performed include the removal of debris attached to the inner surface of

cylindrical conduits using focused ultrasound beams. The achieved Technology Readiness Level (TRL) is TRL = 3-4 and patent applications have been filed.

System design comprised 3D computational models with several ultrasound transducers and a detailed mesh structure of the biological layers (skin, skull, white and grey matter of the brain) and shunt systems (valve and catheters) under variable parameters, including scar tissue around the valve [6] [7].

Ultrasound focusing is achieved by the overlapping of individual beams emitted by transducers with a given phase pattern [8]. The emitters were modelled as dipolar sources. Many different configurations and parameters [9] were tested to achieve the desired level of ultrasound fields and power density at the location of the implanted catheters and valve (sonication volume) while preserving the environment of increased temperature. **Fig. 2** shows a detailed view of the 3D mesh model of the geometrical setup. It can be observed how the size and features of the mesh differ according to the required spatial resolution.

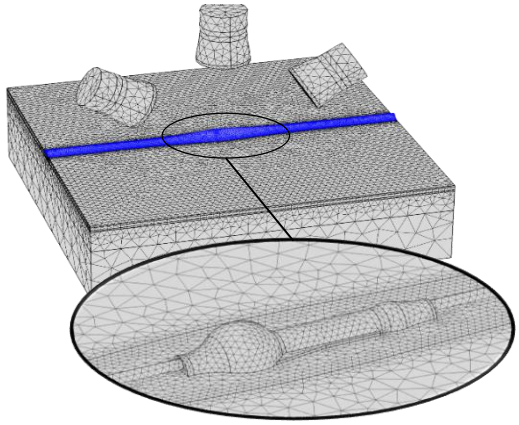

Fig. 2. 3D model of a hydrocephalus shunt (valve and catheters) under the skin and three transducers in a plane.

Acoustic fields from simulations are represented in **Fig. 3**. Higher levels of energy are obtained at the location of the valve without entering the brain region under the skull. Ranges of ultrasonic (20-350 kHz) and megasonic (400 kHz to 2 MHz) frequencies were explored.

Experimental tests were developed in the physical laboratory to compare with numerical 3D simulations. Ultrasound transducers were arranged in the same geometrical setup and their operation was controlled by a specific function generator.

Models of transparent plastic conduits of different diameters were employed to visualize deposits and debris. They were filled with tap water, blue dye and particulate materials (graphite powder). Highly viscous fluid was simulated by adding egg white to the water. This is a useful model with a very high concentration of proteins, conceptually similar to cerebrospinal fluid of patients with conditions –severe infections, haemorrhages– seriously affecting their CSF flow.

Deposits adhered to the (inner) walls of the conduits were reproduced by drying egg white inside them for several days. When ultrasound beams were activated, image and video recordings showed the vibration of suspended matter and how deposits were removed from the walls and graphite particles diffused, and would therefore be washed away with the physiological fluid flow (**Fig. 4**).

During the concentration of ultrasound beams it is important to monitor the temperature of the skin [10] [11]. Image guidance and monitoring is achieved by the combination of optical (visible and thermal infrared) imaging of the shunt and catheters, located only a few millimetres under the skin (over the skull bone).

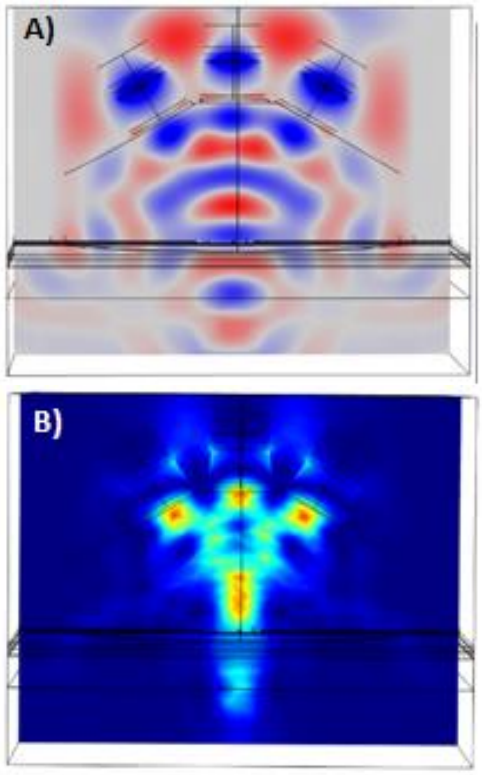

Fig. 3. Numerical results of a 3D computer simulation of the ultrasound field generated by the combination of three transducers emitting at 39 kHz in the middle plane. A) Acoustic pressure field (Pa). B) Acoustic power density (W/m^2). Higher values are depicted in reddish tones.

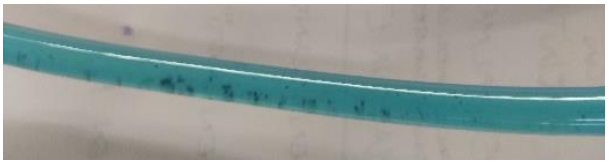

Fig. 4. Graphite particles vibrating inside a test tube. Inner diameter is 8.0 mm to allow for easier visualization.

However, under the exceptional circumstances of the COVID-19 pandemic, both the computer simulations and the experimental work had to be stopped at the beginning of March 2020, when the State of Alarm and a nation-wide lockdown was declared by the Spanish Government. The closure of the university facilities was extended until June 2020 causing a very significant accumulated delay. There were additional delays in the acquisition of some of the devices due to disruptions in logistics during those months. The intended tests in human phantoms and cadaveric model and the optimization of the prototype could not be carried out. They were planned within the framework of the Practical Laboratory of Anatomy of the College of Medicine of the University and these activities were cancelled due to the pandemic.

5. FUTURE PROJECT VISION

5.1. Technology Scaling

The results of this project present the intended development of a proof-of-concept and the design of an early prototype of a technological device. Part of the programmed tests and optimization stages could not be carried out under the exceptional circumstances of the COVID-19 pandemic. The use of artificial intelligence tools was planned in the last stage to optimize the design and for the development of a user interface for personalized determination of the sonication parameters (energy, time cycles) for individual patients.

The existing prototype must be further developed and engineered into an operational device suitable for extensive testing and certification. Its relative simplicity and the availability of the required components are positively relevant factors for the potential development of a commercial product.

5.2. Project Synergies and Outreach

FUSCLEAN current consortium is truly multidisciplinary and complementary, with close collaboration between the scientific, technical and clinical teams. However, the support of industrial and funding partners is required for the engineering process to take the device to TRL 5-7.

Regarding the capability of dissemination of results, preliminary communication actions had a warm welcome, as the issue addressed by FUSCLEAN has a deep, clear social impact both for children and for the elderly population. As further results be achieved in the coming months, the intensity of communication actions, supported by the participant Universidad de Sevilla, University Hospital “Virgen del Rocío” and Technological Corporation of Andalusia will also increase significantly.

5.3. Technology application and demonstration cases

At any neurosurgical healthcare institution, a great proportion of resources is devoted to shunt revision and replacement. The participant University Hospital “Virgen del Rocío” (UHVR) is a tertiary reference centre in Seville, Spain, covering about 2.200.000 inhabitants that treats about 200 (100 adult, 100 paediatric) patients of hydrocephalus per year. The complication rate agrees with that in literature, about 5% per year and about 50% during the lifetime of the shunt implant, corresponding to 30-40 adult cases and 30-40 paediatric cases of complications per year. The cost of a standard implantable shunt is about 3.000 €. Each new case costs 4.000-5.000 € and the treatment of (only) an obstruction is about 10.000 € and a valve infection about 15.000 €. Thus, the average cost of the most common complications (requiring shunt replacement and treatment of infection) is in the range of 15.000-25.000 €/case. Then, the total average cost of complications in hydrocephalus is in the range of 400.000-800.000 €/year in pediatric cases (similar in adult) and a total of 800.000-1.600.000 €/year in this institution.

Only in Spain, considering 40 million of habitants, the total impact of complications of hydrocephalus can be estimated as 20 times the data of UHVR yielding a total cost in the range of 16-32 million euros per year.

5.4. Technology commercialization

The first step at this point is the definition of a suitable intellectual property protection strategy. It is remarkable that the authors’ team has obtained some specific funding for this issue and to extend the technology to other areas.

The exploitation strategy is also being developed and different options are being considered. The initial approach would be a research agreement with an industrial partner, experienced in medical instrumentation and devices, and funding support. This collaboration would provide the necessary resources for the engineering, testing, industrialization and certification process, and would also facilitate the future commercialization of the device.

Initial contacts with entities interested in imaging and ultrasound technologies in neuroscience have been made but the unexpected situation given by the COVID-19 pandemic has delayed further advances. European industry is advancing in its positioning in the field of ultrasound technology and, particularly, in the healthcare and medical sectors, and our development –in neurosurgery– is clearly aligned with this strategy.

5.5. Envisioned risks

The design of technology for medical applications involves particularly demanding challenges. In our proposal it is required to develop a prototype suitable for initial testing in cadaveric models which can later be employed in real patients. The support of a highly experienced clinical team is essential to conduct proper protocols and procedures. In the proposed application of ultrasound focusing it is particularly important to avoid overheating the tissues (mainly skin) around the shunt. Specific 3D modelling and simulations have been performed, and –as envisioned– infrared thermal imaging is a very useful tool for monitoring the sonicated area in real time. Additional cooling elements can also be included after testing.

The difficulties associated to the certification of medical instruments also define relevant concerns for the future commercialization of the results of this project. This issue can be effectively tackled by industrial partners capable of supporting researchers and boosting the project.

Obviously, the current situation given by the COVID-19 pandemic presents relevant risks regarding the availability of clinical resources to perform validation actions and further trials.

5.6. Liaison with Student Teams and Socio-Economic Study

The FUSCLEAN project is led by the Universidad de Sevilla, and students were involved since the beginning. One Master of Engineering Thesis was carried out [12] in this project.

As related to the socioeconomic study, the authors have already performed an initial feasibility analysis, including potential impact in terms of cost savings and improvement of health and wellbeing. The team has already published studies about the economic impact of new medical treatments [13] and their experience and deep knowledge about the potential application and the benefits expected in different scenarios is contributed to the ATTRACT Project.

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