Publishable Summary for 17IND01 MIMAS
Procedures allowing medical implant manufacturers to demonstrate compliance with MRI safety regulations

Overview

Medical implants represent a multi-billion market across Europe. A majority of the 50 million EU citizens carrying a medical implant will likely need a magnetic resonance imaging (MRI) scan during the lifetime of their device. However, the powerful electromagnetic fields of MRI systems in these cases represent a unique hazard for patient safety. Therefore, it is vital for both patient wellbeing and the success of a medical implant on the market that implant manufacturers can demonstrate safety compliance for their device in an MRI environment. This project will improve the competitiveness of European implant manufacturers by providing innovative, metrologically sound and legally safe methods to demonstrate the compatibility of their products with MRI safety regulations.

Need

With more than 30 million MRI scans per year across European countries, safety for patients with medical implants is an ongoing concern with some carriers having suffered fatal accidents due to the interference of their device with the electromagnetic fields (EMF) from the MRI scanner. MRI compatibility of an implant thus represents a key factor for the competitiveness of a manufacturer. This was exemplified in 2011 when Medtronic Inc. achieved the first ever MRI approval for a cardiac pacemaker and within a few years virtually all non-compatible devices disappeared from the market. However, the currently applied procedures to demonstrate MRI compatibility are either outdated (ASTM F2182) or incomplete (ISO/IEC TS10974). Additionally, large producers of high-end active implantable medical devices are facing technological challenges to demonstrate MRI compatibility, and SMEs manufacturing passive medical implants are overburdened by the necessity to demonstrate MRI safety for each new size and shape of a particular device, therefore limiting their innovation potential.

The established state of the art technique is currently the numerical modelling of field distributions in human subjects. However, even though this technique has been used to include the presence of metallic implants, an experimental verification of the results was limited as mostly generic or simplified implants with non-detailed features were modelled. Parallel-transmit (pTx) radiofrequency systems can be used to steer, within certain limits, the electromagnetic field in MRI scanners as well as temperature distributions in and around the implant. The use of pTx for risk mitigation has an enormous potential to ensure safety for a wide range of different implants and boundary conditions. These systems can be combined with sensor-equipped implants to provide real-time feedback. However, this concept is still in an early stage of development and further work is needed to prove its use.

The EMRP project ‘HLT06 MRI safety’ discovered that heating of metallic implants due to switched magnetic-field gradients is an underestimated hazard in MRI. As some normative documents ignore this effect completely, whilst others mention the possibility of such effects only in the context of protecting the device rather than the patient, it is now essential that the risks are subjected to further investigation.

Objectives

To enable manufacturers of medical implants to demonstrate that patients carrying their products can safely undergo an MRI scan, the project aims to achieve the following objectives:

1. To develop **anatomical models of human subjects with realistic medical implants** and millimetre resolution. The models to be sufficiently detailed for use with *in silico* medicine concepts, with resolution to be determined according to image analysis needs.

2. To dev5elop validated computational tools for the **numerical simulation of electromagnetic fields (EMF) and temperature distributions** in a virtual human subject **during MRI exposure**. The computational tools should be able to process high-resolution anatomical models.

3. To develop validated methods and sensor-equipped reference implants for quantifying real-time implant-induced hazards during MRI exposure. This should include an assessment of parallel transmit (pTx) radiofrequency (RF) systems in MRI with real-time feedback and the **development of appropriate mitigation strategies**.

4. To investigate numerically and experimentally the hazards associated with **the interaction between bulk metallic implants and switched magnetic fields** in the kilohertz regime. In addition, to develop a reference set-up for testing metallic implant heating, using switched magnetic-field gradients of a few mT/m with a target gradient uncertainty below 5 %.

5. To develop and apply a **suitable statistical method to demonstrate MRI compliance** for small (< 10 cm) orthopaedic implants without extensive testing or numerical modelling, by determining an upper limit for the hazard associated with the new implant by comparison with a similar surrogate implant, which has already been fully assessed, thus enabling small manufacturers of a large variety of similar small metallic implants to dramatically reduce their costs for compliance demonstration.

6. To **interact closely with manufacturers of implants, MRI and test equipment and with standards developing organisations** (e.g. ISO/TS 10974, IEC TC/SC 62B and ASTM Subcommittee F04.15 on Material Test Methods) to align the project and facilitate the take up of the technology and measurement infrastructure developed in the project.

Progress beyond the state of the art

Safety testing of metallic implants for MRI is today largely based on unreliable phantom measurements. The project will improve this unsatisfactory state of the art by applying more meaningful numerical modelling of realistic virtual models. High precision numerical models will be developed and subsequently used as an input to electromagnetic field (EMF) simulations. While the utilisation of EMF modelling in this context is becoming more and more accepted as the adequate approach to the problem in the scientific community, it has still not fully arrived at the level of small manufacturers and test houses. Still unique to this project is the use of calibrated sensor measurements to validate those simulation results with metrological rigour.

The project will go even further by exploring technical means to actively mitigate metallic-implant related hazards in MRI. This will be achieved by steering the RF electric field (E-field) away from the implant by using pTx technology, an approach with a high potential for ensuring safety for a wide range of implants and scan conditions. In contrast to some recently published work, where this E-field steering approach has been pursued using the regular RF transmit coil (“body coil”) driven as a two-channel coil, the present project aims to exploit the much larger parameter space of true parallel transmission with at least eight independent channels.

Compared to RF heating, the potential heating of an implant by the switched gradient fields of an MRI scanner is a largely unexplored field. While preliminary results convincingly demonstrated the existence of the problem, this project will be the first ever to systematically investigate this issue. Up to now, this young field is still driven by the work from the project consortium.

Finally, a procedure to demonstrate MRI safety compliance will be developed allowing the manufacturers of small implants, e.g. screws, clips, or fixation devices, to reduce their costs by simplified safety assessments. Instead of performing numerical simulations and heating experiments for each and every new item, as it is the present state of the art, simple scaling laws can be applied to infer a valid safety assessment for their new product from previous, extensive investigations of similar devices.

Results

Objective 1

The project is developing virtual models of human subjects carrying a metallic implant. For the first time, precision planning tools from a virtual surgery will be applied to position the implants with sub-mm accuracy.

Data on main orthopaedic implants, one-dimensional implants and small stand-alone implants has been sourced and analysed. Implant types, implant materials, most relevant locations in the body and human types have been defined. Implant samples for experimental validation have been collected and for certain orthopaedic implants CAD models for virtual surgery could be obtained from manufacturers. CAD models of

small implants were created by uniting data from catalogues with measurements made using a combination of micro-scale CMM and optical scanning probes. The geometric tools within the simulation software Sim4Life were used to manipulate the virtual implants to ensure that they reflected the real-world usage of the devices.

Objective 2

A large selection of different human body types, implant positions and RF transmit coils was investigated via validated computational tools developed by ZMT with the IT'IS Foundation, in particular IMAnalytics with MRIxViP and BCLib, which were qualified by the FDA as part of the Medical Device Development Tool (MDDT) program. Thus, general conclusions are being derived from a systematic exploration of the parameter space for implant related RF hazards in MRI. The project output will underpin the ambitious concepts of the new ISO/TS 10974 standard with specific and validated procedures and thus contribute to advancing this document from its present state (a *Technical Specification)* to a full standard.

Existing methods to assess MRI safety of metallic implants have been adjusted, enhanced, and tailored for the specific needs of this project. The joint effort in identifying and categorising relevant medical implants allows all relevant safety assessments at and beyond the state of the art to be performed. Methods for simplified and accurate estimations have been developed, including an iso-electric exposure scenario within tissues of different relative permittivity (e.g. water-like, fatty, bone) and on their interface (e.g. orthopaedic implants on the bone-muscle interface).

To complement the verified solvers and validated measurements, a general and comprehensive uncertainty budget of the ISO 10974 Tier 3 evaluation of RF-heating of elongated medical implants, compliant with the GUM, has been developed. Predictions with meaningful confidence intervals can now be made and validation success or failure can be defined.

Objective 3

A safety concept to control and mitigate RF heating of metallic implants during an MRI scan is being developed. The central idea is to combine the information from ex-ante simulations and in situ sensor measurements to assess and quantify the momentary safety hazard for the patient. A new RF setting for the MRI scanner is then calculated ensuring that implant heating is reduced to an acceptable level. If the scanner is parallel transmit (pTx) capable, an optimisation algorithm is used to find the setting which combines patient safety with the best possible image quality.

In the next step, a simulation approach was developed to relate *steady-state* temperature at the implant tip, i.e. the true but not directly accessible hazard parameter, to different surrogate parameters that can be measured by sensors. Various sensor types were investigated, and it was found that time-averaged *E*-field (E_{rms}) and point SAR (without spatial averaging) are the most suitable as sensor-measurable safety surrogates. The approach allows to actually calibrate the surrogate signals in terms of the true hazard parameters. The sensor can thus be used to monitor compliance with established safety limits in real time which gives implant manufacturers the incentive to develop such sensor-equipped devices.

A procedure was subsequently developed and tested, using pTx to optimise the distribution of the RF *B*-field, determining the image quality, while keeping the maximum tip-SAR below a predefined limit. Compared to the standard method used in most clinical scanners today, the optimised approach produces 2.5 times higher RF B-field without any compromise in tip-SAR or image homogeneity. This is significant progress underlining the power of the pTx approach to mitigate implant-related risks in MRI.

For a systematic exploration of this approach, a comprehensive 'Parallel Transmission Implant Safety Testbed' was developed, a compact setup allowing to investigate different sensor feedback methods, perform validation measurements and assess the safety of a variety of implants for a wide range of MR settings (from 1.5 T to 7 T).

Objective 4

For a long time, the possible heating of an implant by the switched gradient fields in MRI was overlooked as a safety issue. For a systematic investigation of this problem this research project combines modelling results with validating measurements. Real-life implants, e.g. hip prostheses, are being investigated in a clinical MRI scanner under real-life imaging conditions, but simultaneously a test stand has been built and is being utilised for systematic experiments in a precisely controlled environment.

A wide database containing the magnetic field distributions from different gradient-coil designs has been built. Seven gradient designs were considered, adopted for different types of MRI scanners, ranging from

conventional clinical scanners to special-purpose designs. This database has been used to select the potentially most hazardous positions in the scanner, for a patient carrying a knee/hip/shoulder metallic implant. In parallel with the hardware analysis, an extensive examination of clinical sequences has been performed, to select the most relevant cases for a subsequent investigation. This refers to sequences which are in widespread clinical use and/or are expected to be very 'aggressive', in terms of gradient heating, because of a high duty cycle of rapid gradient switching.

A new laboratory with a gradient test-stand was built which will be used to investigate thermal effects of gradient coils on real metallic implants, systematically under controlled conditions.

New computational tools designed to simulate the exposure to MRI gradient fields of a patient carrying a prosthesis have been implemented. They have been validated, for the first time, against experimental data available in the literature, obtaining an excellent agreement. These validations will be further extended using the aforementioned gradient test-stand.

Large number of simulations of implants embedded in virtual human models or phantoms, and exposed to realistic or simplified gradient fields, have been already collected based on two different approaches, both comparing the heating risk due to gradient and RF fields. First results were compared to corresponding dosimetric analyses of MRI typical RF exposures, with the aim to explore the feasibility of developing a *joint* assessment procedure for the exposure to all MRI fields.

Objective 5

A statistical approach is being employed to assess the MRI safety for small metallic implants like screws or fixation parts; groups of devices with a large variety of sizes and shapes within each group. Very few reference implants of a given type are being investigated in detail and scaling laws will then be derived to transfer this knowledge, including its uncertainties, to a whole class of similar devices.

Mathematical models of parameterised implants have been used to explore how shape factors, field strength scan sequence, and orientation affect the heating of implants during scanning. Extensive simulations of simplified orthopaedic implants in gradient fields have shown that there is a strong correlation between maximum temperature rise and deposited power per unit surface area, and a parametric model has been developed to describe these correlations.

Advances have been made to link and compare the simulation results for gradient coil heating and RF-induced heating. A set of parameterised models of idealised and realistic implants has been created and will be compared. The different physical effects that dominate each heating model can be linked to physical properties of the implants, enabling enhanced clinical guidelines. A more detailed analysis of the simulation results will take place in the remainder of the project, with the aim of developing parameterised models to predict heating from implant properties.

Initial steps towards analysis of the effects of variability of humans has begun. Data has been generated that represents the electrical field (E-field) occurring during MRI scanning in six regions within the human body where implants are commonly placed. A large number of implant locations and scanner configurations were investigated, and an initial analysis identified which factors have the strongest effect on the E-field. The E-field exposure will be linked to the electromagnetic properties of the tissue in that region, providing a method to account for person-to-person variability when assessing exposure risk.

Impact

MIMAS results have led to several journal papers, most notably an invited review paper on implant safety co-authored by multiple consortium members. Project findings were disseminated in 36 conference contributions, one third of which were invited oral presentations. Lectures on gradient-induced heating of implants were given for PhD students in Engineering and for students of a Health Physics course.

Impact on industrial and other user communities

In December 2019, ZMT's in-vivo RF-exposure libraries *MRIxVIP 1.5* and *MRIxVIP 3.0T* and the standardised evaluation tool *IMAnalytics* were qualified, as the first computational tool ever, by the U.S. Food and Drug Administration (FDA) as a Medical Device Development Tool (MDDT). This is a major success, since the MDDT label certifies that evaluations of the health risk posed by medical implants to patients undergoing MRI are traceable, easy-to-conduct, and standardised at the most comprehensive level. The combination of *IMAnalytics* and *MRIxViP* data libraries enables the medical device industry to accelerate their approval processes with standardised risk evaluations of approved, high quality.

At the end of 2019, IMAnalytics v3.0 was released, which also supports Tier 2 evaluations with a workflow for extracting field data from the MRIxViP libraries in customised regions of interest, with derivation of all statistics necessary for Tier 2 of ISO/TS 10974. The development of this functionality enables the quantification of worst-case *E*-fields in the human body in implant regions, which played a key part in MIMAS deliverables. IMAnalytics v3.0 has been submitted to the FDA in the first half of 2020 as part of a proposed extension to the qualified MDDT.

Impact on the metrology and scientific communities

The successful cooperation within the MIMAS project and the deeper insight into mutual research interests and capacities led consortium members to join forces in a different research field, too. MIMAS partners were the key drivers in conceiving and procuring a new joint research project on quantitative imaging which will be coordinated by a MIMAS consortium member.

The scientific community learns about the newly developed methodologies through journal publications and conference presentations. For the first time ever, numerical models of tissue and implant heating in MRI, which are already in widespread use in the research community, will be supported by a metrological underpinning.

Impact on relevant standards

The Technical Specification ISO/TS 10974 on MRI safety of active medical implants is still lacking key procedures necessary for progression to a standard. The project is developing specific procedures and validated tools for the safety assessment of implants and provide a metrological underpinning to ensure that ISO/TS 10974 will i) become a full standard and ii) be continuously developed and improved. This will also contribute to the future development of IEC 60601-2-33, the international standard on MRI equipment and safety, since a complementary co-development of the MRI and the implants standard was agreed upon by a joint ISO/IEC working group. IEC 60601-2-33 will further be amended by the project results on the gradient induced heating of bulk metallic implants.

Longer-term economic, social and environmental impacts

European implant manufacturers will benefit from a faster market introduction of their innovative products as metrologically approved methods to assess the MRI safety of medical implants will be available. Manufacturers of small and diverse implants (screws, clips, etc.), which are predominantly SMEs, will particularly benefit from simplified compliance testing.

Approximately 32 million MRI patients p.a. in EURAMET countries would benefit from personalised safety assessments based on sound scientific methods. About 50 million implant carriers would gain safe access to a potentially lifesaving imaging modality. Manufacturers and clinicians will have reliable metrics to assess the MRI safety of medical implants and legal certainty about their safety measures. The proposed work will facilitate the inclusion of implant MRI compatibility in future revisions of the EU Medical Device Regulations, enhancing the safety of EU citizens bearing implants.

The most hazardous implants in MRI are active devices with long electrodes or leads. For these, a novel safety concept is being developed within MIMAS, utilising the information from sensors on the implant to adjust the RF settings of a parallel-transmit capable MR scanner. No longer the MRI operators in the clinics but rather the implant and scanner manufacturers would be chiefly responsible for the safety of implant carriers, then. The concept assigns new responsibilities and it requires technical changes to both implants and MRI scanners. Manufacturers may be reluctant to adopt it, therefore. If it is adopted, it will change the MR scanning of implant patients forever.

List of publications

[1] *In silico* evaluation of the thermal stress induced by MRI switched gradient fields in patients with metallic hip implant. Arduino A, Bottauscio O, Brühl R, Chiampi M, Zilberti L. Phys Med Biol. 2019. doi: 10.1088/1361-6560/ab5428.

[2] RF-induced heating of metallic implants simulated as PEC: Is there something missing? Zilberti L., Zanovello U., Arduino A., Bottauscio O., Chiampi M. Magn Reson Med 2020. doi: 10.1002/mrm.28512.

[3] MRI-Related Heating of Implants and Devices: A Review. Winter L, Seifert F, Zilberti L, Murbach M, Ittermann B. J Magn Reson Imaging 2020. doi: 10.1002/jmri.27194.

[4] Parallel transmission medical implant safety testbed: Real-time mitigation of RF induced tip heating using time-domain E-field sensors. Winter L, Silemek B, Petzold J, Pfeiffer H, Hoffmann W, Seifert F, Ittermann B. Magn Reson Med 2020. doi: 10.1002/mrm.28379

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