Publishable Summary for 15HLT05 PerfusImaging
Metrology for multi-modality imaging of impaired tissue perfusion

Overview

This project addressed metrology needs for the health sector by developing a physical standard for quantitative medical imaging applicable to a range of imaging techniques (modalities) and new data analysis techniques for patient care. This supports the reliability and traceability of clinical data and ensures the comparability of diagnostic and treatment information in clinical trials. In addition, the project investigated metrological approaches for radiation protection to support the health protection of citizens.

Need

Cardiovascular disease (CVD) is the leading cause of death in Europe and costs the European economy approximately €196 billion each year [1]. Until now, most medical treatments have been designed for the "average patient". As a result of this "one-size-fits-all" approach, treatments can be very successful for some patients but not for others. For instance, a large clinical study has demonstrated that up to 60 % of patients with chest pain might not need expensive catheterisation, which is the current diagnosis and treatment of CVD [2]. Therefore, there is a strong need for a reliable diagnostic test to triage patients at intermediate risk of CVD for the appropriate treatment. Over the last two decades, several clinical landmark studies have shown that accurate measurement of heart muscle blood supply (perfusion) could serve as a gatekeeper for treating the right patients. Perfusion is essential for the integrity of the heart and is an early marker of the so-called ischemic cascade that leads to non-reversible tissue damage and thus chronic heart disease. Accurate quantification of perfusion is currently only possible through invasive measurements with catheters, which is a costly procedure with side effects. As an alternative, different medical imaging techniques (modalities) have been developed to measure perfusion non-invasively.

Since each imaging modality is based on different principles and images are analysed with different techniques, the results can vary significantly. Some of the medical imaging modalities also involve ionising radiation, which presents a health hazard, as it can lead to cancer. There is a compromise between image quality and the applied radiation dose, i.e. higher image quality involves a higher dose. However, dose estimations are currently neither scan- nor patient specific and suffer from relatively high uncertainties in the order of 20 %, for similar image quality. For multiple scans, this can even lead to higher uncertainties of accumulated dose for individual patients. All perfusion imaging techniques require the injection of contrast agents, which is limited to one or very few injections at one scan. Therefore, a comparison of different protocols within one imaging modality and cross-modality validation is challenging. In most cases perfusion images are diagnosed by visual inspection, which makes the diagnosis highly dependent on the observer's experience. Prior to this project, quantitative approaches based on comparable biophysical parameters were necessary in order to avoid this observer's bias. This project addressed important aspects in measurement standards and quantitative analysis techniques in perfusion imaging.

Objectives

The aim of this project was to establish a metrological framework for traceable, accurate, reproducible and ultimately comparable blood perfusion measurements of impaired heart tissues using medical imaging technology. The specific technical objectives of the project were:

1. **To construct a novel physical standard phantom for perfusion imaging (phantom V2), based on an existing prototype (phantom V1), that mimics realistic perfusion conditions and is applicable in multi-modality imaging**. In addition to design a second phantom (phantom V3) based on a novel two-compartment design to study the reproducible exchange of contrast agents.
2. **To develop methods for data analysis and uncertainty evaluation for quantitative perfusion imaging**, including two new approaches to deconvolution: parametric extensions of the Fermi function and new Bayesian approaches. Further, to investigate classification techniques to identify disease-related

perfusion states, and to investigate the accuracy and uncertainty by comparing calculated perfusion rates to the reference values of the standard.

3. **To perform uncertainty analysis of multi-modality imaging** to assess the reliability and traceability of imaging data. To perform a comparison of imaging results across different modalities and provide uncertainty values. To test Bayesian approaches for a combined analysis of imaging data from different modalities of the standard V2.
4. **To develop personalised dosimetry for imaging with ionising radiation**, to include a mobile device for determining CT scanner hardware properties (an “equivalent source model”) and software for the calculation of patient specific dose estimates.
5. **To integrate the standard V2 and techniques developed by the project into clinical practice**, by demonstrating the proposed physical standard in a clinical feasibility study and the development of draft clinical guidelines for quantitative perfusion imaging.

Progress beyond the state of the art

Prior to the start of this project, there was an identified need for: 1. A new calibrated physical standard with known flow values allowing comparison between different methodology and at different centres; 2. New data analysis for assessing perfusion differences in clinical studies; 3. An uncertainty analysis of perfusion quantification and an investigation of new approaches to combine different values; 4. New mobile equipment for the verification of procedures of personalised dosimetry in clinical CT scans; and 5. clinical application of developed techniques.

The project has gone beyond the state of the art by producing a prototype of a physical standard, which allows the quantification of spatially varying flow. For this simulations and experiments were used to achieve the target relationship between flow rate, tube length and geometry. The phantom mimics realistic perfusion conditions and thus allow practical application and comparison in clinical conditions.The simulation results were then used in the design and construction of a 3D-printed phantom, consisting of a myocardial compartment with spatially varying flow. The spatial variation was observed in perfusion data with multiple imaging modalities, while flow measurements with reference techniques showed that the uncertainty was below the target 5 %. This represents the first physical standard for the assessment and validation of myocardial perfusion imaging methodologies. The physical standard was presented as an upcoming product by ZMT at the ISMRM-conferences in 2018 and 2019. A journal paper was also submitted.

Current perfusion analysis techniques were summarized in a state-of-the art report, giving a succinct overview of the latest methods on quantification. Two novel analysis techniques were developed for voxel-wise quantification of perfusion. One approach employed Tikhonov regularisation to improve precision of quantification despite low signal-to-noise ratio. The second technique was based on a Bayesian approach that allowed the pixel-wise calculation of uncertainty in data analysis for the first time. Furthermore, two novel classification techniques were developed to automatically quantify the severity of myocardial perfusion defects in patients. In particular a new risk-based decision-making framework was developed that is based on a predefined guideline for perfusion measurements and has been applied to clinical Positron Emission Tomography (PET) perfusion data. Furthermore, a novel deep-learning classification algorithm was developed to allow the detection of ischemia directly from a patient’s PET scans.

The project proved the suitability of J.M. Boone’s COBRA (“characterization of bow tie relative attenuation”) method for mobile equipment to test CTs in a clinical environment allowing assessment of the radiation dose of cardiac perfusion scans for different scanners and protocols. The equipment was tested on different CT-scanners at PTB and HUS to allow verification of the equivalent source model. Different types of phantoms with dosimeters have been used for validation. Personalized dose was calculated through Monte-Carlo simulations and compared to the values of the dosimeter. The target accuracy with an uncertainty of below 10% was achieved.

Previously, many technical developments were often developed independently from the clinical user perspective resulting in longer development cycles. In contrast, this project was performed in close collaboration with internationally leading clinical experts at King’s College London, University hospital in Helsinki and the Turku PET centre. Clinical expertise was used to steer technical development to the clinical needs. New data analysis techniques were applied to clinical data from King’s College London and the Turku

PET centre. A small feasibility study at King's College London has been performed to compare results from two different scanner types. This demonstrated their potential in direct comparison to current techniques using real-world clinical data and showing the potential to trace results back to reference values as provided by the prototype of a physical standard.

Results

Objective 1: To construct a novel physical standard phantom for perfusion imaging (phantom V2), based on an existing prototype (phantom V1), that mimics realistic perfusion conditions and is applicable in multi-modality imaging. In addition to design a second phantom (phantom V3) based on a novel two-compartment design to study the reproducible exchange of contrast agents.

Several iterations of a new phantom were developed using modern 3D-printing techniques and materials. These were tested within the consortium and produced substantial improvements on the initial design, leading to a prototype of a calibrated physical standard incorporating a myocardial compartment with spatially varying flow. This prototype mimics physiological transmural perfusion gradients through radial variation of flow velocities. The prototype is based on flow simulations as well as experiments. It was calibrated using MR-flow reference techniques to ensure traceable flow perfusion values.

Furthermore, a new concept for a physical standard with two-compartments representing vascular and interstitial space in tissue was tested. This prototype is important to validate pharmacokinetic models, which are usually used in the analysis of dynamic PET and Single Photon Emission Computed Tomography (SPECT) perfusion imaging. Initial tests have demonstrated the feasibility of the approach and consistent values were found after applying a pharmacokinetic analysis.

Objective 2: To develop methods for data analysis and uncertainty evaluation for quantitative perfusion imaging, including two new approaches to deconvolution: parametric extensions of the Fermi function and new Bayesian approaches. Further, to investigate classification techniques to identify disease-related perfusion states, and to investigate the accuracy and uncertainty by comparing calculated perfusion rates to the reference values of the standard.

The project delivered a validated methodology for the quantitative analysis of perfusion images. The uncertainty of this analysis technique was determined in comparison with current approaches. Furthermore, the feasibility of Bayesian classification was shown using multi-modality imaging data. Progress has been made using voxel-wise quantification of myocardial blood flow (MBF), applying Tikhonov regularisation to exploit data smoothness, thus allowing quantification despite low signal-to-noise ratio. This also decreases the relative error compared to non-regularised data. A paper describing a new pixel-wise analysis based on spatial Tikhonov regularisation which exploits the spatial smoothness of the data and ensures accurate quantification even for images with a low signal-to-noise ratio was published.

Objective 3: To perform uncertainty analysis of multi-modality imaging to assess the reliability and traceability of imaging data. To perform a comparison of imaging results across different modalities and provide uncertainty values. To test Bayesian approaches for a combined analysis of imaging data from different modalities of the standard V2.

A novel Bayesian approach was developed that allows the pixel-wise calculation of uncertainty in data analysis for the first time. A paper was accepted for publication. The uncertainty in the quantification of a single imaging modality was initially determined via measurements from different scanners. This data is the foundation of work on statistical meta-analysis of the consistency of multi-site data and to obtain an improved estimate of blood perfusion. A multi-centre multi-modality study is planned to compare different measurements on the same physical standard and to apply the developed meta-analysis technique.

A novel risk-based decision-making framework based on predefined guidelines for perfusion measurements was applied to clinical Positron Emission Tomography (PET) perfusion data. The results of the decision-support systems were compared to the current gold-standard, i.e. invasive catheter examination.

Objective 4: To develop personalised dosimetry for imaging with ionising radiation, to include a mobile device for determining CT scanner hardware properties (an "equivalent source model") and software for the calculation of patient specific dose estimates.

Mobile equipment for the verification of procedures for personalised dosimetry in clinical CTs was developed, consisting of several hard- and software modules, e.g. a special holding frame for aluminium plates, real-time dose detectors, time resolved readout (kHz-range) and special dosimetry phantoms. This equipment is easy to assemble and transport and allows for fast measurements of the scanner properties in a clinical environment. The equipment was tested on the CT-scanner to allow verification of the equivalent source model and assess target accuracy.

The whole dose estimation procedure was applied in the clinical environment at HUS using two Siemens SOMATOM Definition Edge and Flash scanners in April 2018. Equivalent sources of the two scanners were determined by use of the mobile equipment and software as developed in the project. Different types of phantoms (standard CTDI and anthropomorphic) containing 5 representatively placed dose probes were scanned. During the scan the dose was measured simultaneously at these five positions. The dose absorbed in the phantoms was calculated by Impact MC using the previously determined equivalent source models, the scanned image, segmented in its different material types, and the scan parameters. Complete uncertainty budgets of both measurements and calculations were set up and evaluated. The overall result was that calculated and measured dose values agreed within the estimated uncertainties of about 10 %.

Objective 5: To integrate the standard V2 and techniques developed by the project into clinical practice, by demonstrating the proposed physical standard in a clinical feasibility study and the development of draft clinical guidelines for quantitative perfusion imaging

The project was performed in close collaboration with internationally leading clinical experts at King's College London, University hospital in Helsinki and the Turku PET centre. Clinical expertise was used to steer the technical developments to the clinical needs. New data analysis techniques were applied to clinical data from King's College London and the Turku PET centre. A small feasibility study at King's College London has been performed to compare results from two different scanner types. This pilot data has been used to apply successfully for funding of a clinical study by the British Heart Foundation. Furthermore, a multi-centre multi-modality study using the physical standard is planned. This study will include DZHK as partners.

Impact

This project created impact for European healthcare by supporting the reliability and traceability of imaging data, which allows diagnostic information to be compared. A total of 7 papers have been published in peer-reviewed journals and are open access, one paper is accepted for publication and a further 6 papers have been submitted.

A public engagement event was held in London in Aug 2019. The keynote was delivered by Andrew Arai (NIH). Project results were demonstrated to a broader audience, which consisted of representatives from industry, academia, clinicians and patient advocacy groups. The project results have been received with very positive feedback using an online survey. Industry (GE, Philips, Siemens, Canon) representatives stressed the importance of the clinical consensus paper as a guideline for developing products rather than normative standards (e.g. ISO).

Over the course of its lifetime, the project organised 4 external workshops and 5 webinars or training workshops that brought together researchers in metrology, clinical opinion leaders, and industrial stakeholders. The first stakeholder workshop discussed the clinical need for perfusion imaging of the myocardium, test objects / phantoms for perfusion imaging, and the related data analysis and uncertainty evaluation. Other workshops have included a symposium on PET modelling, as well as a multi-partner workshop in November 2017, on PET quantification in clinical MBF measurements. A satellite workshop on patient specific dosimetry for cardiac CT perfusion imaging was held at the European Congress of Medical Physics (ECMP) in August 2018. Results were presented at the annual meeting of the Society of Cardiovascular Magnetic Resonance (SCMR) and the International Society of Magnetic Resonance in Medicine (ISMRM) in 2018 and 2019. An

advisory meeting was held at ISMRM 2018 with representatives from industry, academia and university hospitals.

Impact on relevant standards

The consortium collaborated with members of the European Association of Cardiovascular Imaging (EACVI) to disseminate new methodology and standards into clinical practice. EACVI provides individual certification and laboratory accreditation programmes for good clinical practice in Europe and publishes guidelines. A consensus paper on quantitative perfusion imaging has been published in Nature Reviews in Cardiology with international experts and members of the European association of cardiovascular imaging (EACVI). Recommendations for standards development in personalised dosimetry were submitted to the IEC committees (IEC TC62B MT 30 and IEC TC62C WG3).

Impact on industrial and other user communities

Zurich Medtech (ZMT) produced a commercial exploitation plan of the physical standard as a product following the end of the project, and has already proven the feasibility, expediency and accuracy of its 3D-printing capabilities in producing the current iterations of the prototype. Commercialisation will be supported by input from industrial and clinical stakeholders to compare current commercial software with respect to reference values. To ensure a best match with stakeholder needs, the design of the prototype was discussed with stakeholders (advisory committee) in a satellite workshop at a clinical conference (ISMRM) in June 2018. The committee consisted of industrial representatives from all major imaging vendors (GE, Philips, Siemens, Canon) analysis software (Circle Cardiovascular) and clinical/academic experts (ETH Zurich and Charité Berlin). In particular, the imaging vendors stressed the importance and need of a clinical consensus paper that defines standard imaging and analysis protocols as guidelines for commercial developments. As a consequence, a working group of leading international experts was formed and a clinical consensus paper submitted to Nature Reviews Cardiology. All consortium partners contributed either directly to the paper or shared their expertise. A session on perfusion quantification was also held at the annual meetings of cardiovascular magnetic resonance (SCMR) in 2018 and 2019.

Impact on the metrology and scientific communities

As a result of the project, the British Heart Foundation funded a grant of £250,000 to KCL for a clinical study that employs the new physical standard for perfusion imaging as quality control. KCL has updated its annual training course on perfusion imaging accredited by the Society of Cardiovascular Magnetic Resonance in response to the project's findings. This course usually attracts 20-25 clinicians from different European countries to learn CMR with SCMR accredited exams. This will allow dissemination of the project's results to a much wider community.

The project contributed a chapter on Cardiac perfusion MRI to the book "Quantification of Biophysical Parameters by Medical Imaging", in 2017. Training videos on CARIMAS, myocardial PET perfusion, PET modelling and phantom studies were produced and shared with the consortium. The importance of uncertainty analysis in data analysis was discussed during a stakeholder workshop at NPL in 2017(see above) and in a dedicated session at a clinical conference SCMR 2018. Finally, a new mobile test equipment for determining personalised dose of different CT scanners was discussed in a dedicated workshop at ECMP 2018, as well as a presentation on the Verification of Procedures for Personalised CT Dosimetry at AAPM 2018.

Longer-term economic, social and environmental impacts

This project developed a calibrated physical standard that allows one-to-one comparison of different approaches and imaging modalities. in this way the project will contribute to the global market of medical imaging devices, which has overall compound annual growth rate CAGR = 5 %. The consortium has linked with the small enterprise ZMT for exploitation of the physical standard into a commercial product. The physical standard V2b has been redesigned by ZMT as commercial product and this was shown as an upcoming product in the clinical meetings ISMRM 2018 & SCMR 2019, ISMRM 2019. Three physical standards were produced and shipped to London, Berlin, Helsinki. A multi-centre and multi-modality study is planned after project at Berlin, London and Turku/Helsinki. This study will include DZHK as partners.

Large companies (Philips, Siemens, GE, Circle-CVI) have expressed their interest in the phantom for validation of quantitative imaging techniques, which is a market driver in future medical imaging.

List of publications

1. Stephan Rosendahl & Ludwig Büermann, *Dynamic determination of equivalent CT source models for personalized dosimetry,* Current Directions in Biomedical Engineering - Joint Journal of the German Society for Biomedical Engineering in VDE and the Austrian and Swiss Societies for Biomedical Engineering, 2017, https://doi.org/10.1515/cdbme-2017-0167
2. Reetta Siekkinen, *LYSO-SiPM-ilmaisintekniikkaan perustuvan digitaalisen PET-kameran suorituskyvyn arviointi H215O-torsofantomilla (Assessment of Digital and Analog PET/CT Systems for Accurate Myocardial Perfusion Imaging with a PET Flow Phantom)* (Masters thesis in Finnish), Publications of University of Turku (UTUPub), http://urn.fi/URN:NBN:fi-fe2018092736833
3. Judith Lehnert et al., *Large-scale Bayesian spatial-temporal regression with application to Cardiac MR-perfusion imaging,* Society for Industrial and Applied Mathematics (SIAM) Journal on Imaging Sciences, pp. 2035-62) 12-4 (2019), https://doi.org/10.1137/19M1246274
4. Ludwig Büermann et al., *Steps Towards Personalized Dosimetry in Computed Tomography*, Book of Extended Synopses (pp. 216-217), 2019, https://www.iaea.org/sites/default/files/19/06/cn-273-book-extended-synopses.pdf
5. Matteo Ippoliti et al., *3D nonrigid motion correction for quantitative assessment of hepatic lesions in DCE-MRI*, Magnetic Resonance in Medicine, 2019 Nov;82(5):1753-1766. https://doi.org/10.1002/mrm.27867
6. Nazir MS et al. *Simultaneous ^{13}N-Ammonia and gadolinium first-pass myocardial perfusion with quantitative hybrid PET-MR imaging: a phantom and clinical feasibility study*. European Journal of Hybrid Imaging. 2019;3(1):15. https://doi.org/10.1186/s41824-019-0062-6 Epub 2019 Sep 3.
7. Marc Dewey et al. *Clinical quantitative cardiac imaging for the assessment of myocardial ischaemia-Consensus Statement,* Nature Reviews Cardiology 2020 Feb 24. https://doi.org/10.1038/s41569-020-0341-8

Project start date and duration:	01 July 2016, 36 months	
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Internal Funded Partners: 1 PTB, Germany 2 LNE, France 3 NPL, United Kingdom 4 STUK, Finland 5 VSL, Netherlands	External Funded Partners: 6 KCL, United Kingdom 7 TU Delft, Netherlands 8 TUCH, Finland 9 UH, Finland	Unfunded Partners: 10 HUS, Finland 11 ZMT, Switzerland
RMG: -		

[1] European Cardiovascular Disease Statistics, *European Heart Network and European Society of Cardiology*, September 2012

[2] Patel MR, Peterson ED, Dai D, Brennan JM, Redberg RF, Anderson HV, Brindis RG, Douglas PS. Low diagnostic yield of elective coronary angiography. *N Engl J Med.* 2010;362: 886–895.