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

Overview

The aim of this project is to address 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 will support the reliability and traceability of clinical data and ensures the comparability of diagnostic and treatment information in clinical trials. In addition, the project will investigate 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, currently dose estimations are neither scan- nor patient specific and suffer from relative high uncertainties of the order of 20 %, for similar image quality. For multiple scans, this can even lead to higher uncertainties of accumulated dose for individual patient. 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. Therefore, there is a strong need for standards in measurements and analysis in perfusion imaging.

Objectives

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

1. **To construct a novel physical standard phantom for perfusion imaging (phantom V2), based on an existing prototype (phantom V1), that will mimic realistic perfusion conditions and will be applied to 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

Over the last decade significant work has been carried out to develop reliable quantification techniques that are independent of the observer. In order to be adopted, new methods need to be validated in large clinical studies at different centres. Recently a perfusion phantom has been introduced that allows the efficient simulation of myocardial perfusion which would be helpful to support large studies. However, this phantom has a number of limitations that hinders its broad application. In this project, a new phantom will be developed that will be calibrated with reference techniques to establish a physical standard with known flow values. It will incorporate a physiological flow distribution in time and space to mimic more realistic perfusion conditions. The phantom will be applicable across imaging modalities, and will be validated through a cross-modality comparison. Furthermore, the project will assess the uncertainty of quantification techniques with a metrologically sound approach and will investigate new Bayesian approaches for quantification.
Sometimes imaging techniques with ionising radiation (e.g. Computed Tomography) are applied requiring accurate dose calculation for the patient. A new concept for personalised dosimetry in ionising radiation will be investigated. Finally, the new techniques and standard will be tested in clinical studies to demonstrate their potential with respect to current techniques.

Results

Construction of a novel physical standard for perfusion imaging

A novel phantom will be constructed that for the first time mimics more realistic blood flow in the heart. This phantom will be calibrated with flow reference techniques to establish a new physical standard phantom with traceable flow values. The proposed standard will be applicable to different imaging modalities and will allow for a direct comparison of different measurement protocols. Additionally a new concept will be tested to establish a two-compartment phantom (representing vascular and interstitial space in tissue), enabling the examination of contrast agent flow across a membrane or through a filter. Initial tests will demonstrate the difference between the physical standard and two-compartment approach.

Methodology for quantitative perfusion imaging

The project will deliver a validated methodology for the quantitative analysis of perfusion images. The uncertainty of this analysis technique will be determined in comparison to current approaches. Furthermore, the feasibility of Bayesian classification will be shown using multi-modality imaging data.

Uncertainty analysis of multi-modality imaging

The uncertainty in quantification of a single imaging modality will be determined including measurements at different centres and an assessment of the influence of quantification. Furthermore, the uncertainty between different modalities will be assessed and new methods for integrating multi-modal imaging will be demonstrated.

Personalised dosimetry in imaging with ionising radiation

The project will deliver equipment and methodology to determine the dosimetry for an individual patient. This allows better radiation dose calculation for dynamic and multiple perfusion scans with computed tomography.

Integration of standards and techniques in clinical practice

All approaches mentioned above will be tested in a small clinical feasibility study to demonstrate the impact in clinical practice. The results will provide important information about the different imaging modalities to set up large clinical studies.

Impact

The results of this project will create impact for European healthcare to support the reliability and traceability of imaging data allowing the comparability of diagnostic information. The consortium has linked with the German Centre for Cardiovascular Research (DZHK), which consists of 28 clinical centres that perform clinical studies of new diagnostic tests and therapies. For such studies, quality assurance and **comparability of results** is essential to **pool imaging data from different sites**. The project plans workshops (eg. at major clinical conferences) bringing together researchers in metrology, clinical opinion leaders, and industrial stakeholders to create impact in three areas:

Impact on relevant standards

The consortium will collaborate with the European Association of Cardiovascular Imaging (EACVI) to disseminate new methodology and standards into clinical practice. The EACVI aims at raising quality standards of practice and equipment across Europe in a uniform manner. For this EACVI provides **individual certification and laboratory accreditation** programmes for good clinical practice (GCP) in Europe. EACVI organises training courses and publishes guidelines, and an E-journal of cardiology practice. The project will exploit the EACVI framework to develop guidelines for quality assurance of perfusion imaging using standards. The project will also report to the IEC committees (IEC TC62B MT 30 and IEC TC62C WG3) to develop a new standard in personalised dosimetry.

Impact on industrial and other user communities

The US and Europe are world-leaders in medical imaging R&D. The medical imaging equipment market depends on the reimbursement of imaging examinations, which is more and more regulated. In many countries reimbursement depends on objective measures (evidence-based medicine) and the usage of clinical guidelines. The development of quantitative imaging supports this trend and industry is investing in new methodology requiring standards for comparison. In the consortium the small enterprise ZMT will be responsible for the commercial exploitation of the physical standard as a product following the end of the project. The consortium will invite industrial stakeholders to compare current commercial software with respect to reference values. The results of the metrological uncertainty analysis will provide important input for the further development of commercial software in quantitative perfusion imaging.

Impact on the metrology and scientific communities

Metrology for healthcare is still in its infancy with a gap between scientific developments and clinical application. It is necessary to define measurands that properly describe the relevant physiological parameters and that allow traceability to appropriate standards. The consortium consists of NMI, academia and clinical experts to develop new metrological standards in perfusion imaging. The results of the project will be disseminated through scientific conferences, workshops and publications. The knowledge and infrastructure will be directly accessible to other NMIs and academic researchers via collaboration with partners. Although the project focuses on cardiovascular disease, the establishment of reliable and quantitative perfusion is also highly relevant for other major disease areas, such as oncology or neurology.

List of publications

None published yet.

<table>
<tr><td colspan="2">Project start date and duration:</td><td>01 July 2016, 36 months</td></tr>
<tr><td colspan="3">Coordinator:
Tobias Schaeffter, PTB Tel: +49 303 481 7343 E-mail: tobias.schaeffter@ptb.de
Project website address: to be determined</td></tr>
<tr><td>Internal Funded Partners:
1 PTB, Germany
2 LNE, France
3 NPL, United Kingdom
4 STUK, Finland
5 VSL, Netherlands</td><td>External Funded Partners:
6 KCL, United Kingdom
7 TU Delft, Netherlands
8 TUCH, Finland
9 UH, Finland</td><td>Unfunded Partners:
10 HUS, Finland
11 ZMT, Switzerland</td></tr>
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[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.