FINAL PUBLISHABLE REPORT

Grant Agreement number	15HLT05
Project short name	PerfusImaging
Project full title	Metrology for multi-modality imaging of impaired tissue perfusion

Project start date and duration:		01 July 2016, 36 months
Coordinator: Tobias Schäffter, PTB Tel: +49 30 3481 7343 E-mail: tobias.schaeffter@ptb.de Project website address: https://www.ptb.de/empir2018/perfusimaging		
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: -		

TABLE OF CONTENTS

1 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.

2 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.

3 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.

4 Results

4.1 Objective 1 (physical standard)

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.*

4.1.1 Relevance to the project’s needs and objectives

Over the last decade medical imaging has been established as a non-invasive tool to objectively assess perfusion in-vivo. In particular quantitative analysis tools have been developed to measure perfusion defects from obtained imaging data [4.1.1]. However, the accuracy and reproducibility has not been systematically evaluated under identical conditions. This is partially attributed to the lack of a clearly defined and transferable gold standard. The ultimate validation of tissue perfusion is based on microspheres, which are delivered to large animals and is quantified on ex vivo tissue. Another validation proposal is a perfused heart in a hardware phantom for physiological perfusion experiments (so-called Langendorf set-up), which requires large animals and thus cannot be performed routinely. Therefore, perfusion phantoms have been proposed for quality assurance inside institutions with the possibility to establish a physical standard for comparison of measurements across institutions.

4.1.2 Description of the work

In this project two novel cardiac phantoms with a synthetic myocardial component that mimics tissue perfusion curves were developed. One phantom aims at spatially varying perfusion values whereas the other addresses exchange of contrast agent between two compartments. The phantoms were based on an initial prototype V1, which had been developed before the project. It consisted of four-chamber components of which two mimicked contrast dispersion across the capillary bed in the myocardium. However, that phantom set-up lacked diversity in capillary size and allowed only global perfusion validation, while its low manufacturing reproducibility hampers its commercialisation. The phantoms were developed in several design phases with the major and minor version numbering being V2, V2a, V2b and V3. The development of the prototypes included design updates, computational fluid dynamics (CFD) simulations, 3D printing of the phantom and flow measurements by ultrasound imaging velocimetry (UIV) and MR flow measurements involving different partners. The activity was led by the industrial partner ZMT, who produced all prototypes, making use of their CAD and 3D-printing capacities using industrial high-precision stereolithography (SLA). The material used is a thermoplastic compound, which has been tested for compatibility with all major imaging modalities.

A) Phantom with spatially varying perfusion (V2)
The design goal of version 2 was to mimic a change of perfusion values across the capillary component by 30%. For this, a channel configuration with a rotationally symmetric flow profile with maximum flow velocity at the centre and linearly decreasing flow velocity to -30 % at the outer wall was chosen. For this, 230 channels with different lengths were used, i.e. a conical taper with a 30% linear length reduction. This decrease in channel length results in a transmural decrease in flow resistance and, consequently, a 30% transmural increase in flow rate towards the center of the myocardium. The OpenFOAM CFD solver was used by VSL to confirm this expectation and to ensure that the flow regime would be rotationally symmetric, at least in the model. The final design had four inlets from the sides to the pre-chamber in which a laminar flow element upstream of the channels was installed to remove any form of potential pressure gradient and turbulence in the cross section. Approximately 4 million cells were used in CFD simulation and different channel configurations were simulated.

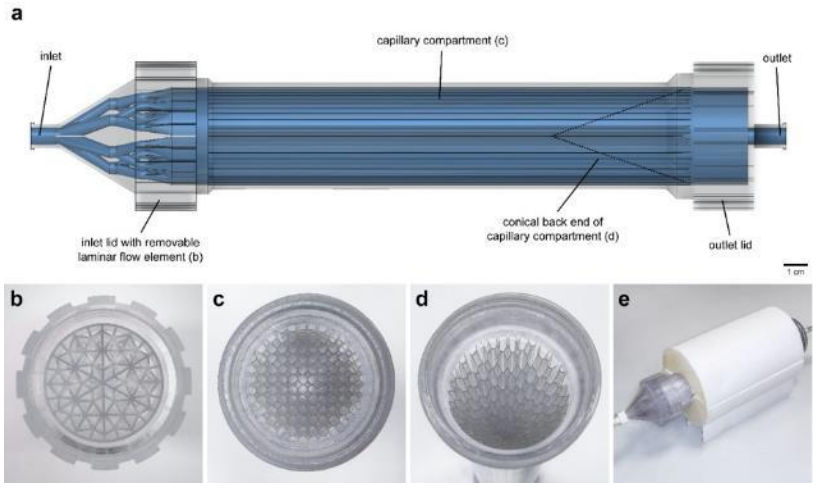

Figure 4.1.1: a) The geometry of the synthetic myocardium component b) photo of the inlet lid with the coronary tree structure (b), the front end of the capillary compartment (c), and the back end of the capillary compartment with the conical taper applying a 30% transmural difference in capillary length (d).

In order to measure the actual flow rates through the channels of the phantom, measurements with ultrasound imaging velocimetry (UIV) were performed by TU Delft. The earlier version of the phantom was based on thin walled channels. However, the 3D-printed version had thicker walls, which turned out to be problematic for the UIV measurements. Some indicative results were finally obtained suggesting flow velocities linearly decreasing with radius, but with an uncertainty higher than the target uncertainty of 10 %. Due to this poor ultrasound penetration (low acoustic window) UIV was discarded as a reference technique for the physical standard.

As alternative to the UIV measurements phase contrast (PC) MR-flow measurements were performed at KCL and PTB with an estimated uncertainty of 3% for the flow velocities. Five flow rates between 85.3 and 426.5 mL/min were each measured twice, and the results were analysed in various ways by KCL, PTB and VSL. A decrease of 30 ± 10 % with respect to the maximum was validated as predicted by the CFD simulations. Therefore MR-flow measurements were used as a reference to validate MR-perfusion imaging.

Another challenge was achieving the required equal mixing of the contrast agent in the phantom (due to sedimentation), and air bubbles in the channels. For this, two further prototypes V2a and V2b were built, where a bubble trap was optimised, and the inlet structures were modified with respect to number of inlets and their injection angles. In the final configuration, the inlet lid connected to a designed coronary tree that splits a main coronary artery (inner diameter 7 mm) into 90 arterioles with fixed area (8.5 mm^2) and variable cross-sectional shapes after three branching iterations. The path from the coronary artery to each arteriole has the same volume and length to evenly minimise the transport energy and ensure uniform distribution of the contrast agent in the arterioles.

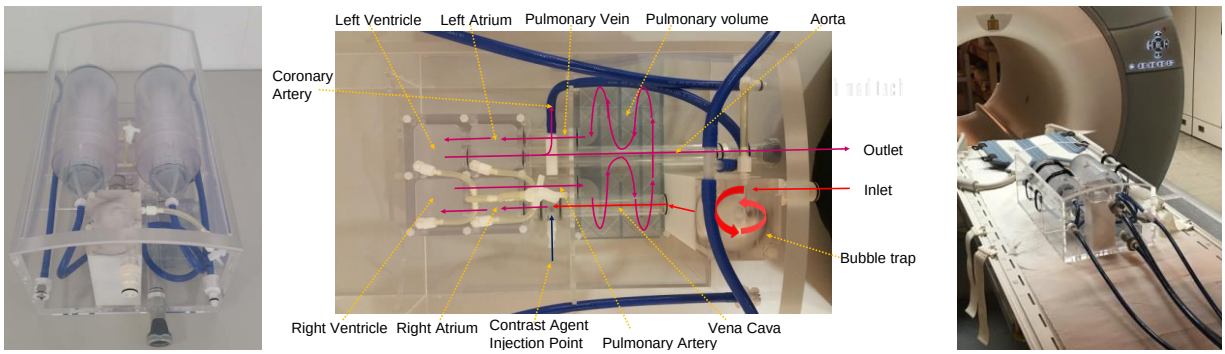

Figure 4.1.2 Phantom V2b with spatially varying perfusion rates

The phantom was used to evaluate a standard clinical DCE-MRI protocol for pixel-wise quantification of first-pass perfusion over a range of physiological perfusion rates. The phantom was supplied with water doped with

Gadobutrol (Gadovist®, Bayer AG, Leverkusen, Germany) at 0.1 mmol/L to achieve clinical baseline T_1 values in the blood pool at 3T. Scanning was performed on a 3T system (Achieva, Philips Healthcare, Best, The Netherlands) equipped with a 32-channel cardiac phased-array coil. A bolus of contrast agent (CA, e.g. gadolinium) is injected in the phantom representing the vena cava. The bolus of CA mixes with the blood (or water) and passes through the four heart chambers. Then, the MRI signal is measured in front of the myocardial component and the resulting time series is called the arterial input function (AIF). Imaging with each sequence was repeated several times in an interleaved fashion for each of four different true myocardial flow rates (100, 200, 300 and 400 mL/min). For pixel-wise perfusion quantification the AIF and myocardial signal intensity curves were converted to gadolinium concentration using the pre-contrast T_1 values and a signal model. Pixel-wise perfusion rate was then estimated using Fermi function-constrained deconvolution. In addition, phase contrast (PC)-MRI was used to validate the transmural variation in flow and perform cross-method validation.

PC-MRI indicated good reproducibility in perfusion rate (coefficient of variation (CoV) 2.4-3.5%) and correlation with reference values (R^2 = 0.985) across the full physiological range. Similar results were found for first-pass perfusion MRI (CoV 3.7-6.2%, R^2 = 0.987). Pixel-wise maps indicated a transmural perfusion difference of 28.8-33.7% for PC-MRI and 23.8-37.7% for first-pass perfusion, matching the reference values (30.2-31.4%).

The novel 3D printed phantom simulates transmural myocardial perfusion gradients over the full physiological perfusion range. The phantom can be used for evaluating and validating perfusion pulse sequences and quantification algorithms before their introduction into routine clinical use. It is also compatible with all other medical imaging modalities. In particular it has been used on a clinical PET-MR system that allows simultaneous acquisition of PET and MRI perfusion data [4.1.4]. NPL has written a report on the comparability between PET and MRI measurements obtained for the V2b phantom and provided the relevant radionuclide (Ammonia) to KCL for the comparison, thus providing KCL with a primary standard.

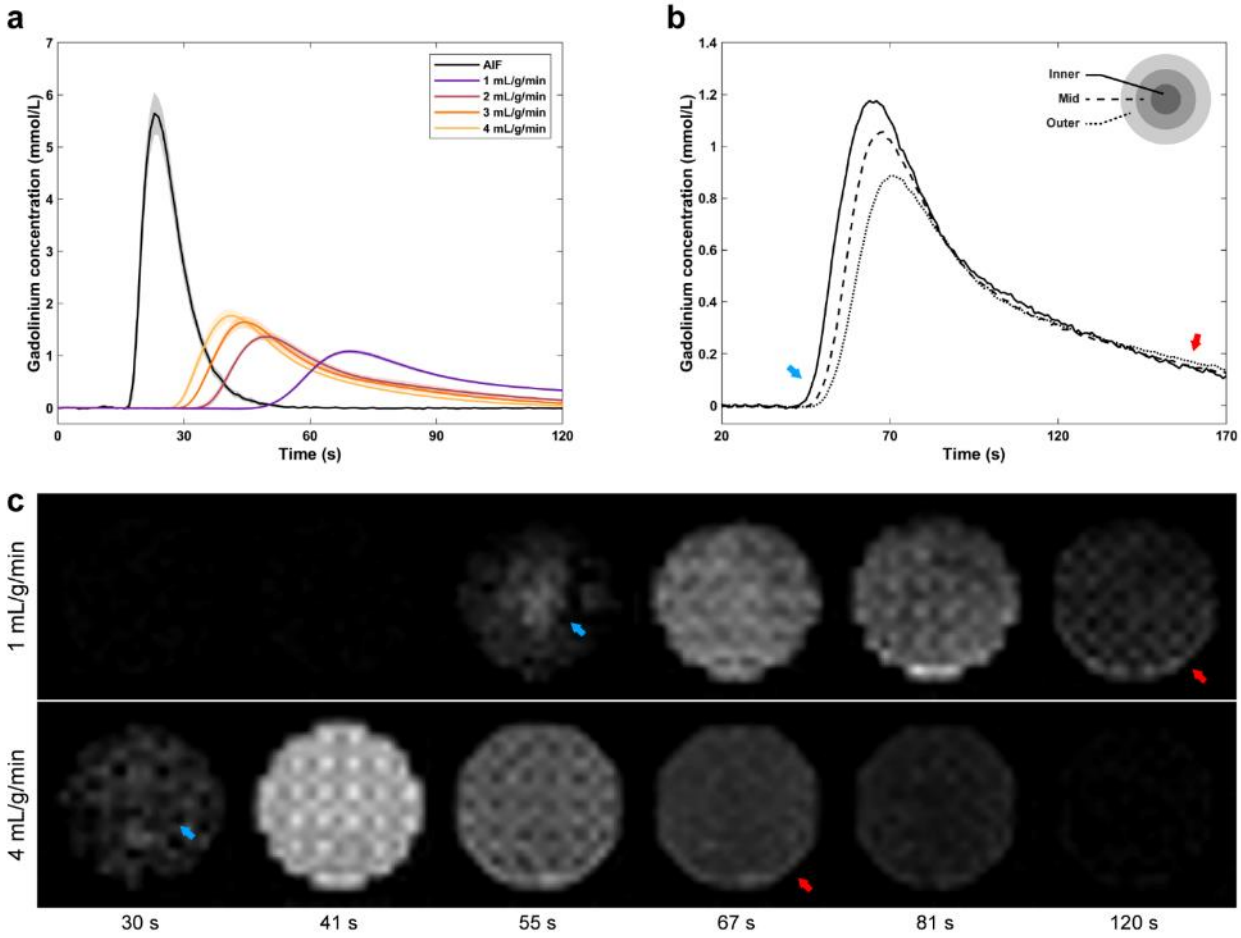

Figure 4.1.3: Dynamic contrast enhancement in the phantom. Plot (a) shows the mean arterial input function (AIF) sampled in the aorta and the mean myocardial tissue curves for four different reference mean perfusion rates.

B) Phantom with two-compartment exchange (V3)

An initial prototype for a two-compartment phantom was designed to study the exchange of contrast agent between two chambers by applying pharmacokinetic modelling. For this KCL and PTB applied semi-permeable polysulfone membranes (PSU), which were placed in seven tubes with Gd-doped water and washed out with solutions ranging from 3 to 7 pH. MRI experiments with the 3T Philips Achieva revealed that the membranes are incompatible with gadolinium-based contrast agents, as the gadolinium binds to the PSU and does not wash out entirely. The PSU have been tested with PET in TUCH with a GE Discovery MI PET/CT system. After repeat scans with 100, 200 and 300 ml/min flow the tracer distributed uniformly in the filter but that current modelling for extravasation and recirculation is not accurate enough (measured flow accuracy of <20%).

Therefore, a fully 3D printed two-compartment phantom (V3) was developed with advantages in terms of cost, reproducibility and performance. The first prototype consisted of a set of nine capillaries with two different diameters, along which small pores have been embedded. Extravasation of contrast agent can be controlled by changing the pressure between an inner and outer shell. Dynamic contrast enhanced MRI measurements have been performed for different extravasation rates, i.e. using different pressure differences.

Imaging data was analysed using two-compartment exchange modelling. MRI perfusion experiments suggest that the contrast exchange varies with different pressures. Further studies are necessary to improve reproducibility in the data analysis. The advantage of the two-compartment module that is compatible with all the previously developed components (e.g. pump inlets, control software). As such, exchange module can potentially be used as an interchangeable module in phantom V2. ZMT is further refining the design of V3 to enable contrast exchange between its two compartments at a microscopic level and improve the flow homogeneity and control of bubbles in each compartment.

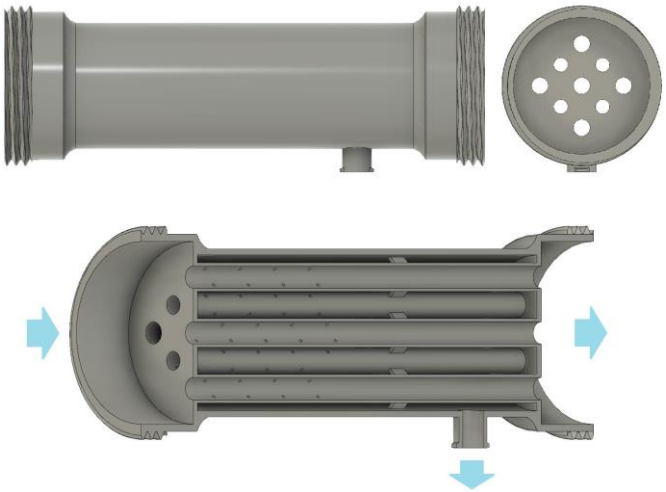

Figure 4.1.4 Design of the prototype V3 with small holes across the tubes for exchange of contrast agent between compartments. The arrows indicate the flow of water into the whole filter and out of the two compartments.

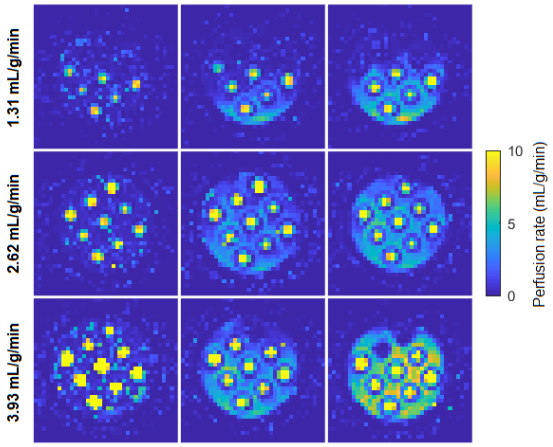

Figure 4.1.5: Perfusion rate maps for three perfusion rates and the three extravasation percentages. Air started filling the filter halfway through, as seen in the maps.

Additionally, TUCH tested a multi-modality perfusion phantom that also employs pores in a tube for the exchange of contrast agent. PET-perfusion imaging was performed, and two-compartment pharmacokinetic modelling was applied. However, validation of the microscopic contrast exchange with a reference method remains difficult and unsolved. Additionally, here air bubbles in the phantom affect the interstitial compartment especially, requiring a better outlet design, as more air bubbles accumulate than in protypes V2s.

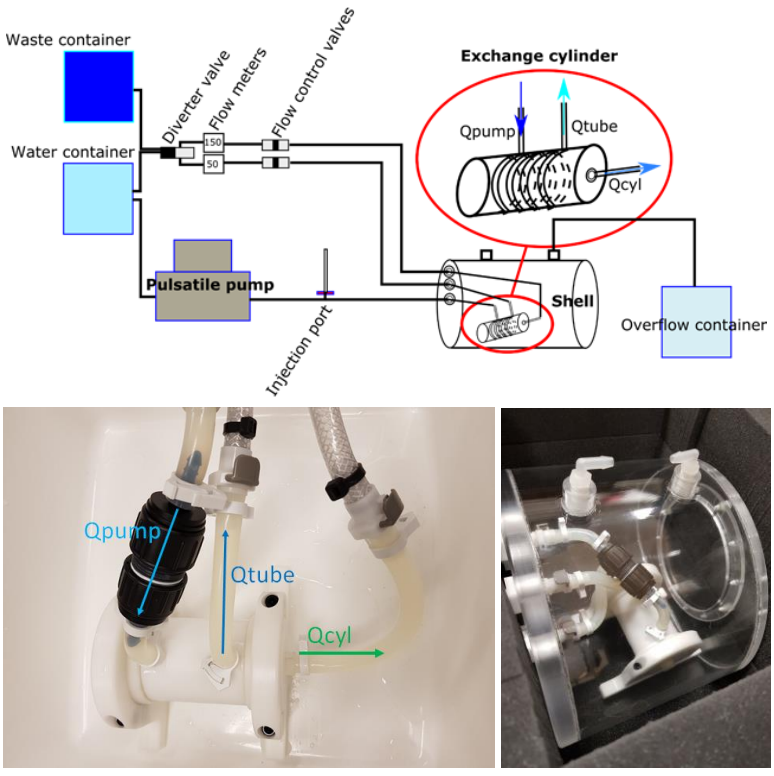

Figure 4.1.6: A schematic diagram of the phantom set-up for PET imaging, with the exchange cylinder and set-up of the phantom.

4.1.3 Summary and key outputs

In conclusion, the project successfully developed two types of phantoms, one for measuring perfusion values, which spatially varying flow and one for measuring exchange of contrast agents. The latter is especially important for PET imaging, where perfusion is measured as exchange (flow) from the blood pool to the tissue compartment. The first prototype was designed, developed and built by the industrial partner ZMT and will be commercialised for use in quality assurance in clinical multi-centre studies.

Key-outputs

1. Development of a perfusion phantom with spatially varying perfusion values (V2b)
2. Experimental comparison of perfusion values with MR-flow measurements
3. Development of a perfusion phantom for exchange between two compartments (V3)
4. Clinical application to PET-MR perfusion imaging

KCL received support of £11,500 from Wellcome/EPSRC Centre for Medical Engineering for further development of the phantom and £250,000 from the British Heart Foundation for multimodality assessment and clinical application of prototype V3.

References:

4.1.1 Amedeo Chiribiri, Cardiac Perfusion MRI, in Book Quantification of Biophysical Parameters by Medical Imaging, Springer 2018, https://doi.org/10.1007/978-3-319-65924-4

4.1.2 Xenios Milidonis, Sohaib Nazir, Myles Capstick, Sita Drost, Gertjan Kok, Nikola Pelevic, Christian Poelma, Tobias Schaeffter, Amedeo Chiribiri, Dynamic contrast-enhanced and phase contrast MRI of a novel 3D printed cardiac phantom mimicking transmural myocardial perfusion gradients, ISMRM 2018, 3327

4.1.3 Gertjan Kok, Nikola Pelevic, Xenios Milidonis, Muhummad Sohaid Nazir, Myles Capstick, Sita Drost, Christian Poelma, Tobias Schaeffter, Amedeo Chiribiri, A Calibrated Physical flow standard for medical perfusion imaging. FloMeko 2019

4.1.4 Nazir MS, Gould SM, Milidonis X, Reyes E, Ismail TF, Neji R, Roujol S, O'Doherty J, Xue H, Barrington SF, Schaeffter T, Razavi R, Marsden P, Kellman P, Plein S, Chiribiri A. Simultaneous ^{13}N-Ammonia and gadolinium first-pass myocardial perfusion with quantitative hybrid PET-MR imaging: a phantom and clinical feasibility study. Eur J Hybrid Imaging. 2019;3(1):15. https://link.springer.com/article/10.1186/s41824-019-0062-6

4.2 Objective 2 (uncertainty evaluation for quantitative perfusion imaging):

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.*

4.2.1 Relevance to the project's needs and objectives

Currently, assessment of perfusion is performed mainly qualitatively or semi-quantitatively by visual inspection or describing the image intensity (e.g. upslope of intensity function or area under the curve). For full quantification different mathematical models have been proposed. However, the low signal-to-noise ratio offered by current models (uncertainties up to 40 % for voxel-based analysis and larger than 10 % for segment-based analysis) can often result in physically and physiologically meaningless solutions. As a result of this, and the variability inherent in clinical practice, perfusion imaging is not yet fully quantitative, and results cannot be reliably compared across imaging modalities.

4.2.2 Description of the work

The aim of the project was to improve quantitative perfusion imaging by evaluating the uncertainty of current quantitative analysis, applying Bayesian approaches to integrate prior-knowledge and developing classification techniques to identify disease-related perfusion states. These improvements will enable pixel-wise perfusion

imaging and ultimately provide relevant quantities to clinicians. The tasks and activities, which were carried out within the mathematics work package to achieve these project aims are summarised below.

A) Uncertainty analysis. The aim of this task was to apply the uncertainty methodology of the Guide to the expression of uncertainty in measurement (commonly known as the GUM) to deconvolution methods for tissue perfusion quantification. The deconvolution methodologies and impulse response parameters were studied, and sensitivity analysis was carried out of to identify the most influential parameters in the perfusion quantification pipeline.

B) Extension of deconvolution. The aim of this task was to identify and study the feasibility of alternative deconvolution methods. In particular a new pixel-wise analysis method with spatial Tikhonov regularization was developed exploiting similar signal characteristics in neighbouring pixels

C) Bayesian deconvolution. This task developed a novel Bayesian approach for cardiac blood perfusion quantification. Because of the novelty that arose from the application of Bayesian techniques to clinical perfusion imaging, the project has produced reports and presentations to the clinical community.

D) Classification. This task developed and assessed a classifier for perfusion data to identify clinically relevant perfusion states. The project used the outputs of the previous tasks in this work package to build classification algorithms that were applied to clinical data.

A) Uncertainty analysis

An extensive literature survey was performed by NPL with input from LNE and PTB to assess the state of the art in perfusion quantification from a metrological point of view. With consultation between data analysis experts (NPL) and clinicians (TUCH, KCL, UH and HUS) this was used as a guide and reference point for following tasks to aid in the choices of extensions and improvements to the current methods for quantifying perfusion using MR and PET imaging.

In particular, a software package in Matlab was developed by LNE with input from NPL and PTB for perfusion quantification of MR-scans, of patients and the phantom, that produces pixel-wise perfusion maps. This software reads in the time series of DICOM images from the CMR perfusion scans and follows a series of data analysis steps that result in a pixel-wise perfusion or MBF (myocardial blood flow) map using a deconvolution method chosen by the user from a list of the most popular techniques This software tools was adapted to run on a High-Performance Computing (HPC) system

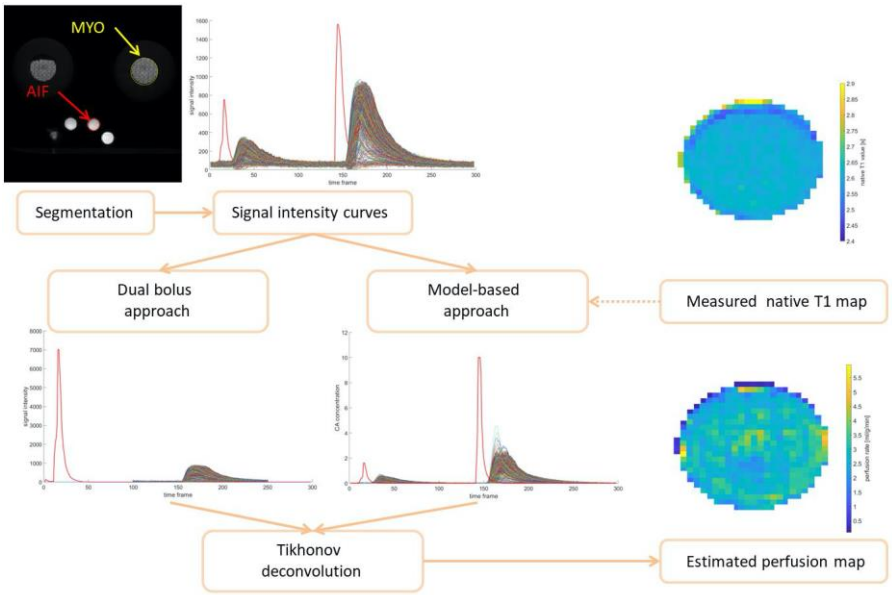

Figure 4.2.1 Software package to automate the CMR perfusion quantification pipeline. The user can choose how to pre-process the data, as well as the deconvolution method used to generate the perfusion maps. The software also carries out a sensitivity analysis of certain parameters of interest and evaluates the performance of pixel-wise perfusion analysis for the phantom by comparing the perfusion maps to ground-truth flow maps.

The software package was used to evaluate the performance of voxel-wise myocardial perfusion quantification methods using repeated measurements of the phantom. A global sensitivity analysis using Monte Carlo simulations was carried out to identify the most influential parameters for two different methods [4.2.1], i.e. dual bolus and model-based approach. It was shown that the native T1 relaxation time is the most influential factor among the physiological tissue parameters leading to a mean RSD in perfusion estimates of 2.5 %. It was shown that 95 % of the computed Relative Standard Deviation (RSD) in perfusion estimates are below 12.47 % and 9.00 % for the reference, 13.24 % and 8.25 % for dual bolus (i) and 26.90 % and 22.46 % for the model based approach (ii) for a perfusion rate of 3 ml/g/min and 4 ml/g/min, respectively. Repeated DCE-MRI measurements have highlighted the need for accurate and repeatable measurements to fulfill perfusion quantification especially for the model-based approach.

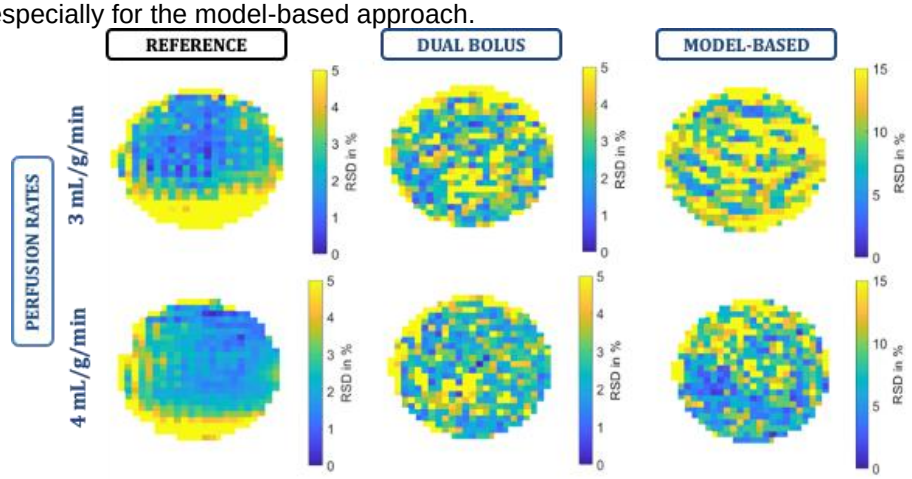

Figure 4.2.2 Relative standard deviation (RSD) calculated from 3 repetitions shown in percentage for the perfusion rate of 3 and 4 ml/g/min. From left to right: flow maps generated by PC-MRI of the perfusion phantom (reference), estimated perfusion maps using (i) the dual bolus approach and (ii) the model-based approach.

Methods for PET perfusion quantification and the associated sources of uncertainty were also studied in this project by TUCH in collaboration with NPL. The effect of PET image reconstruction on the image-derived flow values in terms of accuracy and reproducibility with a wide set of parameters was analyzed [4.2.2]. Using a recently introduced PET flow phantom and radiowater as a tracer, the effect of image matrix size, Gaussian filter size (GFS), point spread function (PSF) modelling, time-of-flight (TOF) and regularized reconstruction

(Q.Clear, Trademark of GE Healthcare Inc.) to flow quantification were assessed on a recently introduced digital PET/CT system. The effect of different matrix sizes, Gaussian filter size, TOF and/or PSF implementation as well as the Q.Clear reconstruction to image-derived flow values was found to be small, showing a variation with a standard deviation of less than 2 mL/min between subsequent measurements as well as to absolute relative errors of less than 7 %.

The repeatability of the flow phantom PET measurements was investigated by TUCH image-derived flow values was investigated in order to minimize possible error sources [4.2.3]. The results show that the PET flow phantom produces repeatable flow values, with very low standard deviations between repeats and very small absolute errors. These variations between the flow values and the errors to the reference flows were not significant, and the fluctuations in flow values between the tests are due to flow changes because of the bolus injections to the system.

B) Extension of deconvolution.

Pixel-wise quantification of myocardial perfusion by dynamic contrast-enhanced magnetic resonance imaging allows for a non-invasive, observer independent and reproducible evaluation of the perfusion with high spatial resolution. Pixel-wise quantification has been proposed more recently for the quantification of myocardial perfusion by several groups. Since fitting the signal from a single pixel is challenging due to the low SNR, *a priori* filtering in the spatial domain or in the spatial and temporal domain has been proposed. However, there are several drawbacks of filtering the data *a priori*. Inherently, this decreases the spatial resolution of the results. Since filtering and fitting are separate steps, they cannot be balanced against each other, and errors introduced during the filtering cannot be reversed. Furthermore, the filter parameters were determined heuristically in the mentioned work.

NPL, PTB & LNE, with input from TUCH and KCL, developed a new approach to stabilise the quantification of perfusion that is based on a spatial Tikhonov regularisation [4.2.4]. It makes use of the spatial smoothness of the data: the essential idea is that during the fitting process, configurations where neighboring pixels display similar parameter values are favored compared to spatially heterogeneous ones. After motion-correction, segmentation and baseline subtraction, data were approximated by the first four modes of a truncated singular-value decomposition (SVD). To this end, the myocardial signal was written as a matrix with the first-dimension denoting time and the second one space. From the approximated data, a first estimation of perfusion parameters on the pixel-level was calculated with the Fermi method. The employed model is linearised around this estimate and the Tikhonov regularisation term is added. When solving the linearised problem, the non-SVD-approximated data such that the approximation in the first step has no direct influence on the results is used. The regularisation term increases as the spatial heterogeneity of the parameters rises. Note that this is in contrast to other authors who use a temporal Tikhonov regularisation when fitting the data. The degree of regularisation λ is obtained from an L-curve as the point of maximal curvature where both the regularisation term and the residuum of the fit are small. The method was investigated in a numerical phantom that includes a realistic distribution of parameters from clinical scans to simulate dynamic MR-signals as well as clinical data.

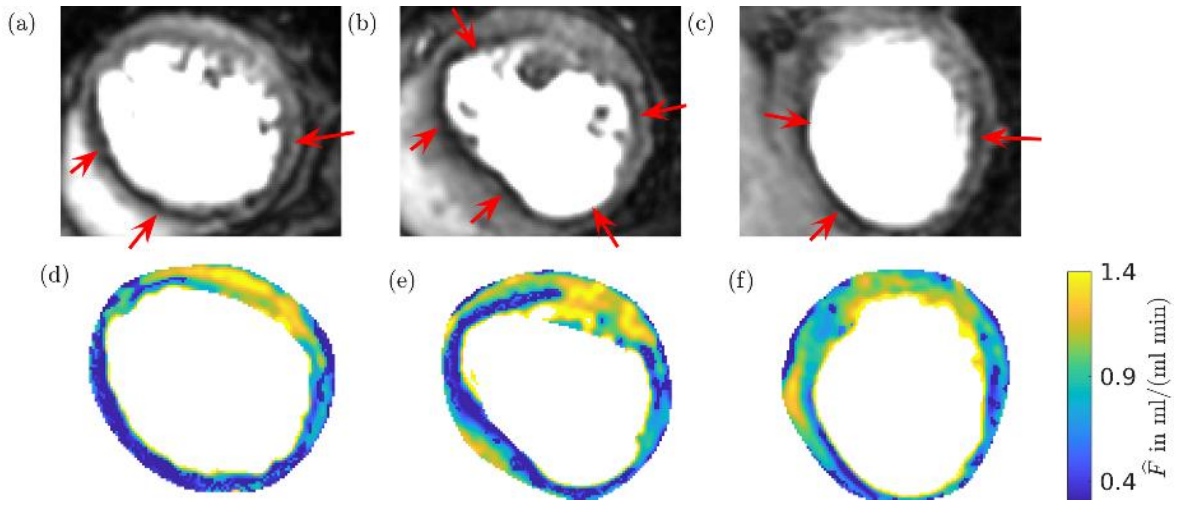

Figure 4.2.3. Quantification of perfusion in patient data. (a) - (c) Myocardial signal for the (a) basal, (b) mid-ventricular, and (c) apical slice of the same patient. Ischemic segments which were visually assessed by a clinician are marked with red arrows. (d) - (f) quantitative perfusion $\hat{F}$ values in ml/(ml min).

Another advantage of the Tikhonov regularisation is that the strength of regularisation can be chosen automatically by means of a L-curve criterion [4.2.5]. It was demonstrated that spatial Tikhonov regularisation results in robust pixel-wise quantification of myocardial perfusion. In patient data, the method provided perfusion maps which correspond well with visual assessment by a clinician.

C) Bayesian Approach for uncertainty assessment

The pixel-wise quantification of perfusion using a Tikhonov regularisation was extended to a fully Bayesian approach [4.2.6]. Bayesian inference has the advantage that it can incorporate prior knowledge in the form of a prior distribution, lends itself naturally to a complete uncertainty characterisation through its posterior distribution, and allows probability statements to be made conditional on the observed data. Prior knowledge can be based on former experiments, physical constraints, or physiological and/or physical expertise. However numerical procedures are needed to calculate the results of a Bayesian inference. A hierarchical Bayesian approach to the quantification of perfusion was suggested. For the deconvolution step the Fermi model for a pixel-wise fit was used and it was assumed that the parameters of the Fermi model vary smoothly motivating the use Gaussian Markov Random Field (GMRF) priors. Incorporating this additional spatial information helps to quantify perfusion on a pixel level despite its low SNR. Most importantly, Bayesian analysis also allowed for a full quantification of the uncertainties. It, therefore, provides not just a perfusion estimate but also a measure for how reliable this estimate is.

A calculation scheme was developed that utilises an approximate analytical expression for the marginal posterior of the amount of smoothness and the strength of the noise in the data, in conjunction with a conditional high-dimensional truncated Gaussian distribution for the spatial distribution of the regression parameters. The propriety of the posterior was proven and the existence of its moments was explored. A hierarchical prior distribution in the form of a Gaussian Markov random field was used to incorporate prior knowledge and to automatically find an appropriate degree of spatial smoothening. The software tools for Bayesian deconvolution developed within this task were adapted to run on a High-Performance Computing (HPC) system.

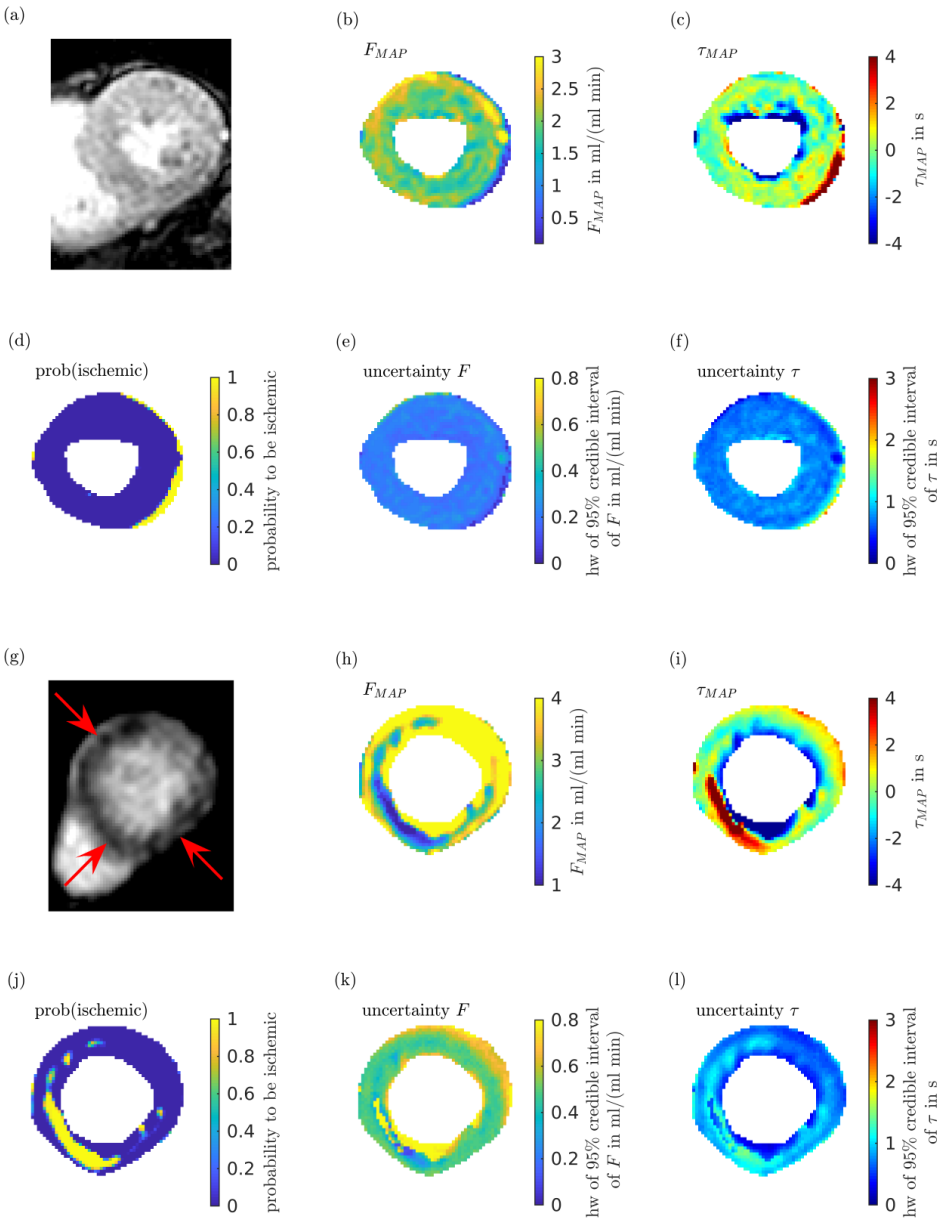

Figure 4.2.4 Results for clinical dataset. Healthy in (a)-(f) and diseased in (g)-(l). Red arrows in (g) mark segments with perfusion defect diagnosed by an clinician on visual assessment. (b) and (h): Maximum a posteriori (MAP) of perfusion values F. (c) and (i): MAP of delay τ. (e,h) and (f,l): Uncertainty as half-width of the 95%-credible intervals in perfusion and delay. (d) and (j): Probability of a pixel to be ischemic.

D) Classification

Two novel classification techniques were developed by NPL with input from TUCH to automatically quantify the severity of myocardial perfusion defects in patients based on predefined guidelines for perfusion measurements using PET data [4.2.7]. One method is based on Receiver Operating Characteristic (ROC) curves to determine an optimised clinical guideline for PET studies was also developed. The methods were applied on clinical data from patients participating in a cardiac PET perfusion study. By combining patient data and expert insights, this framework could (i) help less experienced clinicians make better decisions regarding patient health, (ii) serve as a starting point for further clinical investigation, and (iii) be used as a screening to categorise patients so that the most severe cases can be prioritised on the clinical list. Furthermore, this framework could be used within a machine learning classification pipeline to both label unlabelled data and assess the quality of labelled data. The results of the decision-support systems were compared to cath-lab

data. In collaboration with clinical collaborators, the following clinical guidance was agreed on: if more than 10% of the area of the myocardium has a MBF value less than 1.5 ml/g/min, then the patient is considered to have ischemia.

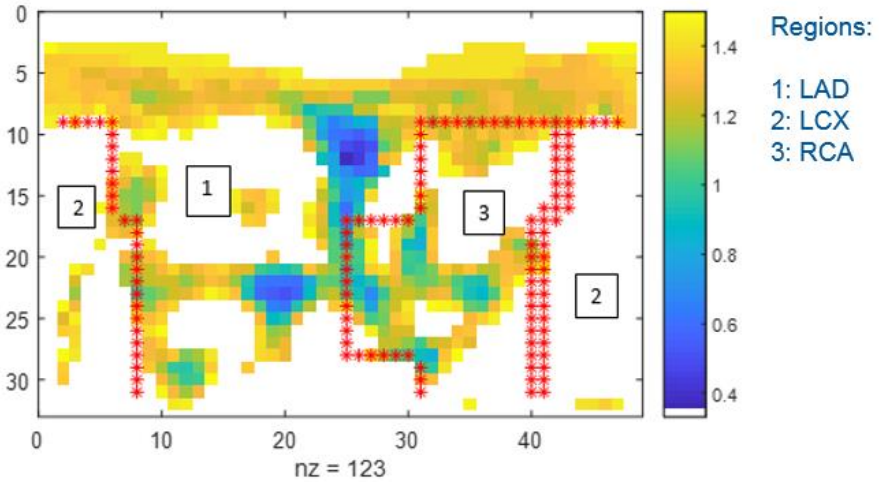

Fig. 4.2.5 Cartesian representation of the MBF values (ml/g/min) resulting from the analysis of perfusion PET scans for a specific patient for affected pixels (those below the threshold of 1.5 ml/g/min).

A different approach to the classification problem was carried out using a deep learning method by NPL using with input from TUCH [4.2.8]. The aim was to detect ischemia using the patients' PET scans directly instead of the perfusion maps derived from those scans as typically done in a perfusion study. A classification task of the state of ischemic disease in patients is performed, using a database of anonymised patient images. Several different deep learning methods are used on voxel time series, allowing training with a limited number of patients, and their performance compared. To reflect the uncertainty in PET image values, random Gaussian noise is added to the input time series during training. A comparison is made between using an ensemble of residual networks with one addition of noise prior to training, and a single residual network with noise added at each epoch.

4.2.3 Summary and key outputs

In conclusion, the project developed a framework to automate myocardial perfusion quantification pipelines and to assess the influence of parameters on and compare the results of perfusion measurements using MRI and PET. It also successfully developed a more robust analysis technique that allows pixel-wise quantification of perfusion defects with automatic determination of the optimal parameter values for MRI data. This method has been extended to a Bayesian approach that allows characterisation of uncertainty of quantities. Two novel classification techniques were developed to automatically derive the severity of myocardial perfusion defects in patients based on guidelines for PET perfusion imaging.

Key-outputs

1. Framework for sensitivity analysis comparison of different data analysis methods
2. Robust analysis technique for pixel-wise perfusion quantification
3. Bayesian method to assess uncertainty of derived quantities associating for the first-time a probability to clinical diagnosis
4. Novel classification methods on PET perfusion data
5. Application to clinical perfusion imaging

References:

[4.2.1] Loic Coquelin et al., Evaluation of the performance of voxel-wise myocardial perfusion quantification methods using a traceable phantom, ISMRM 2019, accepted as digital poster

[4.2.2] R. Siekkinen et al., Study of the Effect of Reconstruction Parameters for Myocardial Perfusion Imaging in PET with a Novel Flow Phantom, submitted to Frontiers in Physics, section Medical Physics and Imaging (2019)
[4.2.3] R. Siekkinen et al., Study of Repeatability of a Novel PET Flow Phantom, IEEE MIC2019, accepted as a poster and oral contribution
[4.2.4] Judith Lehnert et al. Pixel-wise quantification of myocardial perfusion using spatial Tikhonov regularization, Phys. Med. Biol. 63, 215017 (2018)
[4.2.5] Judith Lehnert et al., High-resolution quantification of myocardial perfusion using spatial correlations, ISMRM 2019, accepted as oral presentation
[4.2.6] Judith Lehnert et al., Large-scale Bayesian spatial-temporal regression with application to MR-perfusion imaging, accepted by SIAM Journal of Imaging Sciences 2020
[4.2.7] Kavya Jagan et al., Risk-based decision-making framework on the degree of severity of myocardial perfusion defects. Submitted to Statistics in Medicine (2019)
[4.2.8] Laura Merritt et al., A classification task of the state of ischemic disease in patients from Positron Emission Tomography (PET) scans using a deep learning approach, ENBIS 2019. Accepted as oral presentation

4.3 Objective 3 (uncertainty analysis of multi-modality imaging):

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.*

4.3.1 Relevance to the project's needs and objectives

Comparison of different imaging modalities requires either a relatively large number of participants to average out the variability of perfusion among participants or an intra-individual comparison by using the same participants on different imaging modalities. The latter is preferable but usually not practical. The proposed physical standard developed in this project allows for a direct comparison of different imaging modalities and the application of different quantification approaches

4.3.2 Description of the work

The aim of this task was to use the methodology developed in previous tasks, apply it to multi- modality imaging and extend the methodology for a combined analysis. The output of this task is an assessment of whether the measurements of the different modalities are consistent with each and if the combination of multimodality data yield an improved result, associated with an uncertainty that is smaller than the uncertainties associated with the measurement results obtained by each single modality. Throughout the project, however, the scope of this task has changed due to some technical issues with the phantom including delays in its production, leakage when scanning and software problems. The data that was agreed and that would have been needed to perform a multi-center and multi-modality comparison (i.e. data from different partners on MRI, PET and CT scans) was not available, so the combined analysis described in the aim of the task could not be carried out.

Instead, two datasets from one imaging modality (MRI) carried out at the same center (KCL) using two different scanner manufacturers (Siemens and Philips) were available. Therefore, a multi-scanner comparison on the measurement of perfusion was carried out by NPL with input from LNE, PTB & TUCH, as well as a comparison of the different perfusion quantification methods.

The two available datasets provided by KCL of the V2b phantom scanned using two different MRI scanners (Siemens and Philips) were analyzed using different CMR perfusion quantification methods developed in previous tasks, namely regularized Tikhonov, Fermi, Spatial Tikhonov and Bayesian methods. A comparison of these different methods was carried out on the phantom datasets from both scanners.

Comparisons of the data are first carried out visually by plotting the means and standard deviations of the perfusion measurements extracted from the images against the various factors investigated (i.e. different software implementations, different deconvolution methods and different scanners, different numbers of replications). Example box plots are also shown as the means and standard deviations were found to not fully capture the skewness of the pixel-wise data. Finally, an Analysis of Variance (ANOVA) was applied, where the

ratio of the sum of squares of a factor of interest was compared to the total sum of squares variance, in order to examine the relative contributions to the mean of the various factors investigated.

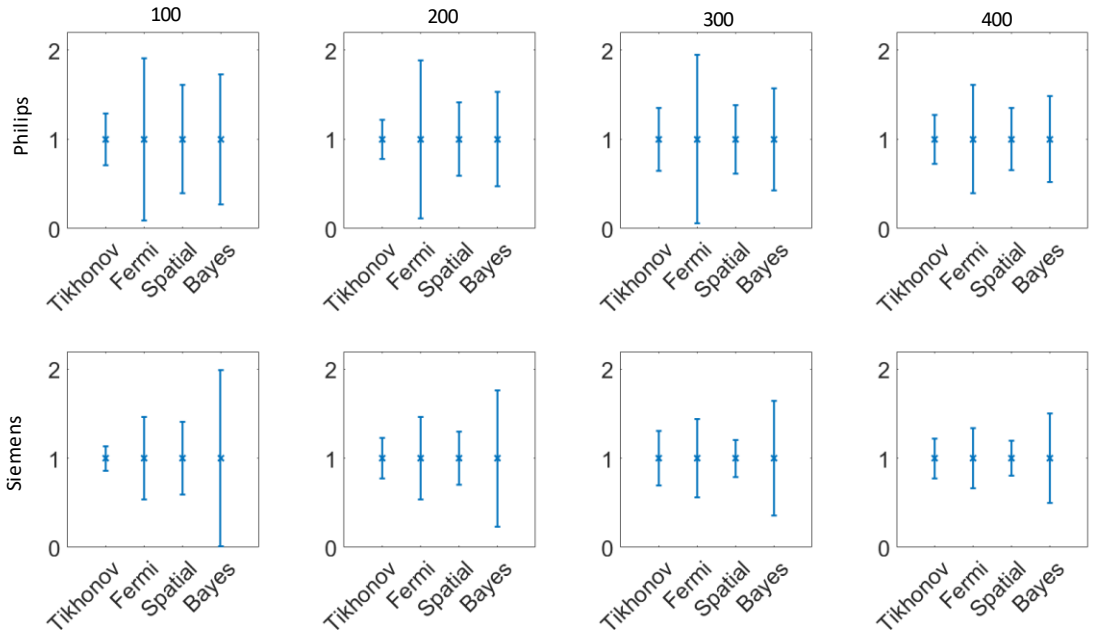

Figure 4.3.1: Plots show the weighted average of the mean perfusion values with error bars corresponding to the standard error on the weighted mean, normalized by the weighted average. Columns are the various flow rates (ml/min) and rows the scanners.

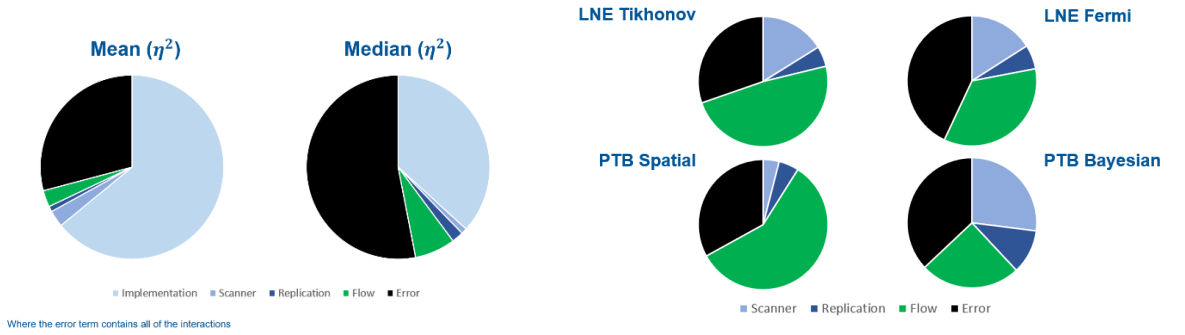

Figure 4.3.2: Results of ANOVA tests. Left: Percentage contribution of investigated factors to the variance of measurements of the mean and the median. Right: Percentage contribution of investigated factors after standardisation of implementation to the variance of measurements of the mean pixel flow.

In general, the effect in the data of different flow rates was visible; the effect in the data of different analysis methods/implementations could be seen; and when the effect of the implementations is normalized, then the effect of different scanners was visible. This suggests that multi-center result comparisons are likely to be difficult unless methods are standardized.

The evaluation of data from a multi-modality comparison can be treated in terms of a meta-analysis. In a meta-analysis, typically data from different sites or laboratories are available where the individual datasets are often obtained using different methodologies and different analysis procedures. In addition to the pure data, often a rating of the uncertainty of the results is available and ought to be included in the meta-analysis. Interlaboratory

or key comparisons play a key role in metrology in order check the ability of different laboratories and to establish equivalence and traceability of measurement results. Meta-analyses are commonly applied in medical studies, e.g., to verify the effect of a certain medical treatment. Another goal of a meta-analysis may be to assess the agreement between the results of different studies. The statistical task of meta-analysis is a challenge on its own, and the development of methods such as the meta-analysis of medical studies is a current topic of statistical research.

4.3.3 Summary and key outputs

Due to unavailability of multi-modality data the project performed an analysis of CMR datasets from one center using two different scanner manufacturers. In general, it was observed:

- the effect in the data of different flow rates;
- the effect in the data of different analysis methods/implementations;
- after normalization the effect of the implementations and effect of data of different scanners.

This suggests that multi-center result comparisons are likely to be difficult unless methods are standardised. Furthermore, the analysis could have been extended to a meta-analysis of multi-modality imaging comparison provided the data required to perform a multi-centre and multi-modality comparison had been available.

Objective 4. To develop personalised dosimetry for imaging with ionising radiation

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.*

4.4.1 Relevance to the project's needs and objectives

Computed tomography has recently moved outside the realm of anatomical vascular imaging and the feasibility of high-resolution CT perfusion measurements has been shown. It offers high spatial (below 1 mm) and good temporal (1 s) resolution in 3D. Since a dynamic acquisition is required, significant ionising radiation is applied to the patient, which is in the order of the patients between about 10 mSv to 20 mSv [4.4.1], depending on the size and shape of the patient. Therefore, an individual dose calculation becomes important. Conventional effective dose estimates in CT are based on the measured dose-length-product multiplied by a calculated conversion coefficient [4.4.2]. Furthermore, new low-dose CT-approaches have been proposed to minimise ionising radiation while obtaining imaging data of sufficiently quality to analyse perfusion. For this, iterative reconstruction algorithms are applied, which influence the image quality in a non-linear way. There is a need to investigate the relationship between individual dose and image quality.

4.4.2 Description of the work

The aim of this work was to lower the high uncertainties of the effective dose estimates for one organ from 20 % - 50 % to significantly lower levels of 10 % - 20 % and to establish and verify a general procedure for Patient-Specific-Dose-Estimates (PSDE) in computed tomography (CT) imaging (Figure 4.4.1) with special application to CT perfusion studies. The procedure is based on the calculation of the post-scan 3D dose distributions within the exposed parts of the patient's body using the commercially available software package 'Impact MC' [4.4.3]. This package enables the users to perform a fast Monte Carlo simulation of the complete scan. Inputs needed for such a simulation are the reconstructed CT-image (DICOM file) of the patient and anthropomorphic model extensions for scatter contribution, the scanner source model and the actual scan protocol parameters.


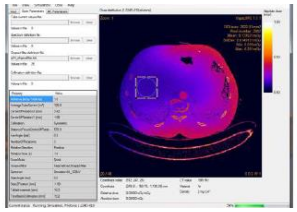
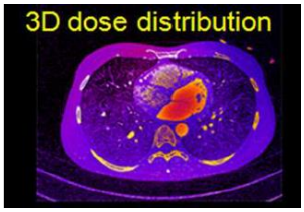

Figure 4.4.1: General procedure to determine scanner- and patient specific dose estimates in CT (from left to right): CT-scan of the patient (1), organ segmentation in CT image (2), 3D dose map from CT-scan simulation (3), organ and effective dose determination (4).

Quick automatic organ segmentation in the 3D CT image is still a challenge although machine learning based approaches are very promising. Scanner simulation with Monte Carlo methods need special input data like the CT-X-ray source model including the permanent and bow tie filtrations. These data are usually confident and not available. Therefore, it was necessary, to develop a non-invasive measurement procedure and equipment in order to obtain so-called “equivalent source models” Next it was necessary to verify the obtained simulated 3D dose distributions by measured values. Finally, an application to dose estimations for CT perfusion imaging was planned.)

PTB provided its research CT scanner of type GE Optima 660 and developed and tested the mobile equipment for equivalent source determinations. STUK was experienced in the use of the Monte Carlo simulation of CT-scans with Impact MC. Further, STUK had experience with CT chamber measurements. HUS had the clinical environment for real CT perfusion studies and provided different scanner types for measurements with the mobile equipment and anthropomorphic phantoms.

A) Mobile equipment for the determination of equivalent CT source models in clinical environments

An essential part of the scanner needed for the simulation are the x-ray beam properties, i.e. the tube characteristics described by the emitted photon fluence spectrum, the fixed filtration and the beam shaping filter, usually called ‘bow tie’ (BT) filter. Photon fluence spectra and the material and shape of the BT-filter are usually not known or proprietary information. However, non-invasive experimental methods are available to determine at least a good approximation to the x-ray spectra and material equivalent representations of the BT-filters. These data usually designated as ‘equivalent source models’ can then be used as inputs to the MC simulation program. The first task was to develop, construct and verify a mobile apparatus and the corresponding evaluation software for the non-invasive determination of equivalent source models that are well suited for on-site measurements at CT machines in a clinical environment. PTB developed such a mobile equipment as shown in Figure 4.4.2 and described in more detail in [4.4.4, 4.4.5]. The special set up and use of the hardware at a CT and a software guide is described in an internal Technical Report (available upon request).

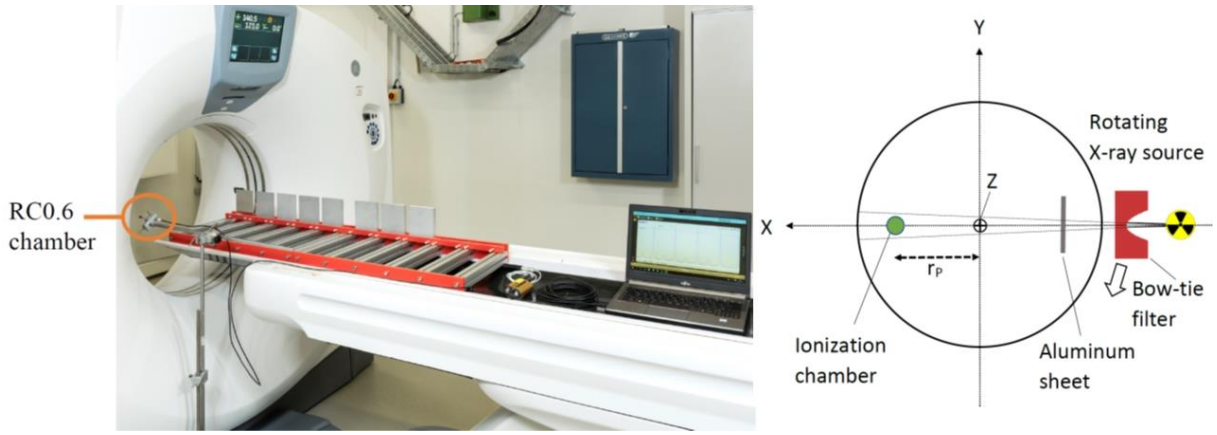

Figure 4.4.2: Mobile measurement setup. With this setup, aluminium attenuation curves and form filter characteristics can be investigated that allow the computation of equivalent CT source models. Aluminium sheets of increasing thickness are placed on the patient table, while the dose rate is measured with an ionization chamber and time-resolved readout. The schematic drawing on the right illustrates the attenuation measurement when the source, the aluminium sheet and the ionization chamber are aligned.

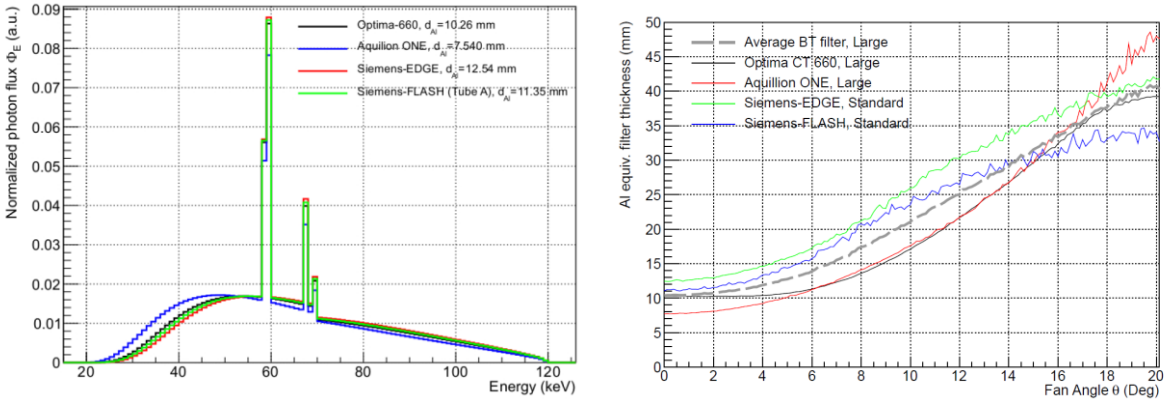

Figure 4.4.3: Left: Photon fluence spectra of different CT scanner types. The photon fluence spectra of the clinical CT scanners is calculated using Al attenuation measurements with the mobile measurement system and the SpecCalc software for determination of photon spectra for tungsten anode material. Right: Aluminium equivalent bow tie filters of four different CT machines.

This mobile system allows application in clinical environments for fast measurement of aluminium half value layer thickness to calculate the X-ray spectra for different anode voltages. Short preparation and measurement times and the minimal amount of hardware that is needed are the big advantages of the system. Custom software has been developed which allows for fast analysis of the data within few minutes to obtain the spectra. In addition, the data is used for the construction of equivalent bow-tie geometries using the COBRA (characterization of bow-tie relative attenuation) method. Within one measurement series both HVL measurements as well as COBRA data are collected without the need of rearranging the system. Results of equivalent source models measured with the mobile equipment at four different scanner types located at PTB, City Hospital Braunschweig and HUS in Helsinki are shown in Figures 4.4.3. The reproducibility of the approach has been tested by comparing the estimated values for the equivalent aluminium thickness to be less than 4%. Further, the implementation of the COBRA algorithm into the software is tested by comparing the attenuation curves with the ones obtained from static measurements.

B) Experimental verification of calculated 3D dose distributions

The second task was to verify calculated 3D dose distributions by measurements with dosimeters in anthropomorphic phantoms at different scanner types. The following steps were required (Figure 3): (1) Determine the equivalent source model of the used scanner type using the mobile equipment developed by PTB; (2) scan the phantom with the embedded dosimeters and measure the dose; (3) simulate the scan with Impact MC and determine the dose at the positions of the embedded dosimeters. The target uncertainties of the calculated and measured dose values for the defined regions of interest within the phantoms were 5 % or less.

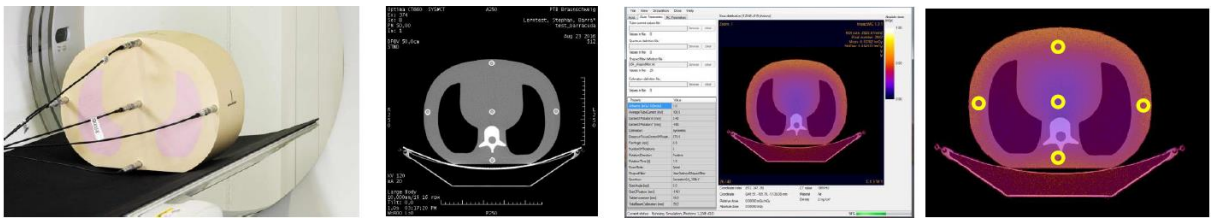

Figure 4.4.4: Procedure to verify calculated 3D dose distributions in anthropomorphic phantoms after the CT-scan by in-phantom dose measurements (from left to right): CT-scan of the phantom equipped with five dose probes (1), region segmentation in CT image (2), 3D dose map from CT-scan simulation (3), dose determination at five positions and comparison with measurements(4).

Measurements were done at four different scanner types: GE Optima 660 (PTB), Toshiba (Canon) Aquilion ONE (Braunschweig city hospital), Siemens SOMATOM Definition Edge (HUS) and Siemens SOMATOM Definition Flash (HUS). Typical results are shown in Table 1 (taken from [4.4.5]).

Voltage (kV)	Position	Measured K_aL (mGy cm / 100 mAs) $\square_c$ = 3.3 %	Measured K_aL Dynamic method (mGy cm / 100 mAs)	Difference %
	12 o'c	75.20	76.17	1.3
	3 o'c	61.49	63.03	2.5
120	6 o'c	63.85	66.54	4.2
	9 o'c	61.02	60.14	-1.5
	center	46.00	49.42	7.4

Table 1. Results of measurements and simulations of the air kerma length product in an anthropomorphic phantom at the Toshiba Aquilion ONE using a spiral scan mode. The dose values at the five positions of the 'Thorax-Medium Adult' anthropomorphic phantom are measured with a 100 mm pencil-type ionization chamber (PTW) and compared to simulated values from Impact MC. The scan parameters have been set to spiral mode, covering 8 cm with 100 mA a rotation time of 0.5 s and a nominal collimation of 40 mm.

Viable procedures were developed that allow the CT scan dose to be measured and calculated at five positions inside physical anthropomorphic phantoms. The relative standard uncertainties of the dose measurements were in the range 1% to 2% and those of the calculations between 3% for axial and 8% for helical scans. In general, measured and calculated dose values inside the phantoms were within the range of uncertainties of 5% to 10%. The procedures are applicable to any scanner type under clinical conditions. Results show that these are well suited for verifying CT x-ray source models needed for personalized CT dosimetry based on post-scan Monte Carlo calculations. The procedures could be part of a potential acceptance test if personalized CT dosimetry is integrated in future CT scanners.

C) Application to dose estimations for CT perfusion imaging

The third task was to apply the new dose estimation procedure to studies in CT perfusion imaging including those conducted with the newly developed physical standards. The objective was to provide a dose estimate in connection with the use of the physical standard and provide estimates of the minimum dose needed to obtain a feasible evaluation data set according to the methods derived in the project. Unfortunately, the physical standard was not available in time for the above described purpose. Instead, realistic source models of a CT scanner and Monte Carlo simulations to real patient data were used to get accurate organ and effective dose estimates for patients undergoing dynamic computed tomography myocardial perfusion examinations.

Source models including bowtie filter, tube output and x-ray spectra were determined for a dual source Siemens Somatom Definition Flash scanner. Twenty CT angiography patient data sets were merged with a modified ICRP 110 voxel phantom. Dynamic computed tomography myocardial perfusion examinations using the shuttle mode were simulated with the Impact MC software for 80 kV and 100 kV spectra. Organs were segmented from patient data using manual and HU-value-based segmentation methods. Organ and effective doses were calculated from simulated 3D-dose distributions. Results: Patients' organ and effective doses varied significantly. For simulations with the 80 kV spectrum the effective dose estimates varied from 5.0 mSv to 14.6 mSv with a mean value of 7.5±2.1 mSv. For simulations with the 100 kV spectrum, the effective dose estimates varied from 8.9 mSv to 24.7 mSv with a mean value of 13.1±3.4 mSv. The absorbed dose to the heart varied from 18.3 mGy to 46.6 mGy with a mean value of 32.1±7.5 mGy for the 80 kV spectrum and from 32.9 mGy to 79.5 mGy with a mean value of 55.7±12.1 mGy for the 100 kV spectrum.

In conclusion, patient specific organ and effective doses were successfully determined. Significant differences between patients' organ doses and effective doses were found. This emphasizes the need to use actual patient data merged with matched anthropomorphic anatomy in the dose simulations to achieve a reasonable level of accuracy in the dose estimation procedure.

4.4.5 Summary and key outputs

Personalized dosimetry in computed tomography (CT) can be realized by a full Monte Carlo (MC) simulation of the scan procedure. Essential input data needed for the simulation are appropriate CT x-ray source models and a model of the patients' body which is based on the CT image.

Mobile equipment together with customized software was developed and used for non-invasive determination of equivalent source models of CT scanners under clinical conditions. Standard and physical anthropomorphic CT dose phantoms equipped with real-time CT dose probes at five representative positions were scanned. The accumulated dose was measured during the scan at the five positions. Impact MC, a MC-based CT dose software program, was used to simulate the scan. The necessary inputs were obtained from the scan parameters, from the equivalent source models and from the material-segmented CT images of the phantoms. 3D dose distributions in the phantoms were simulated and the dose values calculated at the five positions inside the phantom were compared to measured dose values. Results were obtained for four different scanner types of three different vendors. In general, the measured and calculated dose values were within relative uncertainties that had been estimated to be less than 10 %. The procedures developed, which allow the CT scan dose to be measured and calculated at five points inside anthropomorphic phantoms, were found to be viable and rapid. The procedures are applicable to any scanner type under clinical conditions without making use of the service mode with stationary x-ray tube position. Results show that the procedures are well suited for determining and verifying the equivalent source models needed for personalized CT dosimetry based on post-scan MC calculations.

Comprehensive procedures for the determination of CT x-ray source models and their verification by comparison of calculated and measured dose distributions in physical phantoms were successfully developed. It has been demonstrated, that realistic source models of a CT scanner and Monte Carlo simulations can be applied to real patient data in order to get accurate organ and effective dose estimates for patients undergoing dynamic computed tomography myocardial perfusion examinations.

Key-outputs

1. Mobile equipment for the quick determination of equivalent CT source models applicable to any scanner type under clinical conditions.
2. Experimental verification of calculated 3D dose distributions: Measured and calculated dose values inside anthropomorphic phantoms agree within the range of 5% to 10%.
3. Successful application of the personalized CT dosimetry procedure on patients undergoing dynamic computed tomography myocardial perfusion examinations.

Although the planned special measurements with the physical phantom from objective 1 could not be done in time, it can be stated, that the key features of this objective, namely to develop a personalised dosimetry for imaging with ionising radiation, to include a mobile device for determining CT scanner hardware properties and to apply software for the calculation of patient specific dose estimates, were fully achieved.

References:

[4.4.1] Rossi A, Merkus D, Klotz E, Mollet N, de Feyter P, Krestin GP. State of the art: Stress Myocardial Perfusion Imaging with Multidetector CT. Radiology 2014; 270(1):25-46.

[4.4.2] European Commission, Radiation Protection No154: European Guidance on Estimating Population Doses from Medical X-ray Procedures.

[4.4.3] W. Chen, D. Kolditz, M. Beister, R. Bohle, and W. Kalender: Fast on-site Monte Carlo tool for dose calculation in CT applications, Med. Phys. 39(6), 2985-2996 (2012).

[4.4.4] Rosendahl S and Büermann L 2017 Dynamic determination of equivalent CT source models for personalized dosimetry Curr. Dir. Biomed.Eng. 3 791–4; https://doi.org/10.1515/cdbme-2017-0167

[4.4.5] S. Rosendahl, L. Büermann, M. Borowski, M. Kortesniemi, V.-M. Sundell, A. Kosunen and T. Siiskonen: CT beam dosimetric characterization procedure for personalized dosimetry. Phys. Med. Biol. 64 (2019) 075009 (17pp) https://doi.org/10.1088/1361-6560/ab0e97

4.5 Objective 5 (integration into clinical practice):

***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 closely collaborated with three different clinical centres: King's College London (KCL), Turku PET Centre and Helsinki university Hospital. Novel methodologies were developed together with close feedback cycles to guide technical developments to clinical practice. In particular new techniques were applied to patient data and initially tested in clinical settings. Furthermore, KCL adapted clinical training courses based on the results of the project. TUCH is currently conducting a project for optimisation of O-15 H2O perfusion measurements based on the results and experiences of the project. NPL & TUCH are jointly investigating the merits of an SIP follow-up project. A follow-on EMPIR project led by NPL and supported by Turku PET centre (19SIP04) will further integrate the results of the project into clinical practice.

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 (GCP) in Europe and publishes guidelines. The results of the project provided input to & helped shape an expert consensus document between experts from cardiology, radiology, nuclear medicine, and medical physics. In particular, a Delphi approach was used to achieve consensus, where also members of the European association of cardiovascular imaging (EACVI) were involved. The consensus paper has been accepted for publication in Nature Reviews Cardiology in 2020.

5 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 open access papers have been published in peer-reviewed journals thus far, one paper is been 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.

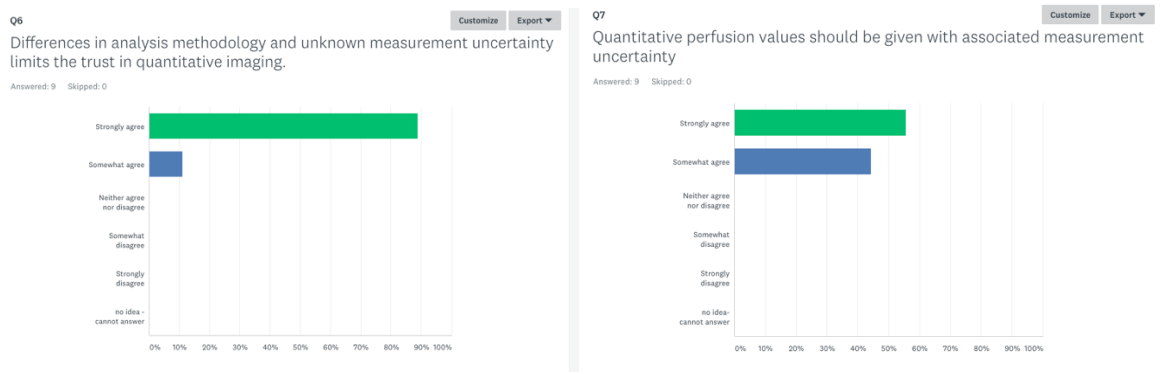

Figure 5.1: Results of two survey questions from representatives from industries (GE, Siemens, Philips, Canon and clinical opinion leaders

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 (a PET data software package developed by Turku PET centre: https://turkupetcentre.fi/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 the 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.

6 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