Aus dem Institut für Radiologie
der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

Noise Reduction and Motion Elimination in Low-Dose 4D Myocardial Computed Tomography Perfusion (CTP): Preliminary Clinical Evaluation of the ASTRA4D Algorithm

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Abstrakt

Abstract (English)

Objectives. To propose and evaluate a four-dimensional (4D) algorithm for joint motion elimination and spatiotemporal noise reduction in low-dose dynamic myocardial computed tomography perfusion (CTP).

Methods. Thirty patients with suspected or confirmed coronary artery disease were prospectively included und underwent dynamic contrast-enhanced 320-row CTP. The presented deformable image registration method ASTRA4D identifies a low-dimensional linear model of contrast propagation (by principal component analysis, PCA) of the ex-ante temporally smoothed time-intensity curves (by local polynomial regression). Quantitative (standard deviation, signal-to-noise ratio (SNR), temporal variation, volumetric deformation) and qualitative (motion, contrast, contour sharpness; 1, poor; 5, excellent) measures of CTP quality were assessed for the original and motion-compensated volumes (without and with temporal filtering, PCA/ASTRA4D). Following visual myocardial perfusion deficit detection by two readers, diagnostic accuracy was evaluated using 1.5T magnetic resonance (MR) myocardial perfusion imaging as the reference standard in 15 patients.

Results. Registration using ASTRA4D was successful in all 30 patients and resulted in comparison with the benchmark PCA in significantly ($p<0.001$) reduced noise over time (-83%, 178.5 vs 29.9) and spatially (-34%, 21.4 vs 14.1) as well as improved SNR (+47%, 3.6 vs 5.3) and subjective image quality (motion, contrast, contour sharpness: +1.0, +1.0, +0.5). ASTRA4D resulted in significantly improved per-segment sensitivity of 91% (58/64) and similar specificity of 96% (429/446) compared with PCA (52%, 33/64; 98%, 435/446; $p=0.011$) and the original sequence (45%, 29/64; 98%, 438/446; $p=0.003$) in the visual detection of perfusion deficits.

Conclusions. The proposed functional approach to temporal denoising and morphologic alignment was shown to improve quality metrics and sensitivity of 4D CTP in the detection of myocardial ischemia.

Abstrakt (Deutsch)

Zielsetzung. Die Entwicklung und Bewertung einer Methode zur simultanen Rauschreduktion und Bewegungskorrektur für niedrig dosierte dynamische CT Myokardperfusion.

Methoden. Dreißig prospektiv eingeschlossene Patienten mit vermuteter oder bestätigter koronarer Herzkrankheit wurden einer dynamischen CT Myokardperfusionsuntersuchung unterzogen.
Die präsentierte Registrierungsmethode ASTRA4D ermittelt ein niedrigdimensionales Modell des Kontrastmittelflusses (mittels einer Hauptkomponentenanalyse, PCA) der vorab zeitlich geglätteten Intensitätskurven (mittels lokaler polynomialer Regression). Quantitative (Standardabweichung, Signal-Rausch-Verhältnis (SNR), zeitliche Schwankung, räumliche Verformung) und qualitative (Bewegung, Kontrast, Kantenschärfe; 1, schlecht; 5, ausgezeichnet) Kennzahlen der unbearbeiteten und bewegungskorrigierten Perfusionsdatensätze (ohne und mit zeitlicher Glättung PCA/ASTRA4D) wurden ermittelt. Nach visueller Beurteilung von myokardialen Perfusionsdefiziten durch zwei Radiologen wurde die diagnostische Genauigkeit im Verhältnis zu 1.5T Magnetresonanztomographie in 15 Patienten ermittelt.

Resultate. Bewegungskorrektur mit ASTRA4D war in allen 30 Patienten erfolgreich und resultierte im Vergleich mit der PCA Methode in signifikant ($p<0.001$) verringerter zeitlicher Schwankung (-83%, 178.5 gegenüber 29.9) und räumlichem Rauschen (-34%, 21.4 gegenüber 14.1) sowie verbesserter SNR (+47%, 3.6 gegenüber 5.3) und subjektiven Qualitätskriterien (Bewegung, Kontrast, Kantenschärfe: +1.0, +1.0, +0.5). ASTRA4D resultierte in signifikant verbesserter segmentweiser Sensitivität 91% (58/64) und ähnlicher Spezifizität 96% (429/446) verglichen mit der PCA Methode (52%, 33/64; 98%, 435/446; $p=0.011$) und dem unbearbeiteten Perfusionsdatensatz (45%, 29/64; 98%, 438/446; $p=0.003$) in der visuellen Beurteilung von myokardialen Perfusionsdefiziten.

Schlussfolgerungen. Der vorgeschlagene funktionale Ansatz zur simultanen Rauschreduktion und Bewegungskorrektur verbesserte Qualitätskriterien und Sensitivität von dynamischer CT Perfusion in der visuellen Erkennung von Myokardischämie.

Manteltext

Introduction

The pathophysiology of CAD and current diagnostic approach. Cardiovascular disease is the leading global cause of mortality [1], accounting for 31% of all deaths worldwide according to the World Health Organization. In coming decades it is expected to become more prevalent for demographic and lifestyle reasons (obesity and diabetes, aging population). Coronary artery disease (CAD) is mainly caused by cholesterol-containing deposits (plaques) building up in the wall of the major blood vessels of the heart, the coronary arteries, and inflammation. Over time these plaque can narrow the coronary arteries and slowly block blood flow. Coronary stenosis is the reduction of the diameter or lumen in one or more coronary arteries. Eventually, reduced blood flow may cause chest pain (angina), shortness of breath, or other CAD symptoms. A completely blocked artery or a sudden plaque rupture can cause a heart attack.

Reducing risk factors, such as high blood pressure, high cholesterol, diabetes/insulin resistance, obesity, smoking, inactivity, unhealthy diet, can help prevent the plaque from forming. Patients with suspected CAD may receive an initial diagnostic test like electrocardiogram (ECG), echocardiogram or a stress test, followed by a cardiac catheterization or heart scan by computed tomography (CT), depending on the results and the pretest probability [2].

Invasive coronary angiography (ICA) is the gold standard to image the coronary vasculature and to assess the presence and severity of CAD. The advantage of this method is the combination of diagnostics and therapy. A significant coronary artery stenosis or occlusion can be detected and possibly stent-fed in one session. Most of the ICA performed, however, are not followed by an intervention. Coronary catheterization may cause major complication in 1.3% of cases and has 0.05% in lab-mortality rate. In addition, radiation exposure and the risk of contrast agent-induced nephropathy should be mentioned.

Technical advances in cardiac CT such as wide detectors arrays, dual-source configuration, low-kV and high-pitch acquisition, current modulation, as well as iterative reconstruction techniques have allowed coronary CT angiography (CTA) to become established as a non-invasive, accurate and rapid imaging modality that provides high temporal and spatial resolution at low radiation exposure (<1mSv) for motion free cardiac imaging and detailed visualization cardiac morphology and coronary or myocardial pathology. Due to its high negative predictive value (>90%) for detecting coronary artery stenosis in the clinical setting it has become the first-line recommendation for patients with suspected CAD. Clinical decision-making for myocardial revascularization is linked to the presence of myocardial ischemia. Pure anatomical evaluation of stenosis severity by CTA does not inform about the hemodynamic significance of a given coronary stenosis [3, 4]. The additional use of physiologic information to detect hemodynamically significant CAD, see Figure 1, has an incremental prognostic value over CTA alone and allows improved risk stratification of patients with CTA-detected stenosis [5-7], as shown, for example, in the CORE320 study [8]. Second line non-invasive functional assessment of a detected coronary artery stenosis is therefore an attractive addition to CTA, but relies mostly on referral to other imaging modalities: non-invasively by cardiac magnetic resonance (MR) perfusion [9,

10], positron-emission tomography (PET) [11] or CT perfusion (CTP) [12]. Though, functional evaluation is not yet routinely applied in clinical practice due to missing standardization of acquisition protocols, valid reference values to discriminate between normal and reduced myocardial perfusion, low spatiotemporal resolution, cost and availability of imaging devices [13].

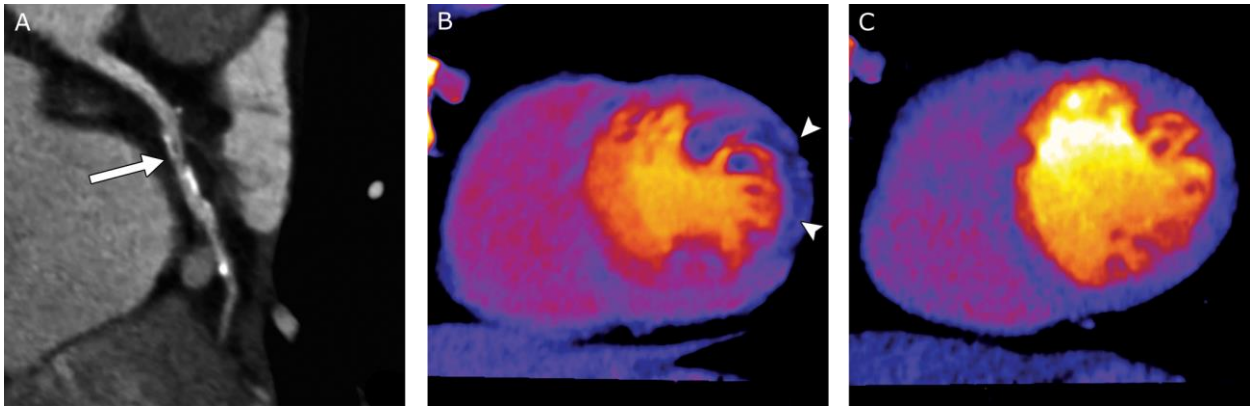

Figure 1. 72-year-old man with multiple cardiovascular risk factors who presented with chest pain suggestive of ischemic heart disease and was referred for coronary CT angiography and myocardial perfusion imaging. The left circumflex artery shows mixed plaque with intermediate-to-severe stenosis (A). At stress, the iodine distribution map (B) shows well-demarcated area of decreased myocardial iodine content in lateral wall of left ventricle, which is reversible on rest image (C). Findings are thus consistent with lateral wall ischemia [14].

Invasive coronary angiography (ICA) with catheter-based fractional flow reserve (FFR) using pressure wire and adenosine is the established reference standard for the functional assessment of CAD [15]. It allows accurate invasive assessment of flow limiting vascular perfusion deficits [4] and is important for ischemia-guided revascularization [12]. FFR quantifies the severity of coronary artery lesions by measuring the pressure loss across a stenosis determining hemodynamic significance but does not assess the functional impairment of the myocardium subtended by the stenotic vessel. Epicardial coronary stenosis is only one of the factors contributing to the pathophysiological process leading to myocardial ischemia. Inflammation, endothelial dysfunction, microvascular dysfunction, platelet dysfunction, thrombosis, and vasomotor dysfunction should also be considered [6]. The explanatory power of FFR is therefore limited for the measurement of myocardial perfusion. Microvascular dysfunction, for example, may be a primary pathology or may coexist with stenosis.
To have a joint anatomical and functional evaluation of CAD available within the single non-invasive modality CT would improve risk stratification. CT can evaluate the functional significance of a coronary stenosis by static or dynamic myocardial perfusion imaging, and, as of recent, non-invasive CT-derived fractional flow reserve CT-FFR, see Figure 2. CT-FFR is an index of epicardial stenosis-related ischemia, a lesion-specific noninvasive FFR estimate derived from conventional coronary CTA using models from computational fluid dynamics (CFD) without the need for additional functional testing, thus providing anatomical and physiological assessment using a single CTA dataset. CTP, on the other hand, reflects the impact of both, epicardial coronary lesions and microvascular disease, on myocardial perfusion [6].

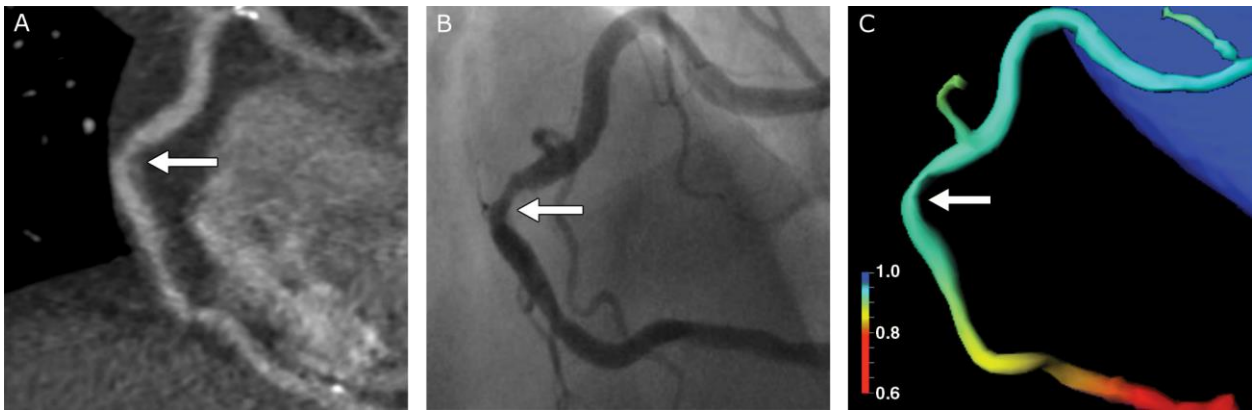

Figure 2. 57-year-old man who underwent non-invasive CT-FFR measurements. The right coronary artery from standard CTA shows intermediate degree luminal stenosis (A). ICA confirms presence of stenosis (B). FFR was measured at 0.93 via invasive flow wire, indicating lack of hemodynamic significance of this lesion. FFR derivation from coronary CTA of lesion of interest (C) using CT-FFR (Siemens Healthineers) revealed value of 0.94, in good correlation with invasive measurement [14].

Contrast-enhanced computed tomography perfusion (CTP) assesses the distribution of intravenously administered iodinated contrast agent in the myocardium as an indicator for myocardial blood flow (MBF), mostly using pharmacological vasodilator stress. Iodinated contrast material attenuates x-rays proportional to iodine concentration, hypoattenuated areas in the myocardium are suggestive of reduced myocardial perfusion (ischemia) and/or reduced intravascular blood volume. Ischemic/infarcted myocardium shows both a slow wash-in and a slow washout of the contrast material, resulting in lower and delayed peak attenuation [16] whereas normal myocardium enhances homogeneously after intravenous contrast material injection. CTP improves the diagnostic accuracy for the detection of functionally relevant coronary artery disease (CAD) [3] and has a similar diagnostic accuracy as other non-invasive modalities for the detection of myocardial perfusion defects attributable to flow-limiting stenosis [9] with ICA and FFR as the reference standard. In static CTP a single data frame, a snap shot, for optimal differentiation of ischemic and non-ischemic myocardium is acquired during arterial first pass, whereas dynamic CTP, which appears to have a higher sensitivity than static CTP [6], images the left-ventricular myocardium over time.

Dynamic imaging allows to quantify absolute myocardial blood flow (MBF in ml/g/min) derived from hemodynamic modeling (e.g. by compartment models or deconvolution). Quantification is not yet routinely applied in clinical practice, it is relatively noise sensitive, there is a significant heterogeneity in normal perfusion vales, and dynamic CTP generally underestimates MBF compared to PET and cardiac MR. Currently there are no established reference cutoff values of MBF to discriminate with high diagnostic accuracy between normal and abnormal myocardial perfusion, which may be attributable to variability in the study design, image acquisition and post-processing techniques.

Reduced myocardial perfusion, potentially caused by flow limiting stenosis in a coronary vessel, is either assessed visually or quantitatively. Myocardial CT perfusion deficit detection is complicated by cardiac motion, especially in stress imaging with higher heart rates, noise from low-voltage scatter radiation, beam hardening from highly attenuating tracer, and the relatively poor contrast resolution (attenuation difference between normal and hypoperfused myocardium in the range of 17-50 HU [17]). Considering its benefits over other modalities (attenuation directly proportional to contrast material,

high spatial resolution, low acquisition time, wide availability [16]), CT may be the adequate basis for joint anatomical and functional assessment of CAD at high diagnostic accuracy in a single modality. Though, wide employment of dynamic CTP protocols has also been hindered by the unavoidably higher radiation dose from repeated CT (5–13 mSv for dynamic CTP [18]), despite advances in low dose acquisition protocols and scanning technology. Further progress in image post-processing and clinical validation will be needed before routine clinical implementation of dynamic CTP.

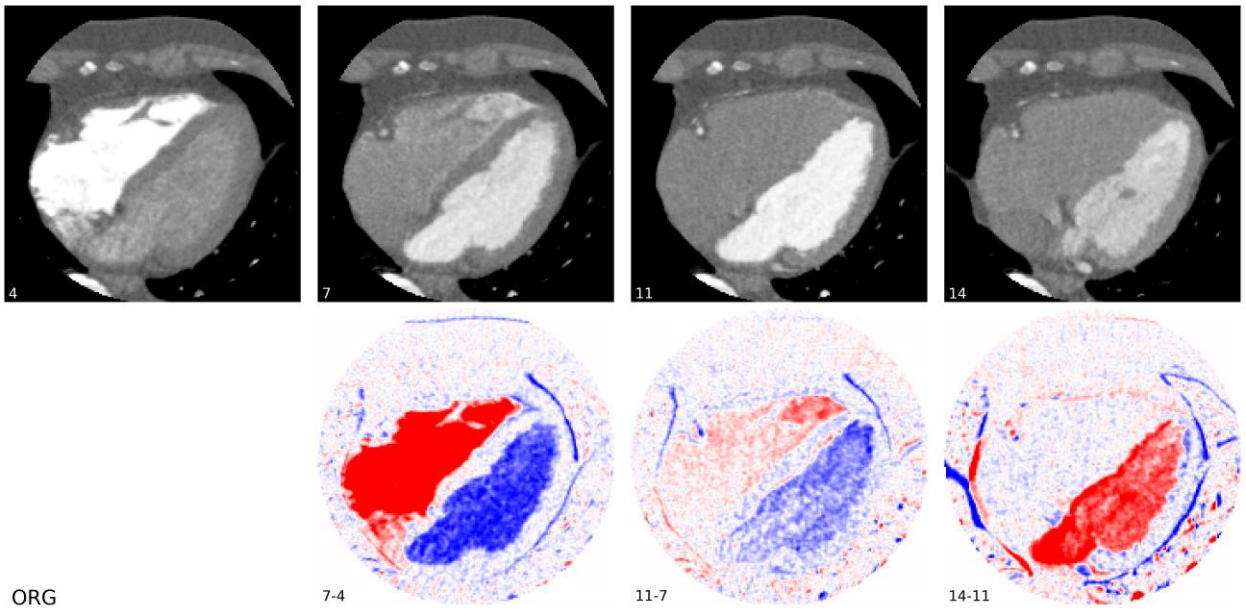

Figure 3. Representative axial slices and corresponding color-coded difference images underneath. Cardiac deformation between different phases of the original sequence can be visually detected by the presence of edges in the difference images for tissues of substantially different attenuation.

Challenges of dynamic CTP motion elimination and current research landscape. Complex cardiac deformation and patient motion (Figure 3), scatter radiation form low-dose scanning, imperfect timing of prospective ECG gated acquisition and beam hardening artifacts from highly attenuating tracer make image quality improvement for dynamic cardiac CTP sequences mandatory for diagnostic evaluation.

Motion correction for dynamic contrast enhanced sequences is challenged by rapid intensity changes compromising common intensity based registration algorithms. Low-dimensionally parameterized tracer-kinetic models have been proposed to distinguish motion from intensity changes due to contrast [19], however, are relatively noise-prone and require a high temporal resolution.

Alternatively, physiologically meaningful behavior of anatomy and tracer flux can, though implicitly, be achieved by using temporal or spatial regularization during motion elimination. Deformations can be controlled by imposing penalty terms on the transformation model (such as, elastic potential or bending energy), or biomechanical constraints such as incompressibility of soft tissue to achieve a more realistic deformation behavior (during the cardiac cycle, myocardial volume varies by at most 5%). Particularly appealing in the high dimensional dynamic setting is the functional treatment of contrast enhanced intensity curves using data reduction techniques. Several algorithms based on a principal component analysis (PCA) have been successfully used to separate physiological motion

and tracer-induced intensity contributions [20-24]. [20] performs a robust principal component analysis (RPCA) to separate motion components from contrast enhancement in a manifold-based registration framework. Also based on RPCA, [21] decomposes the time-series into a low rank and a sparse component, allowing to register the motion component (low rank) using the residual complexity similarity measure. [22] eliminates motion by enforcing sparseness in eigenvectors obtained from a PCA of the joint correlation matrix of the image sequence. [23] removes motion artefacts while preserving long-term contrast enhancement using a progressive principal component analysis (PPCR). [24] uses independent component analysis (ICA) and a time-frequency analysis to identify motion and separate it from the intensity change induced by contrast agent prior to registration. [25] reduces motion by finding the minimal Renyi entropy wavelet representation system of the contrast-enhanced time-attenuation curves (TACs).
Detection of myocardial perfusion deficits relies on the differentiation of healthy and ischemic or infarcted myocardium with reduced and delayed tracer uptake. For accurate semi-quantitative or visual assessment, perfusion defects should be well delineated from healthy myocardium and persist over time, therefore requiring an integrated four-dimensional spatiotemporal approach to image quality improvement of the entire CT perfusion sequence. 3D iterative reconstructions techniques greatly improve noise profile of the cardiac volumes independently, temporally well-behaved smooth contrast enhancement curves require a full 4D treatment, though. None of the aforementioned functional approaches do ensure temporal smoothness of the resulting TACs without explicit regularization. Post-hoc spatiotemporal filtering following motion compensation [26, 27] improves the noise profile (spatial noise and contrast-to-noise ratio) of the sequence but may also introduce artifacts in the filtering process itself. We therefore propose to reduce motion and improve image quality of the 4D CTP sequence at the same time.

Goal of the dissertation. The goal of the dissertation is to assess and to improve image quality and diagnostic accuracy of the dynamic CT perfusion sequence obtained from the CT perfusion pilot study (n=30) for the visual detection of myocardial perfusion deficits with MR myocardial perfusion imaging as the reference standard. In a first step, the notion of temporal averaging of consecutive 3D CTP datasets, without prior motion correction, as a method of noise reduction was introduced [28, 29]. In a second step, we proposed a unified framework comprising both motion elimination and an ex-ante approach to temporal denoising [30] on the basis of exploratory principal component-based alignment [22]. We analysed the benefits and limitations from either stage for the purpose of myocardial perfusion deficit detection.

Methods

Patient cohort, acquisition, and post-processing. The basis of the analysis was the CT perfusion pilot study *Cardiac 4D perfusion: Pilot study of dynamic myocardial perfusion using multi-detector computed tomography* initiated and conducted by Prof. Dr. med. Marc Dewey at Charite University Hospital Berlin, 2012 (trial registration number EA1/251/11). After obtaining ethical approval and written informed consent, 30 patients with confirmed or suspected CAD and an indication for cardiac CT perfusion were examined. Half of the cohort (15 out of 30) also underwent cardiac first pass MR

imaging as the diagnostic reference standard, as clinically indicated, after excluding patients with contraindications to MR. Details on in- and exclusion criteria, patient preparation and patient characteristics can be found in [29]. Stress dynamic myocardial CTP after vasodilator administration was performed on a 320-row CT scanner covering the heart in a single gantry rotation. Iodinated contrast agent was injected at a relatively high flow rate of 7 ml/s, followed by a saline flush, to aid detectability of ischemia by visual assessment in the unregistered CTP sequence from increased peak myocardial enhancement due to higher iodine concentration. No special contrast administration system was employed, large intravenous access was sufficient. Dynamic scanning was realized according to the myocardial low dose acquisition protocol designed for the CTP pilot study, with one prospectively ECG-gated acquisition every heartbeat over a period of up to 20 heartbeats during early first-pass of the contrast, followed by three single late phases, resulting in an average effective dose of 9 mSv [29]. All cardiac volumes were reconstructed using an iterative scheme (AIDR3D, Canon Medical Systems [31]) and downsampled to 1 mm^3 isotropic resolution for motion elimination analysis.

Preliminary analysis: Image quality assessment by temporal averaging. Cardiac volumes were averaged for different sample window widths of (1, 2, 3, 4, 6, 8) time points centered on the reference volume most suitable for visual assessment of perfusion defects. Objective image quality (noise, signal-to-noise ratio, contrast-to-nose ratio) was assessed in the left ventricle, the healthy and the ischemic myocardium, respectively. Subjective image quality was assessed on 5-point scale (1=nondiagnostic, 5=excellent), motion during the whole acquisition on a 4-point scale (0=no motion, 3=severe motion) and the presence of myocardial perfusion deficits according to the 17 segment model of the myocardium by an experienced clinical reader. Diagnostic accuracy was evaluated with MR perfusion as the reference test. Additionally, contour sharpness (width and intensity slope at the contour) was assessed at four distinct edges of the left-ventricular myocardium in averaged volumes reconstructed by filtered backprojection (FBP), and also, in comparison, in volumes reconstructed by AIDR3D (no averaging).

Preliminary analysis: Assessment of existing motion correction methods. Several preliminary motion correction experiments were conducted to study their applicability and limitations for myocardial CTP alignment. First, conventional intensity-based similarity measures (mutual information, sum of squared differences, normalized cross correlation) were applied in a pairwise approach, one-by-one, either sequentially or with regard to a chosen reference time point (phase of best deficit detectability). Second, aiming at physiologically desirable smooth attenuation curves, we implemented a groupwise metric that penalizes strongly varying, either due to noise or motion, time intensity curves (integrated squared curvature). Third, we investigated the dynamic image alignment based on a sparse representation in principal components of the intervolume correlation matrix [22] and variance of intensities of spatially corresponding voxels over time [32]. Fourth, we implemented a dynamic version of [33] in extended state space (morphology and bolus flux) with regularization based on the elastic potential of the deformations and the sparsity-promoting total variation transform on the intensity changes. Registration performance was visually evaluated (morphology, motion, artifacts, deformation field, time intensity curves).

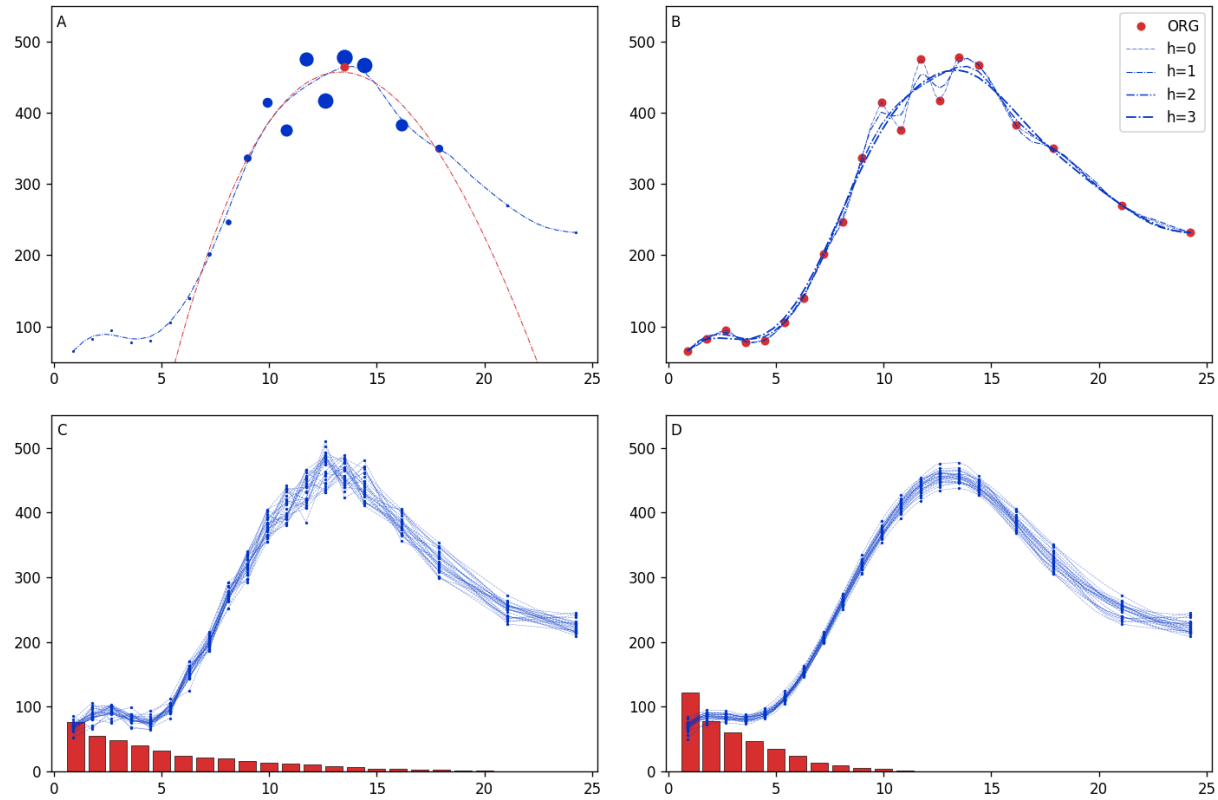

Figure 4. Illustration of temporal regression. (A) Local polynomial regression (LPR) at the selected time point (red circle) with local cubic fit (red) to data points (blue) with Gaussian weights. (B) LPR fit of data points (red) for different bandwidths. (C) Twenty-six random perturbations of the original aortic TAC and their corresponding correlation spectrum (red). (D) Temporally smoothed TACs and their spectrum. As a result of smoothing, the joint evolution of TACs can be explained with few leading eigenvectors.

The proposed method: Joint alignment and denoising. Grounded upon the preliminary analysis and image quality requirements for myocardial perfusion deficit assessment we developed a registration algorithm (ASTRA4D) that combines alignment and denoising [30]. The target metric quantifies misalignment in terms of the spectrum of the intervolume correlation matrix, obtained by a principal component analysis (PCA): Noise or motion are discernible from the high frequency components of the spectrum. For each realization of the deformation model, time-intensity curves of the deformed sequence are temporally smoothed by using local polynomial regression prior to misalignment quantification. The degree of smoothness is controlled by the bandwidth of the Gaussian smoothing kernel (Figure 4). The registration scheme numerically identifies deformations such that the correlation matrix of the resulting sequence admits a sparse spectral representation in smoothed space, thus simultaneously ensuring motion elimination and noise reduction. The result of the algorithm is the jointly aligned and temporally smoothed perfusion sequence. The multi-resolution registration scheme was implemented in the open-source registration package *elastix*, applying a stacked deformable multi-dimensional B-spline deformation model, and the adaptive stochastic gradient descent optimization. No further explicit regularization was employed, though implicitly by the choice of regression kernel bandwidth and spatial grid spacing of the deformation model. All thirty downsampled original perfusion sequences were registered for different combinations of kernel bandwidth (0, 1, 2, 3, 4) and spatial grid size (15, 30, 45, 60 mm) after an initial rigid registration step.

The benchmark method [22] can be recovered in the limiting case of zero bandwidth, i.e. no additional smoothing.

Image quality and diagnostic assessment. Registration performance of the proposed method ASTRA4D was assessed quantitatively and qualitatively and compared with the original and motion compensated series using the benchmark method (PCA). The following quality measures were evaluated in four regions in the myocardium, always averaged over time: image noise (standard deviation), signal-to-noise ratio, temporal variation (mean squared second temporal derivative), volumetric deformation (Jacobian determinant of the transformation model), deviation with respect to the benchmark method PCA. Visual perfusion sequence quality (motion, contrast, contour sharpness) was subjectively graded on a 5-point scale (1=poor, 5=excellent) by two independent readers. The grades were averaged between readers for each measure and patient. Semi-quantitative visual assessment of myocardial perfusion (normal vs hypoperfusion) was performed by two readers for each sequence (CT and MR) in 15 of the 30 patients which underwent both examinations. Myocardial segments were identified using the 17-segment model (American Heart Association guidelines). Diagnostic performance was evaluated as sensitivity and specificity individually for each reader as well as combined on a per-patient, per-vessel and per-segment basis considering the MR consensus reading as the reference standard. Interobserver agreement was determined using the kappa statistic. Heterogeneity in the detection of myocardial perfusion deficits was assessed using Cochran's Q test.

Results

Preliminary analysis: Image quality assessment by temporal averaging. Noise was monotonically decreasing, both signal-to-noise ratio and contrast-to-noise ratio were monotonically increasing with the number of averaging volumes, see Figure 5. Image quality peaked when using 3 combinations and motion classified as little motion [29]. Contour sharpness decreased monotonically with increasing number of averaging volumes reconstructed by filtered backprojection (FBP), while iterative reconstructions (AIDR3D) reduced contour sharpness compared to FBP [28]. Only the use of 3 combinations improved diagnostic accuracy in the detection of perfusion defects relative the original sequence, resulting in a per-patient sensitivity of 82% (9/11) and specificity 100% (4/4), and on a per-segment sensitivity of 31% (10/32) and specificity of 97% (216/223), considering MR perfusion as the reference standard [29].

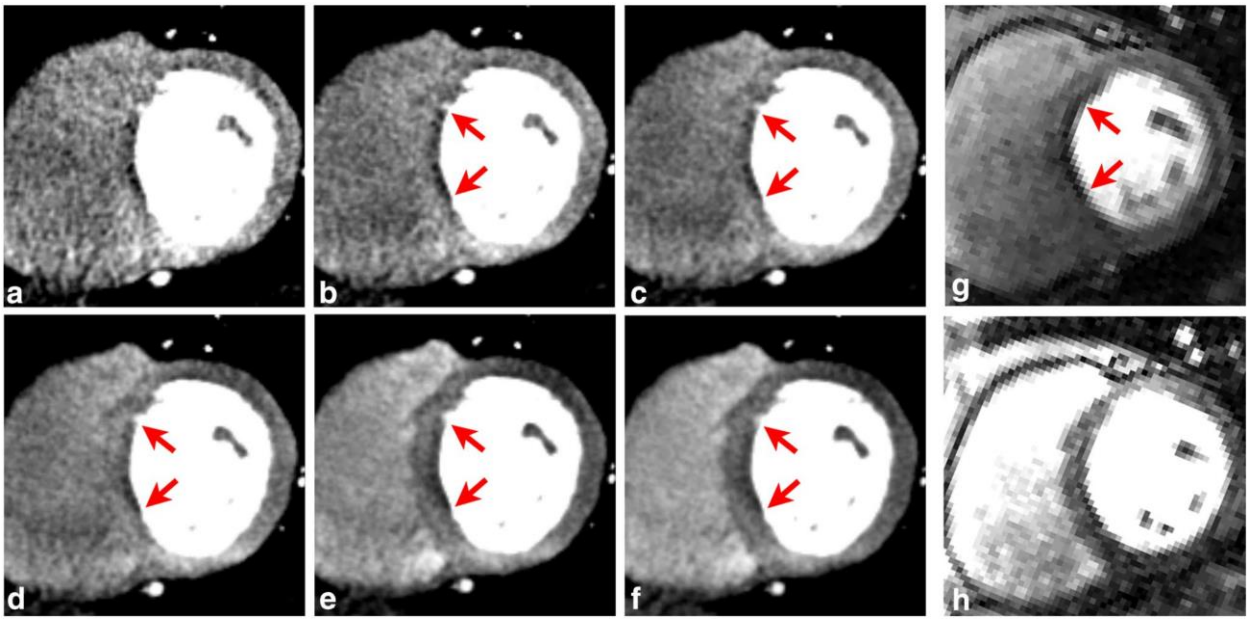

Figure 5. Basal cardiac short axis slice of a 63 year old male with typical angina pectoris and hyperlipidaemia. (a–f) Temporally averaged volumes with increasing number (1,2,3,4,6,8) of 3D CTP datasets from consecutive heart beats. (g, h) Stress and rest MR MPI. The original sequence had no relevant motion artifacts. The subendocardial perfusion defect in the septal wall (arrows) is demarcated very well from (b–f), while it was read as false negative in the original dataset (a). The stress MR MPI as the reference standard confirmed the septal subendocardial perfusion defect (arrows in g), which was not visible on the rest images (h).

Preliminary analysis: Assessment of existing motion correction methods. None of the pairwise approaches yielded subjectively satisfying results for the contrast enhanced sequences (any similarity measure). While sequential registration led to increasing registration errors over time (noise propagation), the pairwise method led to strong misregistrations for significant change of contrast patterns, as may be the case for longer intervals between acquisition time points (reference image bias). In any case, they did neither guarantee a smooth bolus transition nor maintain a temporally stable morphology.

Groupwise registration approaches, on the other hand, explicitly allow to control temporal behavior of the result. Targeting voxelwise temporal smoothness alone, however, was not sufficient, and led to strong volumetric changes over time. Without a proper regularization of the deformation field, time intensity curves were forcibly kept smooth leading to unrealistic shrinkage or expansion of the entire heart.

Jointly optimizing over motion and intensity changes during registration was computationally demanding (total variation penalty on the additive intensity correction) and ill-posed (underdetermined from state space extension) already in the dimension-reduced 2D+t (2D over time) tests and was thus judged not to be feasible for the clinical 3D+t CTP setting without significant computational advancements. Assessing similarity by voxelwise variance over temporal dimension [32] proved not to be applicable in the presence of contrast enhancement (strong distortions). The PCA method [22], finally, assessing the relative temporal changes by means of the joint correlation of the volumes, consistently coped well with the dual presence of tracer induced intensity changes and cardiac motion/deformation, see Figure 6. Thus the motivation for using the independently developed method PCA as the benchmark.

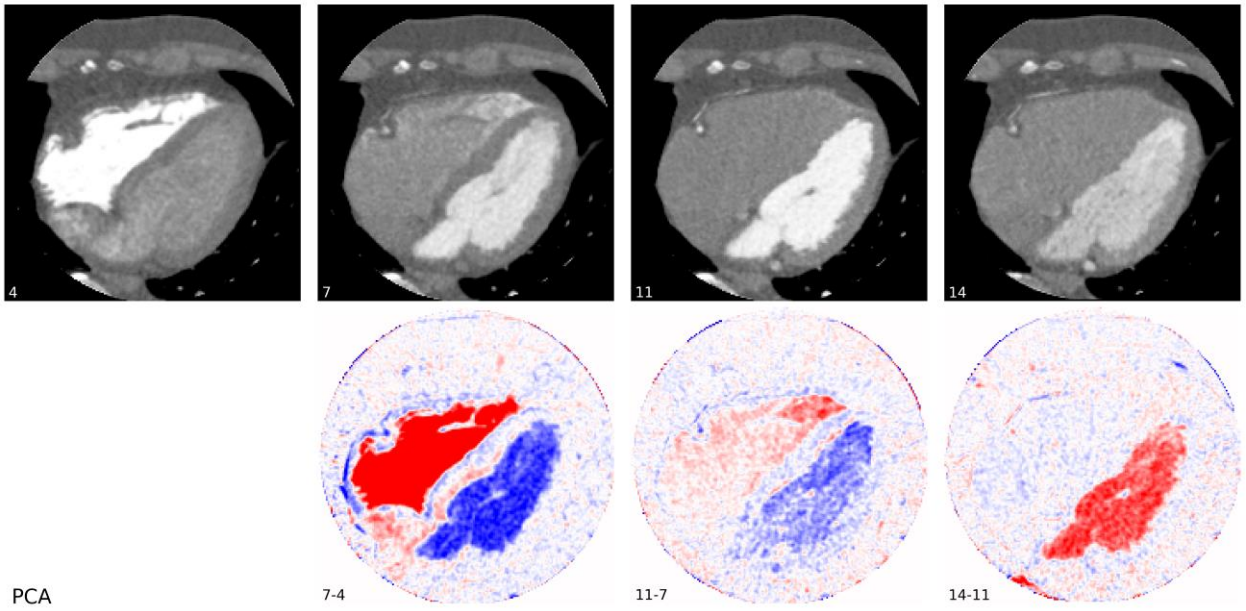

Figure 6. PCA reduced motion in the registered representative axial slices of Figure 3 as seen in the difference images underneath.

The proposed method: ASTRA4D. Registration using the proposed method was successful in all CTP pilot study patients and proved to be superior in the triple performance assessment (subjective, objective, diagnostic) when compared to the unregistered sequence and the sequence obtained from the benchmark method PCA, see Figure 7. Objectively, the use of ASTRA4D significantly reduced spatial and temporal noise compared to the benchmark PCA. Subjectively, ASTRA4D significantly improved perfusion sequence image quality as evaluated by two independent readers compared to both the original and the benchmark sequence, resulting in increased image quality (+1,+1,+0.5) on a 5-point scale for the quality measures (motion, contrast, contour sharpness). The use of ASTRA4D resulted in excellent diagnostic performance with MR perfusion as the reference test. Sensitivity and specificity, aggregated over 2 clinical readers, were 91% (58/64) and 96% (429/446) on a per-segment basis. Reading of the PCA-motion corrected series was significantly less sensitive with a sensitivity of 52% (33/64), while the specificity was similar with 98% (435/446). Interreader agreement on the presence of myocardial hypoperfusion was excellent (CT and MR). Detailed results can be found in [30].

The particular choice of parameters controlling the registration outcome (metric, deformation model, optimization method) proved to be universally applicable for all perfusion sequences analysed. A spatial grid spacing of 45 mm and a temporal kernel bandwidth of 2.0 balanced best between physiologically meaningful deformations and smooth contrast-enhanced time-attenuation curves. Perfusion registration was possible within the few minute range, thus applicable in the clinical setting.

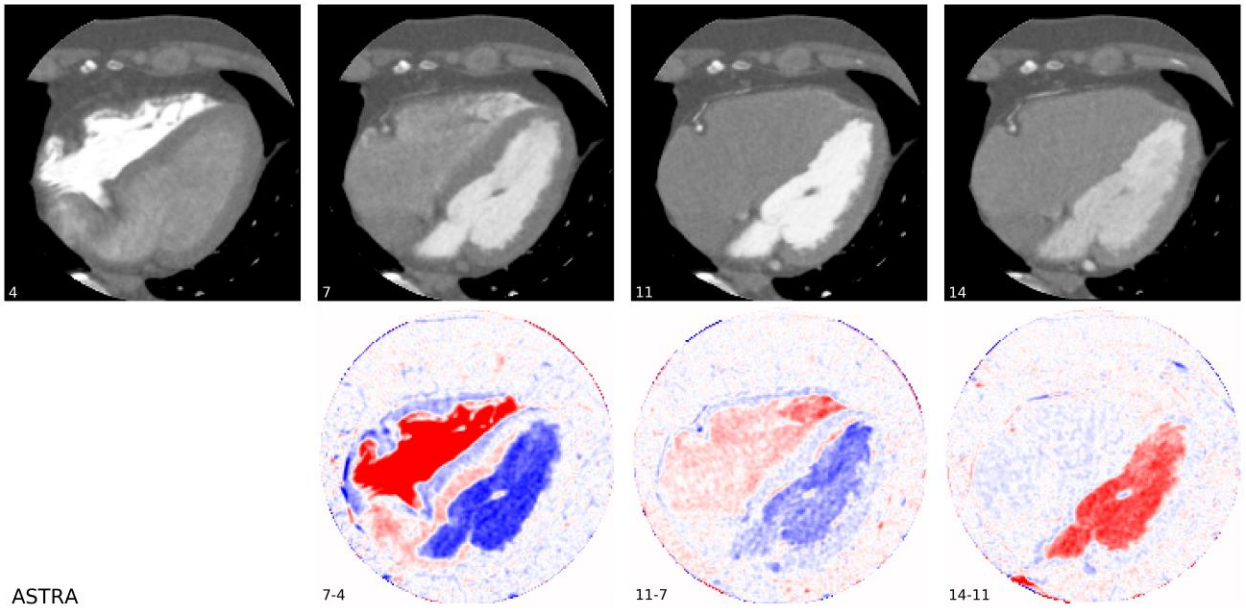

Figure 7. In addition to motion correction using PCA (Figure 6), ASTRA4D reduced noise as seen in the difference images underneath.

Discussion

We addressed two drawbacks of low dose 4D CTP in the current dissertation: noise and motion artifacts. While each of these artifacts can be approached separately, denoising and motion correction, we propose and evaluate a single unified framework for the purpose of myocardial perfusion deficit detection.

Denoising by spatiotemporal filtering. The use of an adaptive iterative reconstruction scheme (AIDR3D strong, Canon Medical Systems) as a method of integrated dose reduction allowed the cardiac CTP volumes to be acquired at a fraction of the dose compared to the conventional filtered backprojection (FBP) with quantum denoising software (QDS, Canon Medical Systems) while preserving diagnostic image quality [34]. The scheme AIDR3D reduces the extent of beam hardening artifact and spatial noise by repeated edge-preserving anisotropic diffusion filtering. Residual artifacts remain, especially in temporal domain (cardiac and patient motion). Considerable motion in the CTP dataset limits the image quality gain from pure filtering approaches that exploit data redundancy arising from the additional temporal dimension. Performance of plain temporal averaging (uniform box filter) was moderate for either evaluation measure [29]. While objective image quality (noise, signal-to-noise and contrast-to-noise ratio) was improved, mainly due to the nature of the averaging filter, subjective image quality could be improved only when combining three cardiac phases with little cardiac motion. Without morphological alignment, moderate to severe motion led to blurring of edges and fine structures [28], spatially, and temporal averaging erased hypoperfused regions, which differ from healthy myocardial tissue only by 17-50 HU [17] and thus in the same range as noise (Figure 8). Myocardial ischemia was badly detected by using temporal averaging without motion correction, manifesting itself in a very low per-segment sensitivity of 31% (3 combinations). Its clinical value for the detection of myocardial ischemia is therefore limited.

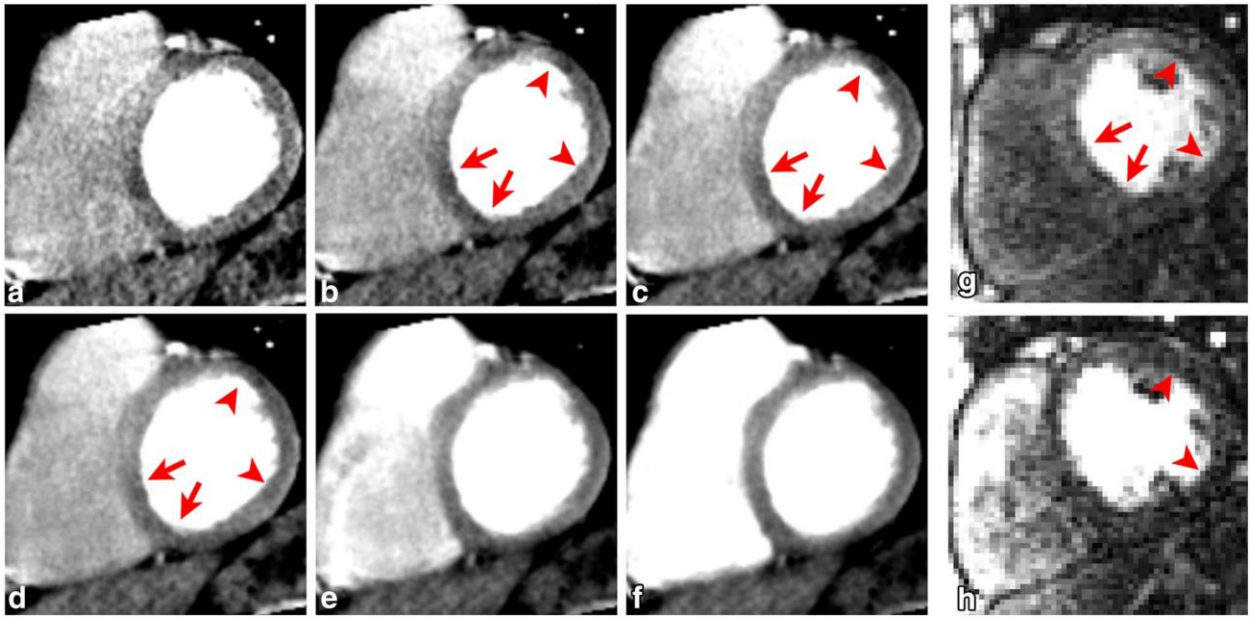

Figure 8. Basal cardiac short axis slice of a 54 year old male with typical angina pectoris and hyperlipidaemia. (a–f) Temporally averaged volumes with increasing number (1,2,3,4,6,8) of 3D CTP volumes from consecutive heart beats. (g, h) Stress and rest MR MPI. (e, f) demonstrate the typical decrease in edge sharpness using 6 and 8 volumes for temporal averaging due to patient motion. (b–d), the subendocardial perfusion defect in the septal (arrows) and lateral (arrow heads) wall was well depicted while it was not seen by the reader in the native dataset (a) and for 6 and 8 combinations (e, f). The stress MR MPI (g) confirmed the septal (arrows) and lateral (arrow heads) wall perfusion deficit. Rest MR MPI (h) demonstrates the lateral wall perfusion deficit (arrow heads; fixed perfusion deficit), while the septal wall perfusion deficit is not visible on rest images (stress induced perfusion defect).

As indicated by the low sensitivity, smoothing in temporal dimension based on a naive strategy (large averaging window, uniform weights) was too strong, different strategies are needed to improve image quality for low dose CTP. Potential candidates are the TIPS, PATEN, GB-TIPS and KMBG spatiotemporal filtering approaches. The 3D time-intensity profile similarity (TIPS) bilateral filter [35] reduces noise by averaging intensity values according to a spatial proximity weight and a temporal weight, measuring the similarity of close time intensity curves based on the averaged sum of squared differences. The partial temporal profile non-local means (PATEN) filter [36] spatiotemporally averages neighboring voxels according to their similarity in a partial time-intensity profile (a partial temporal patch window) if a temporal shift is considered. Noise reduction in excess of 50% was reported for low dose retrospectively gated cardiac CT and brain perfusion compared to filtered backprojection. The guided bilateral GB-TIPS filter [35] introduces an additional weighting factor in TIPS filtering for small structure preservations (weighted average of temporal averaging image and maximum intensity projection according to their temporal autocorrelation). The edge-preserving k-means guided bilateral filter (KMGB) [35] allows to control the transition between different functional structures by classifying voxels according to their TAC similarity using k-means clustering. The success of alternative averaging strategies, such as the above mentioned, relies on sufficient redundancy within the 4D dataset. Low dose TACs dominated by noise, poor contrast resolution and severe motion artifacts, however, as present in our 4D CTP dataset, will also limit their potential for myocardial deficit detection without prior motion correction.

Motion compensation. The high noise level in low dose CTP imaging makes adequate registration challenging. According to our preliminary analysis, assessing functional similarity based on voxelwise trajectories (squared intensity differences [32] or squared curvature along the time-intensity curves) was prone to noise and not a reliable indicator for functional similarity in perfusion sequences. PCA [22] robustly reduced motion based on relative changes between volumes by shifting the correlation spectrum to the dominant entries. Yet, even after motion correction, perfusion deficits were still partly masked by noise due to poor contrast resolution of low dose CTP, resulting in a relatively low per-segment sensitivity of 52%.

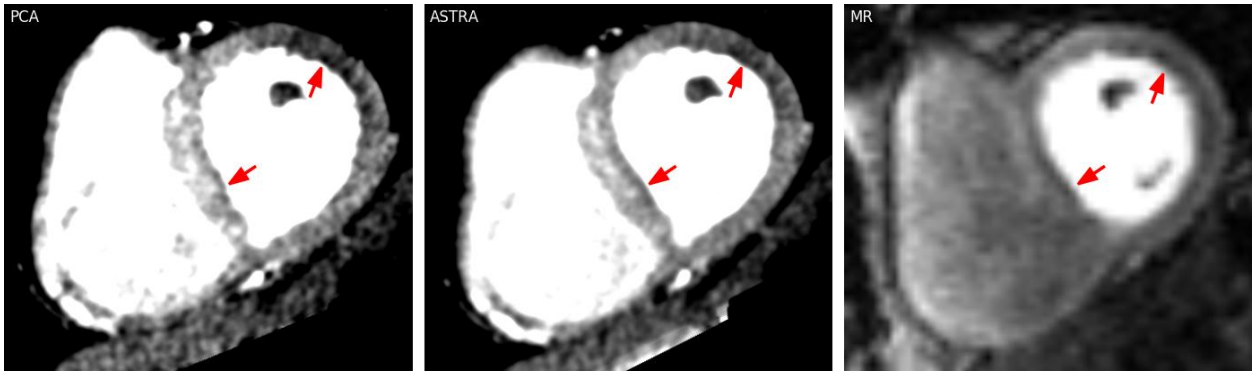

Figure 9. Myocardial ischemia in basal segments (inferoseptal, inferolateral, and anterolateral) is correctly identified (arrows) in CTP (PCA, ASTRA) and MR short-axis views. ASTRA illustrates precise differentiation of hypoperfused areas in this representative patient. MR was acquired in a more diastolic phase and CT in a more systolic phase

The proposed method ASTRA4D [30] as an integrated approach to denoising and alignment pursues an ex-ante strategy to temporal filtering. Only after perfusion sequence smoothing by local temporal regression, the intervolume similarity is assessed during motion correction. The use of spatiotemporal redundancy leads to improved noise-profile in the myocardium, also reported elsewhere [26, 27] by using post-hoc spatiotemporal filtering following motion correction. Artifacts from the usage of plain temporal averaging without registration (blurring [29]) and PCA alone (fluctuating anatomy [30]) could be rectified (Figure 10). Image quality improvements clinically translate into higher temporal persistence and differentiation of the hypoperfused myocardium, resulting in a diagnostic accuracy of 91%/96% (per-segment sensitivity/specificity) for the visual detection of myocardial perfusion deficits (Figure 9). In comparison, [9] reported a per-segment sensitivity/specificity of 78%/76% for the detection of perfusion defects as indicated by reduced myocardial bloodflow estimated from CT using a parametric deconvolution technique (threshold 88 ml/mg/min) related to visual assessment in dynamic rest/stress contrast-enhanced cardiac MR sequences. Deficits derived from quantitatively estimated myocardial blood flow may thus, yet, not be as reliable as visual assessment for the detection of myocardial perfusion defects.

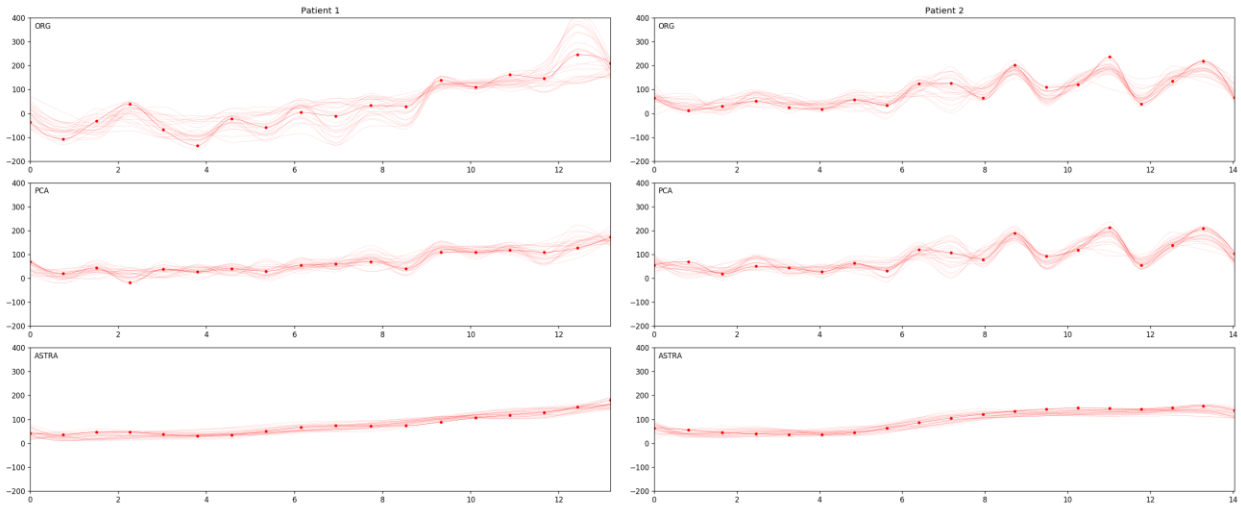

Figure 10. Illustration of TAC-wise motion elimination using PCA and ASTRA4D compared to the original sequence ORG (region size 3×3×3 mm^3, central TAC (solid red line) and its 26 adjacent TACs (dotted)). The left panel shows that motion can be successfully removed using PCA; in addition, ASTRA reduces noise. However, zigzag curves of the original sequence, on the right panel, cannot be resolved by PCA alone. Only the use of temporal regularization in conjunction with motion correction, as in ASTRA, allows the generation of persistent and well-delineated ischemic regions from the original sequence

The dual presence of deformation and tracer flux is the core decision problem for the registration of contrast-enhanced perfusion sequences. Without additional information on cardiac anatomy or haemodynamic, this has been addressed, for example, by state space extension [33], sparseness assumptions [25], variations of PCA [20, 21, 23, 24], or explicit spatiotemporal regularization in order to separate motion components from contrast enhancement. The assumption underlying ASTRA4D and [22] is that intensity changes can be captured by a low dimensional linear acquisition model. Registration as such does not guarantee physiologically meaningful cardiac deformations (during the cardiac cycle, myocardial volume varies by only up to 5%) and evolution of tracer-enhanced TACs which is most often achieved by spatiotemporal regularization. Additional regularizing terms, such as the elastic potential or volumetric change of deformations spatially or integrated curvature along the time-intensity curves temporally, operate, however, on a different scale than the target registration metric aiming at functional similarity, and thus need to be carefully calibrated to each particular task. In contrast, ASTRA4D employs an implicit approach to regularization by means of the coarseness of the deformation grid underlying the deformable registration model and the kernel bandwidth for local temporal regression. Choosing a large bandwidth results in smoother curves, choosing a fine grid may result in better alignment, both at the expense of stronger local deformation. Only the natural scale of the problem is used, the magnitude of cardiac deformations and the perfusion acquisition time sequence, thus avoiding additional high dimensional regularization.

Future research and questions. Only thirty patient were analyzed in this preliminary clinical evaluation of dynamic CTP. No formal assessment of registration accuracy with respect to a given ground truth, necessarily both deformation and intensity change, was done. The temporal filter used, local polynomial regression, had no spatial component; further noise reduction would be possible with a spatiotemporal kernel of a sufficiently narrow spatial bandwidth [35, 36]. Both components of

similarity assessment, PCA and temporal regression, are linear in nature; further gains in registration performance can be expected from the transition to nonlinear and higher dimensional techniques, such as manifold learning. Perfusion deficits may be detected using myocardial blood flow estimates derived from CTP, but quantification, e.g. using haemodynamic models or deconvolution techniques [9, 11], is still relatively prone to noise, lacks modelling consensus and valid reference values. Joint denoising and motion compensation may further stabilize quantification attempts, and replace time-intensive visual assessment in the future. Dose from repeat scanning during dynamic CTP remains high (5–13 mSv CTP [18]). Exploiting anatomical redundancy across acquisition frames can facilitate the reconstruction from sparse angular and temporal projection data. Methods form compressed sensing or deep learning could be applied to reduce streaking artifacts produced by filtered backprojection using limited projections angles only [37, 38]. Reconstruction from highly undersampled projection data would only be possible in combination with a motion elimination algorithm, such as the proposed one, exploiting spatiotemporal redundancy, in particular, its ability to reconstruct volumes from missing and noisy data. Reduced projections during CTP imaging directly translate into radiation dose savings. Whole-heart CTP at sufficient image quality may become technically feasible at <3 mSv by combining low-current low-voltage spatiotemporally sparse acquisition [39, 40] with a method optimally exploiting data redundancy across frames. Time-resolved imaging is suitable for machine learning, since every intensity trajectory may be considered as a feature vector. A clustering method, such as K-SVD, could be used to build patient specific TACs which may be used as basic functions for sparsifying transforms or dictionary learning [35] with wide potential applicability.

Conclusion. Motion correction and noise reduction have a high impact on myocardial perfusion deficit detectability. The proposed theoretically sound unified approach to denoising and registration was shown to improve quality metrics and diagnostic accuracy of cardiac 4D CTP. It may add value in post-processing for any dynamic contrast-enhanced examination and may foster the role of CT as an imaging tool for the comprehensive anatomical and functional evaluation of cardiac stenosis and ischemia and pathophysiological understanding of CAD and thus has high clinical relevance.

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Eidesstattliche Versicherung

„Ich, Steffen Lukas, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Noise Reduction and Motion Elimination in Low-Dose 4D Myocardial Computed Tomography Perfusion (CTP): Preliminary Clinical Evaluation of the ASTRA4D Algorithm“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen werden von mir verantwortet.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Betreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass mir die Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis bekannt ist und ich mich zur Einhaltung dieser Satzung verpflichte.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

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Datum Unterschrift

Ausführliche Anteilserklärung an der erfolgten Publikation

Publikation:

Lukas, S., Feger, S., Rief, M., Zimmermann, E., Dewey, M. (2019). Noise reduction and motion elimination in low-dose 4D myocardial computed tomography perfusion (CTP): preliminary clinical evaluation of the ASTRA4D algorithm. European Radiology 2019.
DOI 10.1007/s00330-018-5899-8

Beitrag im Einzelnen:

- Thema (Lukas, Dewey)
- Entwicklung der Hypothesen, Konzeptionierung, Vorstudien (Lukas)
- Softwareentwicklung, Methodenetablierung (Lukas)
- Datenaufbereitung, -verarbeitung und -analyse (Lukas)
- Auswertung der Ergebnisse (qualitativ, quantitativ, diagnostisch, statistisch) (Lukas)
- Patientenrekrutierung, Patienten- und Untersuchungsbeschreibung (Feger)
- Patientenuntersuchung (Rief, Zimmermann)
- Evaluation der Bildqualität und Herzmuskelperfusion (Dewey, Rief)
- Diskussion von Methode und Ergebnissen (Lukas)
- Manuskripterstellung, Visualisierungen (sämtliche Figuren und Tabellen) (Lukas)
- Korrekturlesen (Feger, Rief, Zimmermann, Dewey)
- Präsentation (European Congress of Radiology, Wien 1.3.2018) (Lukas)

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Unterschrift, Datum und Stempel des betreuenden Hochschullehrers/der betreuenden Hochschullehrerin

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Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	JACC-Cardiovascular Imaging	8,104	10.247	0.026360
2	European Heart Journal-Cardiovascular Imaging	4,630	8.336	0.020640
3	EUROPEAN JOURNAL OF NUCLEAR MEDICINE AND MOLECULAR IMAGING	14,983	7.704	0.024870
4	RADIOLOGY	54,109	7.469	0.063710
5	JOURNAL OF NUCLEAR MEDICINE	27,101	7.439	0.037560
6	CLINICAL NUCLEAR MEDICINE	4,756	6.281	0.006950
7	INVESTIGATIVE RADIOLOGY	6,486	6.224	0.012410
8	Circulation-Cardiovascular Imaging	5,438	6.221	0.020160
9	IEEE TRANSACTIONS ON MEDICAL IMAGING	17,837	6.131	0.024200
10	ULTRASOUND IN OBSTETRICS & GYNECOLOGY	12,420	5.654	0.018820
11	INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY BIOLOGY PHYSICS	46,595	5.554	0.055060
12	JOURNAL OF CARDIOVASCULAR MAGNETIC RESONANCE	4,918	5.457	0.013530
13	NEUROIMAGE	92,719	5.426	0.152610
14	MEDICAL IMAGE ANALYSIS	6,383	5.356	0.011900
15	RADIOTHERAPY AND ONCOLOGY	17,184	4.942	0.027840
16	HUMAN BRAIN MAPPING	20,334	4.927	0.042810
17	SEMINARS IN NUCLEAR MEDICINE	2,285	4.558	0.002990
18	ULTRASCHALL IN DER MEDIZIN	2,201	4.389	0.004310
19	MAGNETIC RESONANCE IN MEDICINE	31,440	4.082	0.034130
20	EUROPEAN RADIOLOGY	18,615	4.027	0.034120
20	SEMINARS IN RADIATION ONCOLOGY	2,480	4.027	0.003620
22	JOURNAL OF NUCLEAR CARDIOLOGY	3,508	3.847	0.004120
23	AMERICAN JOURNAL OF NEURORADIOLOGY	22,667	3.653	0.029840
24	JOURNAL OF MAGNETIC RESONANCE IMAGING	16,398	3.612	0.027440
25	MOLECULAR IMAGING AND BIOLOGY	2,415	3.608	0.005480

Originalpublikation

Lukas, S., Feger, S., Rief, M., Zimmermann, E., & Dewey, M. (2019). Noise reduction and motion elimination in low-dose 4D myocardial computed tomography perfusion (CTP): preliminary clinical evaluation of the ASTRA4D algorithm. European Radiology, 1-11.

https://doi.org/10.1007/s00330-018-5899-8

Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

Publikationsliste

Steffen Lukas, Sarah Feger, Matthias Rief, Elke Zimmermann, Marc Dewey. Noise Reduction and Motion Elimination in Low-Dose 4D Myocardial Computed Tomography Perfusion (CTP): Preliminary Clinical Evaluation of the ASTRA4D Algorithm. European Radiology, 2019.
Impact factor 4.027 (JCR 2017). DOI 10.1007/s00330-018-5899-8

Sarah Feger, Carsten Kendziorra, Steffen Lukas, Ahmed Shaban, Björn Bokelmann, Elke Zimmermann, Matthias Rief, Marc Dewey. Effect of iterative reconstruction and temporal averaging on contour sharpness in dynamic myocardial CT perfusion: Sub-analysis of the prospective 4D CT perfusion pilot study. PLoS One, 2018.
Impact factor 2.766 (JCR 2017). DOI 10.1371/journal.pone.0205922

Sarah Feger, Ahmed Shaban, Steffen Lukas, Carsten Kendziorra, Matthias Rief, Elke Zimmermann, Marc Dewey. Temporal averaging for analysis of four-dimensional whole-heart computed tomography perfusion of the myocardium: proof-of-concept study. The International Journal of Cardiovascular Imaging, 2017.
Impact factor 2.036 (JCR 20217). DOI 10.1007/s10554-016-1011-0

Vorträge

Steffen Lukas. Motion elimination in low-dose 4D myocardial computed tomography perfusion (CTP) using the automated smooth temporal registration for analysis of 4D image data (ASTRA) algorithm (B-0762), New CT protocols to assess coronary artery and myocardium (SS 703), European Congress of Radiology, Vienna 1.3.2018.

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