Image Registration and Analysis for Quantitative Myocardial Perfusion: Application to Dynamic Circular Cardiac CT

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Abstract. Large area detector computed tomography systems with fast rotating gantries enable volumetric dynamic cardiac perfusion studies. Prospectively ECG-triggered acquisitions limit the data acquisition to a predefined cardiac phase and thereby reduce X-ray dose and limit motion artifacts. Even in the case of highly accurate prospective triggering and stable heart rate, spatial misalignment of the cardiac volumes acquired and reconstructed per cardiac cycle may occur due to small motion pattern variations from cycle to cycle. These misalignments reduce the accuracy of the quantitative analysis of myocardial perfusion parameters on a per voxel basis. An image based solution to this problem is elastic 3D image registration of dynamic volume sequences with variable contrast, as it is introduced in this contribution. After circular cone-beam CT reconstruction of cardiac volumes covering large areas of the myocardial tissue, the complete series is aligned with respect to a chosen reference volume. The results of the quantitative perfusion analysis are compared on pig data using the non-registered versus the registered data set. The reduced spatial misalignment leads to an improved characterization of myocardial perfusion confirming the potential of this method.

Keywords: Myocardial perfusion, image registration, computed tomography.

1. Introduction

Myocardial perfusion imaging can be used to measure oxygen supply of muscle tissue in the heart. Therefore, the heart of the patient is imaged in 3D before and during injection of radio-opaque contrast material, and the differences in the reconstructed images can be attributed to the contrast material that is washed in (George et al. 2006). Myocardial perfusion imaging by multi-slice computed tomography (CT) represents a promising tool to detect the significance of a stenosis at the tissue level, i.e. to detect the presence of myocardial ischemia (Nikolaou
et al. 2005, Lardo et al. 2006, Lessick et al. 2007). Moreover, an assessment of the heart muscle viability can allow to distinguish between necrotic and dysfunctional but viable tissues after acute or chronic ischemia, and can support the diagnosis and treatment of acute infarctions (Tilton et al. 1983, Lessick et al. 2007).

Hypoenhanced regions on the initial scan, and hyperenhanced regions on late scans obtained 5-15 minutes after contrast material injection represent two types of abnormal myocardial enhancement patterns which have been described in literature (Nikolaou et al. 2005, Lardo et al. 2006, Lessick et al. 2007). A strong relationship between the presence and size of these two abnormal myocardial defects and the degree of follow-up regional dysfunction after acute myocardial infarction was observed (Lessick et al. 2007). Also, the probability of myocardial functional recovery is significantly inversely related to the presence and size of both early hypoenhanced and late hyperenhanced regions (Lessick et al. 2007). Animal studies have shown early hypoenhancement to be a measure of low reflow regions, which may result from abnormal flow at the level of either the epicardial artery and/or the myocardial capillaries (Rochitte et al. 1998, Mochizuki et al. 1999, Paul et al. 2005, Lardo et al. 2006, Lessick et al. 2007). Late hyperenhancement has been shown to be a marker of necrotic tissue (Rochitte et al. 1998, Lessick et al. 2007). The mechanism of hyperenhancement of healed myocardial infarction or collagenous scar is thought to be related to an accumulation of contrast media in the interstitial space between collagen fibers (Lardo et al. 2006, Lessick et al. 2007).

A cardiac CT scan (e.g. circular scanning-mode) can be applied to generate a sequence of volumes acquired during the first-pass of a contrast agent bolus. Then, the X-ray attenuation changes for each voxel in the acquired images can be visually evaluated by using the corresponding time-intensity curves (Miles 1991, Stantz et al. 2003). Moreover, these time-intensity curves can be used as an input for the assessment of quantitative perfusion-related parameters (Miles 1991, Stantz et al. 2003). A consistent quantitative evaluation of the contrast agent presence during time implies the finding of corresponding voxels in all temporal frames of the 4D perfusion CT data set. Unfortunately, obtaining spatially aligned images is a difficult task in cardiac CT, in which image misalignment due to patient breathing and poor ECG synchronization is commonly observed.

A post-processing misalignment correction, also called image registration, represents a potential solution to increase time sequence alignment (Rueckert et al. 1999, Kybic & Unser 2003). The big challenge in perfusion CT image alignment is the dramatic change of the image intensity over time. This contrast variation has to be taken into account during the registration step. A possible explicit way to get rid of the contrast variation along the time can be to use a time-varying registration reference image. An example of this approach is the serial registration scheme, where only pairs of consecutive images are registered. Here, since the contrast agent diffuses continuously, two consecutive images are almost similar, so this will lead to a more accurate misalignment correction. Nevertheless, an error in the registration of one image pair could affect the alignment of the whole temporal sequence.

An alternative implicit solution can be to use a registration similarity measure (e.g. mutual information (Thévenaz & Unser 2000, Pluim et al. 2003)) which encourages nonlinear intensity variation between images. This solution was already applied in several prior works where rigid or elastic image registrations were applied for magnetic resonance (MR) myocardial perfusion data set alignment, see (Milles et al. 2008) and references therein). The non-negligible drawback of the mutual
information (MI) metric is its quite expensive evaluation in computation terms. In an earlier work (Wollny et al. 2008), Wollny et al. proposed to use a combination of modified normalized gradient fields (Haber & Modersitzki 2005) and sum of squared difference as registration criterion. This alternative normalized gradient based approach is deterministic, much simpler, fast to compute, and also much more suitable to optimization compared to MI. The zero mean normalized cross-correlation (ZNCC) can be an alternative faster image registration metric. The normalization embodied into the ZNCC allows tolerating linear and uniform brightness variations between the images to be registered.

In this paper, a non-rigid registration method is proposed to allow an effective characterization of myocardial perfusion. Given a cardiac 4D CT data set (section 2.1), all frames are registered to a reference image where the myocardial region of interest (ROI) is well delineated (section 2.3). Subsequently, a quantitative analysis is performed by calculating the area under curve (AUC) and the peak intensity (PI) (section 2.4). The method is evaluated on three pigs (two healthy cases, and one pig with myocardial infarction) and quantitative perfusion maps of the registered and non-registered data sets are calculated and visualized (section 3). Sections 4 and 5 contain the discussion and conclusion, respectively.

2. Method

In the following subsections, the components of the proposed perfusion analysis are presented. First, the methods applied for the generation of the 4D CT image (subsection 2.1) and for image filtration (subsection 2.2) are briefly discussed. Subsequently, in subsection 2.3 the image registration applied for the spatio-temporal alignment of the data set is described. Finally, the evaluated perfusion related parameters are introduced (subsection 2.4).

2.1. Generation of 4D image data sets

A 4D cardiac image data set is required for the determination of the perfusion-related parameters. The images are obtained by continuously acquiring projection data \( p \) with a CT scanner equipped with a focus-centered 2D detector and an X-ray source moving on a circular path around the anatomy. The circular scan is performed with multiple rotations \( N_{rot} \). The ECG is recorded in parallel. Depending on the animals heart rate, data are acquired during \( M \) cardiac cycles. The acquisition with a cone–beam CT system can be described as follows. The X–ray source rotates around the object at the position \( z = z_0 \):

\[
S(\lambda) = \begin{bmatrix}
R \cos(\frac{\lambda}{\Lambda_{rot}} \frac{2\pi}{\Lambda_{tot}})
\\ R \sin(\frac{\lambda}{\Lambda_{rot}} \frac{2\pi}{\Lambda_{tot}})
\end{bmatrix}.
\]

(1)

The rotation axis coincides with the \( z \)-axis. The parameter \( \lambda = 0..\Lambda_{tot} \) describes the discrete angular position of the source, \( \Lambda_{rot} \) is the number of angular source positions per rotation, \( \Lambda_{tot} \) is the total number of angular source positions, \( N_{rot} = \Lambda_{tot}/\Lambda_{rot} \) denotes the total number of rotations, and \( R \) is the radius of the circle.

In the same way as already known from helical cardiac CT, a phase point position can be chosen as a percentage of the RR interval, resulting in \( M \) phase points \( P_t \), with
Figure 1. The circular CT data acquisition framework. An ECG is acquired simultaneously to the continuous circular CT scan. Thus, a certain number of timeframes can be reconstructed out of the continuous axial scan, depending on the heart rate of the animal. The timeframes are reconstructed from subsections (grey intervals) with an angular range of 220° centered around the chosen cardiac phase point $P_t$.

$t = 0 \ldots M - 1$, at the angular position $\lambda(P_t)$ (Manzke et al. 2003). The position of the phase points defines the motion state of the heart that should be depicted. A rectangular cardiac gating window (see Fig. 1), is centered at each phase point $P_t$ and only projections $p(\lambda)$ within this time window are used during each single cycle reconstruction. Aiming at the best achievable temporal resolution an angular coverage of 220° is used per cardiac cycle.

For the image reconstruction of each image $f_P(x, t)$ per cardiac cycle, a single cycle variant of the reconstruction method described in (Koken & Grass 2006) for the helical case and in (van Stevendaal et al. 2006) for the circular cone-beam case was used. The reconstruction formula per timeframe reads as:

$$f_P(x, t) = \frac{1}{2\pi} \int_{\lambda(P_t) - \frac{W}{2}}^{\lambda(P_t) + \frac{W}{2}} w_{ap}(\lambda, x) \cdot p_f(\lambda, u, h) d\lambda.$$  \hspace{1cm} (2)

Here, the backprojection interval is limited to an angular range of $\pi$ plus fan angle $\beta$ by $W = \pi + \beta$. The aperture weighting function $w_{ap}$ defines a trapezoidal cone-beam weighting function (Koken & Grass 2006, van Stevendaal et al. 2006) and $p_f$ are the rebinned and filtered cone-beam projections. They depend on the source angular position $\lambda$, the distance of the line integrals from the rotation axis $u$ and the detector height projected onto the rotation axis $h$.

2.2. Spatio-temporal bilateral filtration

Image noise and artifacts can hamper an accurate quantitative analysis of myocardial perfusion. In this implementation, a spatio-temporal diffusion filtration for dynamic
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CT data (Bruder et al. 2009) is applied to overcome this problem. Here, a bilateral filter is applied to the 4D data set \( f_P \) in two different steps. First, given a certain temporal position (i.e. cardiac cycle) \( t^* \) of the dynamic CT data set, with \( t^* \in [0, M-1] \), a filtration is done on the spatial coordinates by:

\[
\hat{f}_P(x, t^*) = \frac{1}{N_{S_{\text{norm}}}(x, t^*)} \sum_{y \in \Omega_{26}(x)} d(|y - x|) \cdot K(|f_P(y, t^*) - f_P(x, t^*)|) \cdot f_P(y, t^*). \tag{3}
\]

Here \( \Omega_{26}(x) \) is the 26-connected neighborhood of the image voxel at position \( x = (x, y, z) \), \( \hat{f}_P \) denotes the filtered image, while the normalization factor \( N_{S_{\text{norm}}}(x, t) \) reads:

\[
N_{S_{\text{norm}}}(x, t^*) = \sum_{y \in \Omega_{26}(x)} d(|y - x|) \cdot K(|f_P(y, t^*) - f_P(x, t^*)|). \tag{4}
\]

\( d \) indicates the inverse euclidean distance, and \( K \) is a function of the local gradient of the grey values.

In a second step the filter operates on image data of adjacent temporal positions, and for a given image voxel \( x^* \) it reads:

\[
\hat{f}_P(x^*, t) = \frac{1}{N_{T_{\text{norm}}}(x^*, t)} \sum_{m = -\nu}^{\nu} \sum_{m \neq 0} d(|t + m - t|) \cdot K(|f_P(x^*, t + m) - f_P(x^*, t)|) \cdot f_P(x^*, t + m), \tag{5}
\]

here \( \nu \) denotes the temporal window radius, while \( N_{T_{\text{norm}}} \), similarly to \( N_{S_{\text{norm}}} \) in Eq. 4, denotes a normalization factor which operates along the temporal direction.

The right choice of the range filter \( K \) is crucial for smoothing noise in homogeneous regions maintaining at the same time spatial and temporal sharpness of the images. As proposed in Bruder et al. (Bruder et al. 2009), a Gaussian weight is applied here as stop function in the spatial domain:

\[
K(|f_P(y, t) - f_P(x, t)|) = \exp \left(-\frac{(|f_P(y, t) - f_P(x, t)|)^2}{S_\sigma}\right), \tag{6}
\]

here the parameter \( S_\sigma \) is correlated to the level of the image noise and has to be carefully adjusted for preserving contrast edges at the same time smoothing noise in homogeneous regions. Similarly, such a weighting function is applied and a corresponding parameter \( T_\sigma \) has to be adjusted for smoothing along the temporal direction preserving at same time the temporal resolution of dynamic CT data (Bruder et al. 2009).

2.3. The elastic image registration (EIR) framework

Even in the case of highly accurate ECG gating or triggering and stable heart rate, spatial misalignment of the cardiac volumes acquired and reconstructed per cardiac cycle may occur due to small motion pattern variations from cycle to cycle. These misalignments reduce the accuracy of the quantitative analysis of myocardial perfusion parameters on a per voxel basis. An image based solution to this problem is 3D-3D elastic image registration (EIR) (Rueckert et al. 1999, Kybic & Unser 2003) of dynamic volume sequences with variable contrast.
Given the filtered 4D image data set, the timeframe with the maximum image energy $E$ is automatically selected as reference image:

$$\hat{f}_{\text{ref}}^P(x) = \hat{f}_P(x, t_{\text{ref}})$$

with

$$E(\hat{f}_P(x, t_{\text{ref}})) = \max_{t=0, \ldots, M-1} \left\{ \sum_{j=0}^{N_{\text{vox}-1}} \hat{f}_P(x_j, t) \right\}^2 . \tag{7}$$

$N_{\text{vox}}$ denotes the number of image voxels. Generally, this frame corresponds to the time when a large amount of contrast agent is present within the heart chambers. Hence, the myocardium is well delineated. Subsequently, this reference volume $\hat{f}_P(x, t_{\text{ref}})$ is propagated to the other timeframes $\hat{f}_P(x, t)$ using an EIR approach. The basic EIR technique can be summarized as follows. Given a pair of images $\hat{f}_P(x, t_{\text{ref}})$ and $\hat{f}_P(x, t)$, which can be called reference and test images, the main task of the EIR is to find a deformation field $g$ such that $\hat{f}_P^w(x, t) = \hat{f}_P(g(x), t) \approx \hat{f}_P(x, t_{\text{ref}})$, where $\hat{f}_P^w(x, t)$ is the warped test image. A minimization problem is solved to determine the deformation field $g$ which minimizes an image similarity measure that is computed for each grid position in the reference $\hat{f}_P(x, t_{\text{ref}})$ and warped test $\hat{f}_P^w(x, t)$ images.

In this publication a voxel intensity-based registration algorithm similar to that described in section II.C of (Isola et al. 2010) is applied. Here, the images and the deformation field $g$ are represented by cubic B-splines bases (Unser et al. 1993a),(Isola et al. 2010)(section II.C.1),

$$g(x) = x + \sum_{l \in L_k} k_l \beta_3(x/l - 1), \tag{8}$$

where $\beta_3$ is a 3D tensor product of 1D centered cubic B-spline, $k_l$ denote the corresponding expansion coefficients, $L_k$ is a set of parameter indices, and $q = (q_x, q_y, q_z)$ is the knot spacing. The scale parameter $q$ can be used to set the desired node spacing, which determines the level of smoothness of the deformation field $g$.

A characteristic feature of myocardial perfusion imaging is the dramatic contrast variation with time that has to be taken into account for a proper registration. Taking into account contrast variations with time at the similarity measure leads to the application of the zero mean normalized cross-correlation (ZNCC) as similarity measure. To encourage invertible solution, a topology-preserving smooth penalty function (Chun & Fessler 2009) is combined with the previous similarity measure (Isola et al. 2010)(section II.C.2). In order to minimize the similarity criterion, differently from what was proposed in (Isola et al. 2010)(section II.C.3), here a stochastic gradient descent optimization method with adaptive step size prediction (ASGD) (Klein et al. 2009) is applied. The stopping criterion for the optimization process is represented by reaching the maximum number of iteration, or when the relative and absolute improvement of the criterion value are smaller than a fixed threshold. Finally, a multi-resolution approach (Unser et al. 1993b) is applied to avoid a local minimum (Isola et al. 2010)(section II.C.4).

2.4. Perfusion parameters

A 4D perfusion CT sequence consists of a set of frames $\hat{f}_P(x, 0), \ldots, \hat{f}_P(x, M-1)$. For a given image voxel $x^* = (x^*, y^*, z^*)$, the time series of the corresponding values $\hat{f}_P(x^*, t)$ of all volumes of the perfusion sequence yields the individual local time-intensity (T-I) curve. The analysis of these curves results in two parameters which are provided in colour coded images: area under curve (AUC) and peak intensity (PI).
2.4.1. The contrast agent arrival time  In order to determine the perfusion-related parameters, the arrival time $t_0$ of the contrast agent (CA) in the selected myocardial ROI is required. The way to evaluate the CA arrival time can change regarding to the particular application and the tissue perfusion model used. Generally, the global CA arrival time $t_0$ is the earliest significant intensity increase in the perfused ROI after the injection of the CA bolus. It corresponds to the frame number when the T-I curve begins to rise. In this work, this global temporal parameter is automatically evaluated by the following procedure (Fig. 2(a)): first, a mean T-I curve $\hat{f}_P(t)$ consisting of the mean voxels-intensity values in each frame of the 4D CT data set is determined by

$$\hat{f}_P(t) = \sum_{j=0}^{N_{max}-1} \hat{f}_P(x_j, t) \quad \text{with} \quad t \in [0, M - 1].$$

(9)

Subsequently, the maximum up-slope of this curve is determined as the maximum of the first derivative while the second derivative changes from positive to negative:

$$\hat{f}_P^\prime(t_{mu}) = \max_{t=0\ldots M-1} \{ \hat{f}_P^\prime(t) \}$$

with $\hat{f}_P^\prime(t_{mu} - 1) < 0$ and $\hat{f}_P^\prime(t_{mu} + 1) > 0$.

(10)

Starting from this timepoint $t_{mu}$, the curve is back-traced until the slope either becomes insignificantly small or negative (Fig. 2(a)):

$$\hat{f}_P(t_0) < \epsilon \quad \text{with} \quad t_0 \in [0, t_{mu}], \quad \epsilon > 0.$$

(11)

![Figure 2. Perfusion parameters. In (a) the automatic global CA arrival time determination approach is shown. In (b) a sketch of a T-I curve is shown. Here, all described parameters except $t_0$ are calculated locally.](image)

2.4.2. Area Under Curve  The parameter Area Under Curve (AUC) is achieved by the summation of the intensities for each voxel starting with frame $\hat{f}_P(x, t_0)$, which corresponds to the frame of first occurrence of the contrast agent (i.e., global arrival time $t_0$). The local baseline intensity $I_0(x)$ of each voxel is subtracted before the summation. The interesting part of the T-I curve for this parameter starts where the curve begins to rise and should include the peak. To be able to compare the sum within the parametric image, the summation must always include the same number of

![Diagram](image)
frames. It is not possible to let the summation stop at the peak frame since the number of this frame varies between different voxels. The solution is to let the summation stop at time $t_0 + r$ with $r$ set manually. The AUC parameter is given by:

$$AUC(x) = \sum_{t=t_0}^{t_0+r} \hat{f}_P(x, t) - I_0(x) \quad \text{with} \quad I_0(x) = \frac{1}{t_0} \sum_{t=0}^{t_0} \hat{f}_P(x, t).$$

(12)

The AUC parameter gives information about the blood volume passing through the selected myocardial tissue (Fig. 2(b)). The baseline intensity $I_0(x)$ is estimated by the voxel-wise mean of all images acquired before the global arrival time $t_0$ of the contrast agent in the ROI. The baseline intensity $I_0$ represents the pure tissue answers without any contrast agent response (Fig. 2(b)).

2.4.3. Peak Intensity  The peak intensity (PI) (also called peak enhancement) flow parameter is obtained by the intensity difference between the baseline intensity $I_0(x)$ and the maximum intensity $I_{max}(x)$ at a point $x$. This is because the PI takes into account only the tissue response based on the contrast agent (Fig. 2(b)):

$$PI(x) = I_{max}(x) - I_0(x) \quad \text{with} \quad I_{max}(x) = \max_{t=0 \ldots M-1} \{\hat{f}_P(x, t)\}.\quad (13)$$

Here, for each image point $x$ the corresponding baseline intensity $I_0(x)$ is calculated as given in Eq. 12. The maximum local intensity $I_{max}(x)$ represents the highest contrast agent response and it is identified as the maximum of the intensity time series at each image position.

3. Experiments and results

To validate our myocardial perfusion imaging method a series of experiments was performed. First, the CT acquisition and the image reconstruction settings are given in subsection 3.1. Second, the filtration approach applied to deal with image noise and artifacts is evaluated (subsection 3.2). Third, qualitative and quantitative results on the geometric misalignment correction achieved using the proposed technique on three pigs cases are shown (subsection 3.3). Finally, visual inspections of the corrected perfusion related parametric maps for the pigs myocardium tissue only are given (subsection 3.4).

3.1. CT scanning and reconstruction settings

Three pig data sets (A-C) were acquired on a Brilliance 64 CT scanner (Philips Healthcare, Cleveland, OH, USA). The animal’s ECG was recorded synchronously with the scan. Pig data have been acquired under ethic commission approval at the University Hospital Hamburg-Eppendorf, Germany, and at the Louis Pradel University Hospital, France. Cases A and B represent two normal healthy pigs, whereas case C is a pig with a coronary artery occlusion (angioplasty balloon inflation) of the the left anterior descending coronary artery. Heart rate statistics of the pigs and parameters of the CT acquisition are listed in Table 1.

In this work, images are reconstructed at phases of slow cardiac motion. To select suitable quiet motion phases within the RR interval, a motion map ($MM$) technique is used (Manzke et al. 2004). Therefore, retrospective ECG-gated reconstructions at the systolic and diastolic phase points 40 and 75%, and 40 and 84% of the R-R cycle
were performed for the case A and B, respectively. For the pig case C a prospectively ECG-gated reconstruction was performed at the systolic phase of 40% RR. Thus, 25, 33 and 52 heart beats were reconstructed from 220° subsections centered around the chosen cardiac phase point, for the case A-C, respectively.

### Table 1. CT scanning parameters

<table>
<thead>
<tr>
<th>Clinical case</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scan trajectory</td>
<td>circular</td>
<td>circular</td>
<td>circular</td>
</tr>
<tr>
<td>ECG gating</td>
<td>retrospective</td>
<td>retrospective</td>
<td>prospective</td>
</tr>
<tr>
<td>Collimation [mm]</td>
<td>64×0.625</td>
<td>64×0.625</td>
<td>64×0.625</td>
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<tr>
<td>Rotation time [s]</td>
<td>0.42</td>
<td>0.42</td>
<td>0.42</td>
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<tr>
<td>Tube voltage [kV]</td>
<td>120</td>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td>Anode current [mA]</td>
<td>238</td>
<td>238</td>
<td>500</td>
</tr>
<tr>
<td>Mean heart rate [bpm]</td>
<td>56</td>
<td>71.5</td>
<td>153</td>
</tr>
<tr>
<td># Heart beats</td>
<td>25</td>
<td>33</td>
<td>52</td>
</tr>
<tr>
<td>Systolic phase point [% RR]</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Diastolic phase point [% RR]</td>
<td>75</td>
<td>84</td>
<td>-</td>
</tr>
</tbody>
</table>

3.2. Effect of noise and artifacts on perfusion parameters

The perfusion parameter determination requires first and second temporal derivative calculation. Due to the presence of noise, a spatial low-pass filter can be applied to the image data set in order to stabilize the derivative calculation. Another problem in perfusion parameters evaluation is the occasional presence of artifacts inside a subset of frames (e.g. beam hardening, cone-beam artifact, ring artifact, etc.). These artifacts can lead to myocardial regions with inconsistent hyper- or hypo-enhancement. As discussed in Sec. 2.2, in this work, a spatio-temporal bilateral filter is applied to each data set to reduce this problem. For the temporal filtration only the two adjacent timeframes are used for filtering. Finally, the range filter parameters $S_\sigma = 26$ HU and $T_\sigma = 260$ HU are utilized, in space and time, respectively.

In Fig. 3, CT axial images of the pig case C without (a) and with (b) filtration, and the corresponding T-I curves (c) of a myocardial ROI (red circles, (a-b)) are depicted. Spatio-temporal filtering helps to reduce both noise and artifacts. Typical over- and undershoot present along the non-filtered T-I curve (c, blue dashed curve) are strongly reduced by the spatio-temporal filter (c, red curve). The residual slight T-I curve’s variations (c, red curve) are mainly caused by spatial misalignment which will be removed by a subsequent registration step.

In the next subsection, colour coded perfusion related parametric maps will be presented for all three pigs. For the sake of comparison, in the pig case C, the results with and without spatio-temporal filtration will be shown (Fig. 8). From the presented images, it will be even clearer that image noise can tremendously degrade the perfusion parameters evaluation and hamper a correct diagnosis of myocardial viability.

3.3. Misalignment correction

Subsequent to 4D data reconstruction and filtration, reference images with the maximum image energy were automatically selected and non-rigidly registered to all other volumes of the 4D data sets. Here, the adaptive optimizer randomly selected 3500 image-samples at each optimization’s iteration. The stochastic
gain settings were automatically estimated by this optimizer. For the multi-resolution approach 2 levels were used, and in each level the deformation field B-spline knot spacing was every 8 voxels. At each resolution level 1500 optimization iterations were performed. Each 3D-3D registration took approximately 2 minutes on a 2.8 GHz AMD Opteron. As a direct measure of registration quality, statistics on the ZNCC similarity criterion before and after the registrations are listed in Table 2.

<table>
<thead>
<tr>
<th>Case</th>
<th>ECG gating</th>
<th>Registered</th>
<th>Mean ± STD</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Retrospective (40% RR)</td>
<td>No</td>
<td>0.92 ± 0.07</td>
<td>0.82</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>0.94 ± 0.05</td>
<td>0.87</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td>Retrospective (75% RR)</td>
<td>No</td>
<td>0.89 ± 0.07</td>
<td>0.78</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>0.92 ± 0.05</td>
<td>0.84</td>
<td>0.99</td>
</tr>
<tr>
<td>B</td>
<td>Retrospective (40% RR)</td>
<td>No</td>
<td>0.98 ± 0.009</td>
<td>0.97</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>0.99 ± 0.006</td>
<td>0.98</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td>Retrospective (84% RR)</td>
<td>No</td>
<td>0.98 ± 0.009</td>
<td>0.96</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>0.99 ± 0.007</td>
<td>0.97</td>
<td>0.99</td>
</tr>
<tr>
<td>C</td>
<td>Prospective (40% RR)</td>
<td>No</td>
<td>0.98 ± 0.009</td>
<td>0.96</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>0.99 ± 0.007</td>
<td>0.97</td>
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</tbody>
</table>

Table 2. Zero-mean Normalized Cross Correlation (ZNCC). The mean, the standard deviation (STD), the minimum (Min) and the maximum (Max) ZNCC values calculated between the selected reference volumes and all others volumes of the 4D data sets are given.

Finally, the AUC and PI perfusion parameters were determined. In Figs. 4-7, the axial, coronal and sagittal views of the AUC and PI perfusion parametric maps for the pig cases A-B without (left) and with (right) registration are presented. Here, the white arrows indicate the artificial hyper-perfusion caused by the spatial misalignment.

In Fig. 8 the perfusion parameters of the pig case C determined without (left column) and with (middle column) spatio-temporal filtering are shown. Moreover, the filtered and registered perfusion parametric maps are shown in the right column. Again, the white arrows indicate the artificial hyper-perfusion visible on the myocardium borders caused by the geometric misalignment. This misalignment is well corrected by the image registration technique (right column).

For the pig case A, in Fig. 9 the T-I curves of the non-registered (dashed black lines) and registered (red-blue lines) systolic reconstructed data sets, are given for four
different regions of interest. Hereeto, the registrations are performed using the mutual information (MI) (blue line) and ZNCC (red line) similarity measures.

The evaluated colour-coded perfusion parametric maps confirm that image registration can help to reduce the severe artifacts caused by the motion state inconsistencies, and to provide quantitative information of the dynamic CA uptake of the myocardium (Figs. 4-8). The usual artificial myocardial hyper-(or hypo-) perfusion caused by the cardiac and pulmonary motions (Fig. 9, dashed black lines) was strongly reduced (Fig. 9, blue and red lines).

3.4. Visual inspection of myocardial perfusion

In order to better highlight the blood perfusion within the myocardium only, a different level and window was applied. Moreover, the determined colour coded perfusion maps were superimposed to the CT axial images to better locate possible necrotic areas positions. Assuming that an ideal mixture of CA is injected in blood, that the blood flow is constant over time, and that the intrinsic permeability and CA response of healthy and homogeneous cardiac tissue are ideally constant in each point, we can conclude that all the perfusion parameters should be approximately constant inside a viable myocardium. A myocardial infarction is strictly related to a suspicious variation of the perfusion parameters visible in the regions where the blood flow is strongly reduced or totally absent, e.g. a reduction is observable in the local AUC or PI parameters.

Therefore, for the healthy pig cases A and B an uniform perfusion was expected
within the whole myocardium. In contrast, in the third pig case C, a hypo-attenuated region was expected in correspondence to the myocardial ischemic zone related to coronary artery occlusion.

In Fig. 10 the perfusion parametric maps for the cases A (a) and B (b) are given. As expected, for both pigs, the whole myocardium presents an almost uniform and homogeneous AUC and PI parameters values distribution.

In Fig. 11 some frames of pig C’s time series are shown. Here, the red arrows indicate the penumbra myocardial tissue. The corresponding perfusion maps are presented in Fig. 12. Differently from the first two healthy pigs, in this case the perfusion maps clearly show a strong reduction of the AUC and PI parameters (red arrows).

4. Discussion

Early perfusion defects at multidetector CT are closely related to the degree of significance of a coronary artery stenosis. Therefore, it is important to accurately detect the presence of myocardial ischemia to support diagnosis and treatment. Myocardial perfusion imaging by follow-up CT scanning is a promising diagnostic tool to assess the extent of infarcted myocardial regions. However, the frequently poor synchronization of the ECG with the real heart movement and respiratory induced motion cause a deformation of the myocardium shape and a consequent spatio-temporal misalignment between successive perfusion sequence
Figure 6. The axial, coronal and sagittal views of the area under curve (AUC) (a,c,e) and peak intensity (PI) (b,d,f) of the pig case B at systole. In order, the colour coded perfusion related parameter maps for the non-registered (left) and registered (right) image data sets are given. The white arrows indicate regions with perfusion artifacts which are removed by the proposed method. (Heart rate: 71.5 bpm, reconstruction phase: 40% RR)

frames. In this work an elastic image registration approach was used to align the 4D data sets. Elastic image registration represents an essential tool to perform myocardial perfusion CT imaging with a higher quantitative accuracy. Promising results have been achieved by applying image registration to a number of animal cases (Figs. 4-8, Table 2).

Against noise and artifacts, a bilateral spatio-temporal filtration has shown to be a good solution to avoid image corruption which can hamper an accurate quantitative and qualitative perfusion evaluation (Fig. 8).

In the pig case C (suffering from myocardial infarction), both AUC and PI parameters showed a strong perfusion deficit in correspondence to the necrotic myocardial region (Fig. 12). However, the sensitivity of these two and other time-dependent perfusion parameters (e.g. time to peak, maximum up-slope) need to be carefully evaluated on a larger data base. This kind of study goes beyond the goal of this paper.

From the presented results it can be concluded that systole represents a superior cardiac motion phase to perform myocardial perfusion analyses compared to diastole. Due to the ventricular motion, at systole a larger myocardial region is available to measure the level of blood perfusion through the tissue, while the perfusion maps showed a comparable artifact level (Figs. 4-8).

Despite the encouraging results, some limitations of the proposed approach are not negligible. First, in this work, the perfusion parameters were calculated assuming a global CA arrival time. This assumption is generally false for a cardiac
Figure 7. The axial, coronal and sagittal views of the area under curve (AUC) (a,c,e) and peak intensity (PI) (b,d,f) of the pig case B at diastole. In order, the colour coded perfusion related parameter maps for the non-registered (left) and registered (right) image data sets are given. The white arrows indicate regions with perfusion artifacts which are removed by the proposed method. (Heart rate: 71.5 bpm, reconstruction phase: 84% RR)

5. Conclusions

In conclusion, an elastic image registration-based method was proposed to improve the characterization of CT-based estimates of myocardial perfusion. The technique’s performance, that was visually and quantitatively assessed on three pig data sets, confirmed its potential. The proposed method may also be applied to other perfusion...
Figure 8. The axial views of the area under curve (AUC) (top) and peak intensity (PI) (bottom) of the pig case C at systole. In order, the colour coded perfusion related parameter maps for the non-registered and non-filtered (left), the non-registered and filtered (center), and the registered and filtered (right) image data sets are given. The white arrows indicate regions with perfusion artifacts which are removed by the proposed method. (Heart rate: 153 bpm, reconstruction phase: 40% RR)

Figure 9. T-I curves for the pig case A at systole. In (a) the four selected ROIs are shown. In (b-e) the corresponding average T-I curves of these four ROIs are given. Here, the curves of the non-registered (dashed black lines) and the registered data sets using the MI (red lines) and ZNCC (blue lines) similarity criterions are shown. (Heart rate: 56 bpm, reconstruction phase: 40% RR)
Figure 10. The axial views of the registered area under curve (AUC) (left) and peak intensity (PI) (right) colour coded perfusion related parameter maps of the pig cases A (top) and B (bottom) at systole. Here, the perfusion maps are superimposed to the CT axial images. (Heart rate case A(B): 56(71.5) bpm, reconstruction phase: 40% RR)

studies being limited by inconsistent motion states.

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References

Figure 11. The axial views of the reconstructed timeseries of the pig cases C at systole. Here, the red arrows indicate a myocardial ischemic zone related to coronary artery occlusion. (Heart rate: 153 bpm, reconstruction phase: 40% RR, L/W: 0/500 HU)

Figure 12. The axial views of the registered area under curve (AUC) (left) and peak intensity (PI) (right) colour coded perfusion related parameter maps of the pig cases C at systole. Here, the perfusion maps are superimposed to the CT axial images. The red arrows indicate the infarcted myocardial region (Heart rate: 153 bpm, reconstruction phase: 40% RR)

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