Original Research

Improvement in the Quantification of Myocardial Perfusion Using an Automatic Spline-Based Registration Algorithm

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Purpose: To improve the quantification of myocardial perfusion by registering the time series of magnetic resonance (MR) images with injection of gadolinium.

Materials and Methods: Eight patients underwent MR scans to perform myocardial perfusion exam. Two short axis views of the left ventricle (LV) were acquired in free breathing. Two masks for performing the spatial registration of the images were evaluated. The registration was based on pixel intensity in a multi-resolution scheme. The efficiency of this correction was evaluated by calculating geometric residual displacement of the LV and by fitting the data to a compartment model fit with two parameters: *K1*, the blood-to-myocardium transfer coefficient, and *Vd*, the distribution volume of the contrast media.

Results: The registration stage allowed a decrease in the observed motion of the LV from more than 1.98 ± 0.68 mm to less than 0.56 ± 0.18 mm (mean ± SD). Variability obtained in the perfusion analysis decreased from 46 ± 103% to 5± 4% for *K1* parameter and from 18 ± 21% to 5 ± 5% for *Vd* parameter.

Conclusion: As with manual correction, this automatic motion correction leads to accurate perfusion parameters in dynamic cardiac MR imaging after contrast agent injection. This automatic stage requires placing only one mask over one frame of the perfusion study instead of manually shifting each image to fit a reference image of the perfusion study.

Key Words: image registration; respiratory motion correction; cardiac perfusion assessment; dynamic MRI; gated MRI
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QUANTIFICATION OF MYOCARDIAL perfusion by dynamic magnetic resonance imaging (MRI) is realized by injection of gadolinium diethylene triamine pentaacetic acid (GD-DTPA) contrast agent, with a contrast media first pass taking from 30 to 40 seconds (1). Because electrocardiogram (ECG)-gated sequence leads are used to freeze the heart beat and because of the dynamic nature of the data of interest, the acquisition sequence takes more than three minutes to obtain reliable information about the perfusion and distribution volume of the contrast medium. With such a protocol, acquisitions are realized without breath-holding and leads to dynamic gated heart images being degraded by respiratory induced motions during the perfusion study.

The simple way to correct this motion is the manual shifting of each image to fit a reference image (2). This effective method is very tedious in practice because there are about 100 images per perfusion study. Another way to cope with this respiratory induced motion is the segmentation of heart-related features, such as the myocardial wall, across the whole perfusion study to be registered (3). After injection of the contrast medium, large intensity variations can be observed in the myocardium and in the blood contained in the right and the left cavities. Application of conventional registration algorithms based on the myocardial contour detection (3) is difficult and may not even work adequately in the case of a perfusion defect. To circumvent these issues, Bidaut and Vallée (4) proposed an automated strategy based on two-dimensional rigid body deformation, which used the information contained within each image to estimate, and to correct in every time frame, the motion of the heart across the whole acquisition. To improve the spatial registration, a simple multiresolution scheme was used with two intermediate steps performed through the convolution of Gaussian kernels.

The purpose of this work was to evaluate a more robust registration algorithm (5) based on image intensity in a multiresolution scheme. One challenge of this work was the definition of an analysis protocol adapted to cardiac perfusion MR images, which have large intensity variations inside the regions to be registered. Correcting cardiac perfusion MR images from the respiratory motion requires defining one mask over the re-

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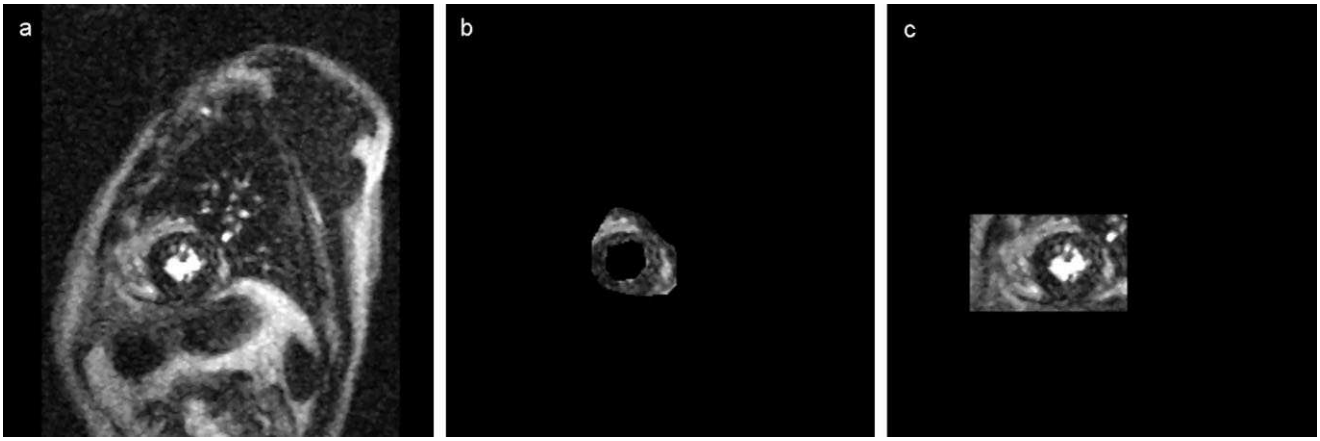

Figure 1. a: Short-axis view of the heart. **b:** Optimal cardiac mask definition for the registration stage. This mask was selected on the image where contrast medium is located only in the LV. The mask is defined in the region where the contrast does not change rapidly along the whole perfusion study. It is defined by including the LV myocardium and by avoiding the cavity where the signal intensity changes rapidly. **c:** Rectangular non-optimal cardiac mask definition for the registration stage.

gion to be registered (left ventricle [LV]). We propose to compare two methods for defining the mask: the first one is manually drawn around the LV and the second one is defined by the rectangle including the heart in short-axis views (6).

MATERIALS AND METHODS

MRI Perfusion Imaging Protocol

Eight patients underwent MRI. Two short-axis views of the heart were acquired on an Eclipse 1.5-T MR system (Picker-Marconi, Cleveland, OH) with a fast gradient-echo sequence (RF-FAST saturation-inversion recovery 90–180, Marconi) (7): body coil, flip angle = 90°, repetition time = 4.3 msec, echo-time = 1.3 msec, field of view (FOV) = 46 × 23 cm, symmetric phase encoding, matrix size = 256 × 192 (pixel size = 1.8 mm), slice thickness = 10.0 mm, preparation time = 150 msec, one acquisition, ECG-triggered with one view every two heart beats, after a manual (1–2 seconds) bolus injection of Gd-DTPA (Magnevist, Schering AG, Deutschland) in a brachial vein (0.07 mL/kg), followed by 20 mL of a saline solution.

Registration Methods

The images were first retrieved from the MR scanner via the PACS in Digital Imaging and Communications in Medicine standard (DICOM). They were brought to the IDL software (Interactive Data Language, Research Systems, Inc., CO), which acts as front-end to an ANSI-C registration routine. This routine is freely available on the web (8) and is based on methods previously described (5). Images are known only through their regular samples; a continuous model (based on B-splines of degree N) was specified for performing geometric operations (9,10). We performed registration in a multiresolution scheme. The registration process can be limited to a part of the images by drawing regions of interest (ROI).

As the registration process is based on signal intensity, the first method for performing the registration uses only one ROI where no signal intensity changes occur along the whole perfusion study. In these studies, the frame with the best contrast between myocardium and left ventricular cavity (Fig. 1a) was chosen for defining the cardiac mask. It was drawn by completely including the LV and by extending the margin of the heart into the lung and generally into the stomach. Inside this mask (optimal cardiac mask), the LV cavity was removed (Fig. 1b). We compared the optimal cardiac mask to a rectangular mask centered on the heart (both the left and right ventricle) in a short-axis view (Fig. 1c). The first author (C.H.D.), who has a high background in image registration, realized the manual shift and the definition of the two masks for all studies. As a gold standard, the images were manually shifted to correct for in-plane motion by a skilled image analysis specialist (C.H.D.).

Registration Validation

Validation of the registration methods was realized by two different methods.

Geometric Model

The geometric method compares the variation of the position of the LV over the entire perfusion study for different registration techniques. Position of the LV is assessed by placing a circular ROI over the LV and by computing the center of mass of intensities inside this ROI. For each registration technique, the minimum, maximum, and SD of the residual motions are computed. The best registration technique is naturally the one that gave the smallest residual motions.

Functional Model

The functional model was validated in two different ways. The first one compared transit time curves obtained with or without a registration stage. The curve obtained on the dataset with manual shift of the images is called the "gold standard curve." The comparison was limited to a ROI centered in the LV cavity. On each of

Table 1
The Range of Translations (in Pixels) and Rotation (in Degrees) for Different Registration Techniques on Data From a Typical Patient (100 Frames)

Registration technique	Translation along X (pixels)		Translation along Y (pixels)		Rotation about Z (deg.)	
	Min mean	Max SD	Min mean	Max SD	Min mean	Max SD
Manual shift	−4.0	8.0	−12.0	4.0	–	–
	1.23	1.96	−2.63	4.34	–	–
Automatic with optimal mask	−4.32	6.27	−9.74	7.52	−8.64	6.80
	1.23	2.20	−0.06	4.86	−0.11	2.99
Automatic with rectangular mask	−4.56	5.98	−9.26	6.99	−5.58	3.19
	0.79	1.76	−0.22	4.35	−0.65	1.87

Axis X is anterior/posterior; axis Y is superior/inferior; axis Z is orthogonal to the image plane. Pixels are 1.8 mm wide. SD = standard deviation.

the images in these studies, blood pool transit curves were plotted. Two parameters were determined from these curves: full-width at half-maximum (FWHM) of the first peak of the contrast medium, and the mean square difference (MSD) between each registered curve and the gold standard curve. The best registration technique is naturally the one that gave FWHM of the first peak of contrast medium equal to those obtained on the gold standard curve and that had the smallest MSD.

The second method compared the perfusion parameters computed from several transit time curves placed inside the myocardium and the LV with or without registration stage. After registration, the image with the best contrast between myocardium and the LV (i.e., the image where contrast medium is inside the LV cavity but not yet in the myocardium) was used to define the ROIs over which the pharmacokinetic model was applied. These ROIs were drawn by one of the authors (M.A.I.) who has extensive experience in cardiac perfusion analysis. The LV was divided into four sectors. For validation purposes, the same sectors were used for the raw data and the various types of registered images. As a gold standard (11), the position of the sectors was controlled on each image of the raw data set and a manual shift of images was performed to correct for the motion of the heart. A single blood pool transit curve per

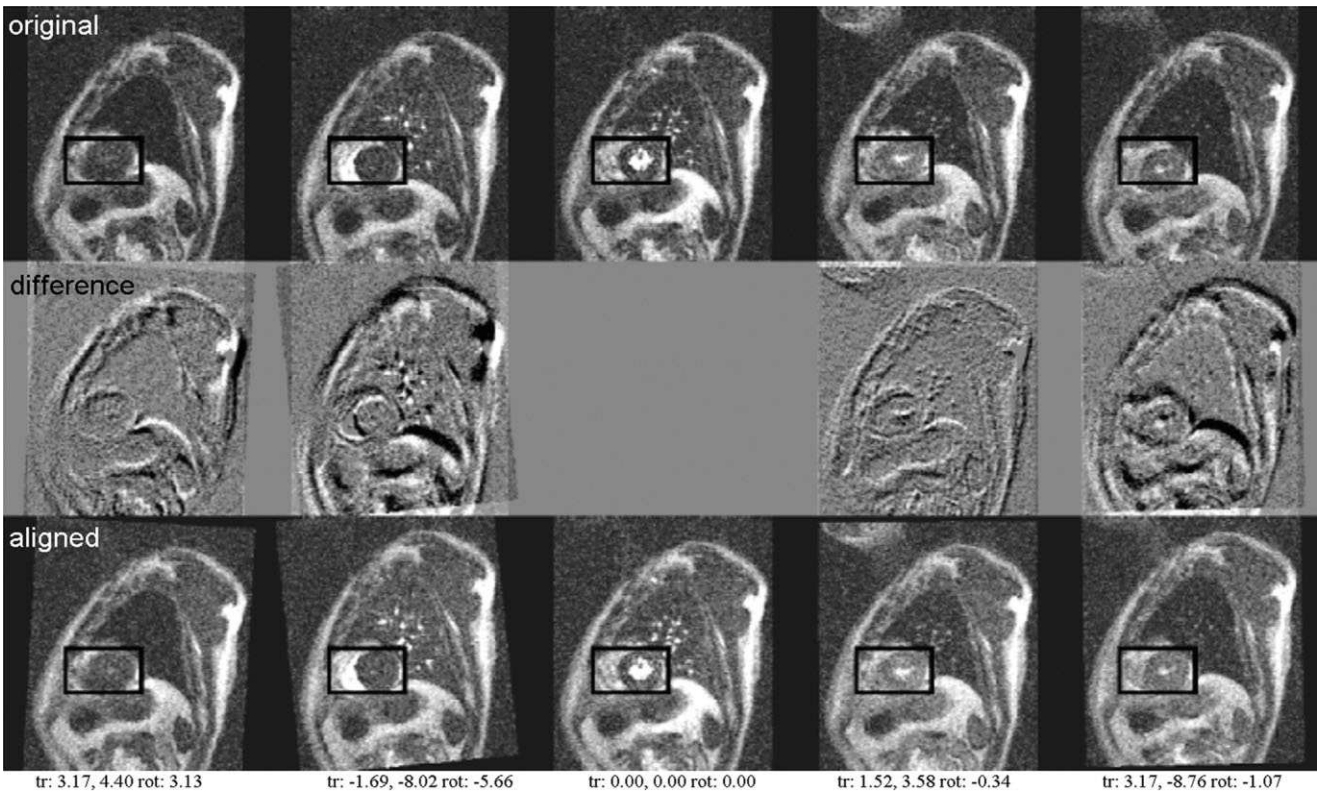

Figure 2. Comparison between original images (top row) and images obtained with the registration process using the optimal cardiac mask (bottom row). Difference images (middle row) show the extent of the correction (parameters at bottom; pixels and degrees). Images on the middle column correspond to the reference frame. The box over the heart in the original and registered images exhibits the need for and the results of the registration respectively.

Table 2
Registration Efficiency: Comparisons of the Positional Variations of the Center of Mass of the LV Intensities From a Typical Patient (100 Frames)

Registration technique	Position variation of the center of mass of the LV intensities						MSD per frame between curves obtained by various registration techniques and gold standard curve (to be minimized)		FWHM of the first peak of the blood pool transit curve ($FWHM_{gold\ standard} = 6$)
	X			Y					
	Min	SD	Max	Min	SD	Max	Min mean	Max SD	
No registration	−6.6	1.9	5.2	−6.8	4.4	9.7	0 9	209 25	3
Automatic with optimal cardiac mask	−0.5	0.2	0.6	−0.8	0.3	0.8	0.00 0.01	0.20 0.03	6
Automatic with rectangular mask	−0.6	0.3	0.7	−1.0	0.3	0.9	0.00 0.04	0.30 0.06	6

Gold standard curve = curve obtained with manual shifting of the region of interest along the whole perfusion study,
LV = left ventricle,
MSD = mean square difference, SD = standard deviation,
FWHM = full-width at half-maximum.

patient was defined from a ROI placed in the left cavity of manually shifted images.

For each patient with the same ROIs, we extracted and compared several transit time curves per sector: one from the raw data alone, one from the raw data with a manual shift (gold standard), one from images registered with the optimal cardiac mask, and one from images registered with the rectangular mask.

The transit time curves sets were fitted to the compartment model for estimating the myocardial perfusion parameters (7): the blood-to-myocardium transfer constant (*K1*) and the GD-DTPA distribution volume (*Vd*) (the model equation is given in Eq. [1]). The relative variation (in % of the manual gold standard, as defined by Eq. [2]) of *K1* and *Vd* were calculated for the raw data sets and the registered images.

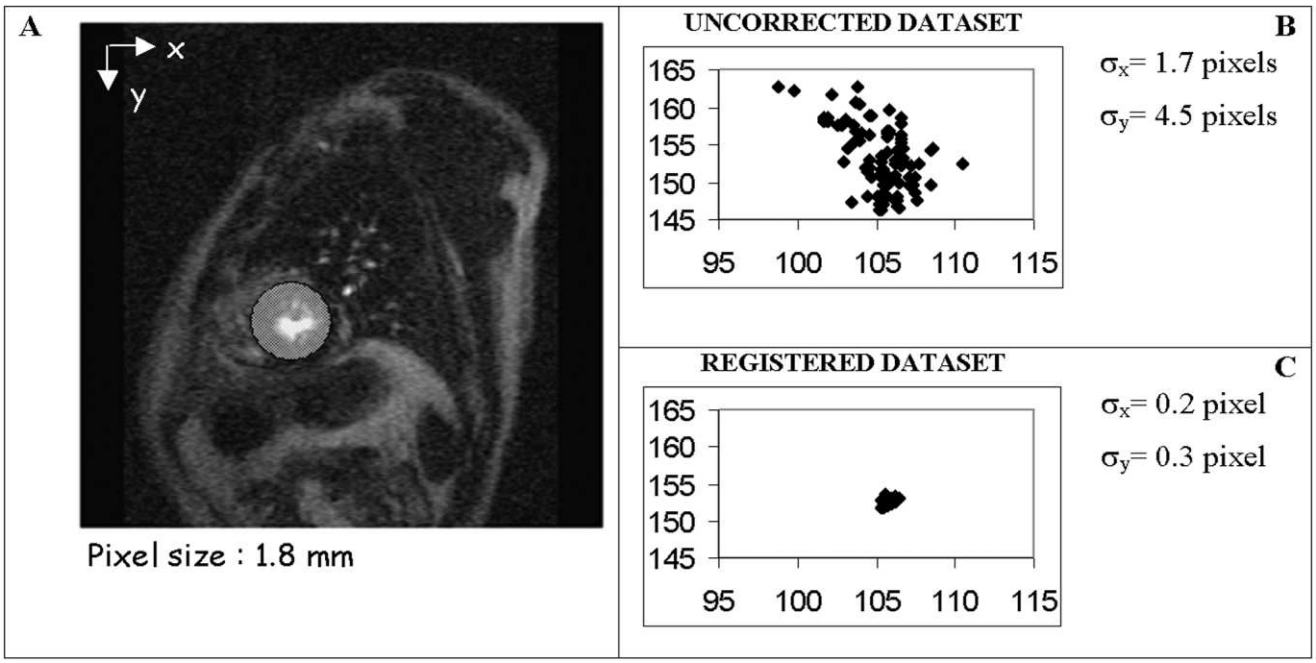

Figure 3. Registration efficiency is estimated by monitoring the position of the LV inside the myocardium (ROI in **A**). **B:** Without the registration process, large variations in the LV position are monitored. SD of these positions are equal to 1.7 pixels in the x-direction and 4.5 pixels in the y-direction. **C:** Using the registration stage with the optimal cardiac mask leads to better results. SD of these positions are equal to 0.2 pixel in the x-direction and 0.3 pixel in the y-direction.

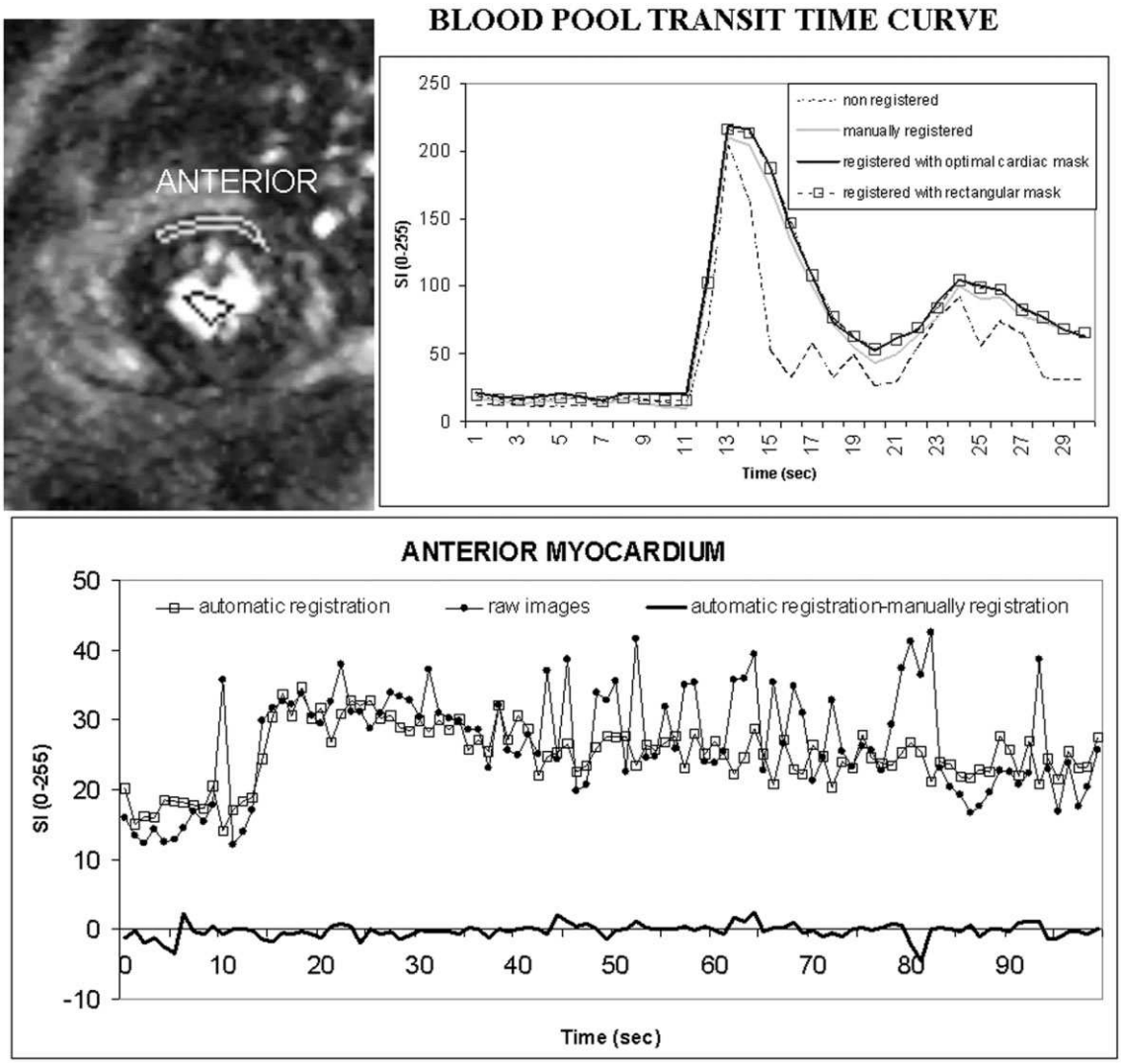

Figure 4. Top-left: Definition of the ROI (black polygon) inside the LV for assessing the blood-pool transit curve, and definition of the ROI (white polygon) inside the anterior part of the myocardium for assessing myocardium perfusion. Top-right: Comparison of the first portion of the blood pool transit curves obtained from various registration techniques on data from a typical patient (100 frames). Only the non-registered curve (FWHM = three frames) is very different from the registered ones (FWHM = six frames). Bottom: Anterior myocardium transit time curves for both the original (raw) and the automatically registered data set. To compare curves obtained by manual registration and automatic registration, the curves difference was plotted. Theses curves were later used as an input to the model fitting.

$$Myo(t) = K1 \cdot \int_0^t Vg(\tau) \cdot e^{-K1/Vd(t-\tau)} \cdot d\tau$$

with Myo = tissue signal, Vg = plasma signal for the ventricle cavity, Vd = distribution volume, $K1$ = transfer constant related to the flow.

Equation [2] is the variability index (× 100 for %). The manual alignment of images is used as a gold standard.

$$K1_{\text{var}} = (K1 - K1_{manual})/K1_{manual};$$

$$Vd_{\text{var}} = (Vd - Vd_{manual})/Vd_{manual}$$

RESULTS

Eight ambulatory patients with stable coronary artery disease were initially processed. This section presents, in the first part, results obtained on one typical patient and, in the second part, the overall results obtained on all the patients included in this study. In this way, it is easier to present and understand the different steps of the analyses.

Results Obtained From One Typical Patient

Table 1 presents information about the geometric parameters calculated by the registration over the whole perfusion study (100 frames) for a typical patient. This table shows that the range of displacement was about 20 mm (12 pixels) wide in the anterior-posterior (AP) direction and about 28 mm (16 pixels) wide in the superior-inferior (SI) direction. Larger values in the SI direction agreed well with major respiratory-induced displacement (12–14). The corrective rotation window was about 15 degrees wide for the mask including only

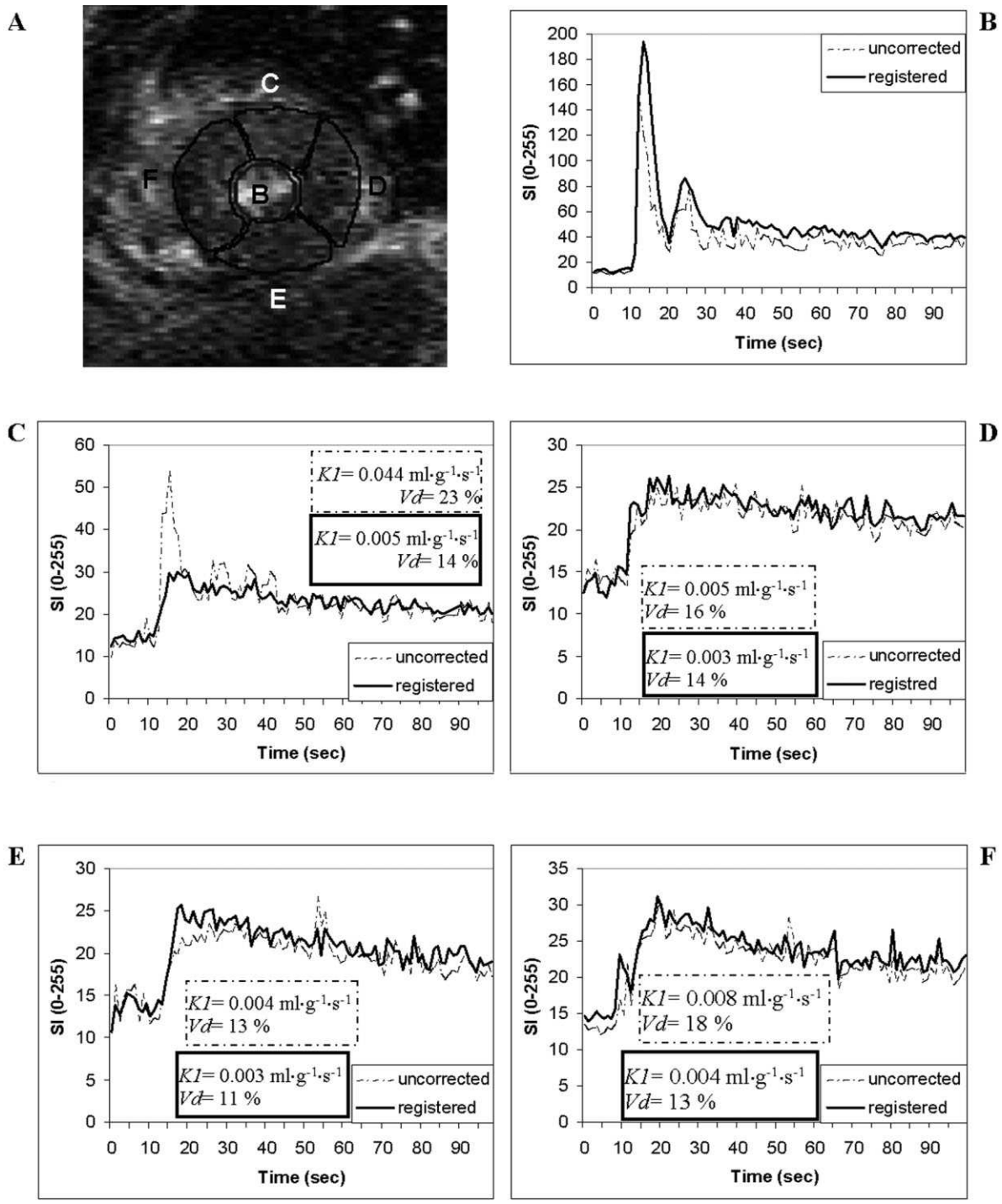

Figure 5. Perfusion analysis obtained on one typical patient (100 frames) with or without a registration stage with optimal cardiac mask. **A:** Definition of the ROI used for this analysis. Transit time curve obtained for the LV (**B**), in the anterior segment (**C**), in the lateral segment (**D**), in the inferior segment (**E**), and in the septal segment (**F**). For each graph corresponding to a myocardium segment, values of *K1* and *Vd* are presented.

the LV and about 9 degrees wide for the rectangular mask including the two ventricles. In Figure 2, selected frames were exhibited before and after the automated registration. The extent of correction is clearly visible on the difference images.

Table 2 presents the registration efficiency obtained from the previous whole perfusion study. Variations in the position of the center of mass of the LV intensities are clearly reduced with registration (Fig. 3). The registration process leads to a decrease in the SD from 3.42 mm (1.9 pixels) to 0.36 mm (0.2 pixels) in AP direction, and from 7.92 mm (4.4 pixels) to 0.54 mm (0.3 pixels) in SI direction. The maximum elongation decreases from 21.24 mm (11.8 pixels) to 1.98 mm (1.1 pixels) in AP direction, and from 29.7 mm (16.5 pixels) to 2.88 mm (1.6 pixels) in SI direction before and after the regis-

Table 3
Registration Efficiency: Summary of the Results Obtained on the Eight Patients

Registration technique	Position variation of the center of mass of the LV intensities (in pixels)			
	X		Y	
	Min mean	Max SD	Min mean	Max SD
No registration	0.25	1.85	0.28	4.48
	1.10	0.38	2.25	1.11
Automatic with optimal cardiac mask	0.18	0.51	0.15	0.46
	0.31	0.10	0.27	0.08
Automatic with rectangular mask	0.15	1.05	0.15	0.55
	0.32	0.21	0.33	0.12

LV = left ventricle, SD = standard deviation, Pixel size = 1.8 mm.

tration stage, respectively, with the optimal cardiac mask.

Without registration, the MSD mean is about 9 with a SD of about 25. The maximum of MSD per frame is about 209, which is very important. With registration (with the two masks), the MSD mean is less than 0.04 with a SD of less than 0.06. The maximum of MSD per frame is less than 0.30, which is about 700 times less than the value obtained without registration.

When observing the blood pool transit curves (Fig. 4), the area under the first peak is related to the contrast medium quantity administered to the patient. Thus, as the intensity of the images were not changed, conservation of the contrast medium quantity leads to a constant FWHM of the first peak on all the blood pool transit curves. Comparing FWHM between different curves obtained by various registration techniques is sufficient for assessing registration efficiency. The FWHM value obtained with the gold standard curve is equal to six frames. Without registration, a very different value of FWHM was obtained (three frames). With the two registration methods (with the two masks), the values of FWHM (six frames) became equal to the value obtained with the gold standard curve.

We performed the perfusion analysis directly on the raw dataset from this typical patient, which was the method used classically, and on the registered dataset (registration realized with the optimal cardiac mask). Definition of the five ROIs required for the perfusion analysis is presented in Figure 5A. Transit time curves obtained from this ROI are presented in Figure 5B–F.

We can observe that in the lateral and septal segments (Fig. 5D and F) small differences in the transit time curves are obtained, which can be explained by the fact that the respiratory motion of this patient is principally along the SI direction. In Figure 5C, large differences between the two transit-time curves were obtained and led to very different values of the perfusion parameters.

Results Summary Obtained From All Patients

As shown in Table 3, the registration stage with the optimal cardiac mask allows reducing the positional variations of the center of mass of the LV intensities from 1.98 ± 0.68 mm to 0.56 ± 0.18 mm in the AP-axis, and from 4.05 ± 2.00 mm to 0.49 ± 0.14 mm in the SI-axis. Using the rectangular mask led to larger dispersions on the position of this center of mass: AP-axis: 0.58 ± 0.38 mm; SI-axis: 0.59 ± 0.22 mm.

After performing all the perfusion analyses on the eight patients (two slices per patient, four sectors: anterior, lateral, inferior, and septal), the goodness-of-fit was assessed by comparing perfusion parameters obtained from the raw dataset, the automatic registered datasets (with the two masks), to perfusion parameters obtained with the manual shift of the images (gold standard). Figure 6A and B plot the absolute variations of the variability of the perfusion parameters determined with raw dataset, and with the two registered datasets. Table 4 presents the variability obtained in the perfusion parameters for the different registration processes.

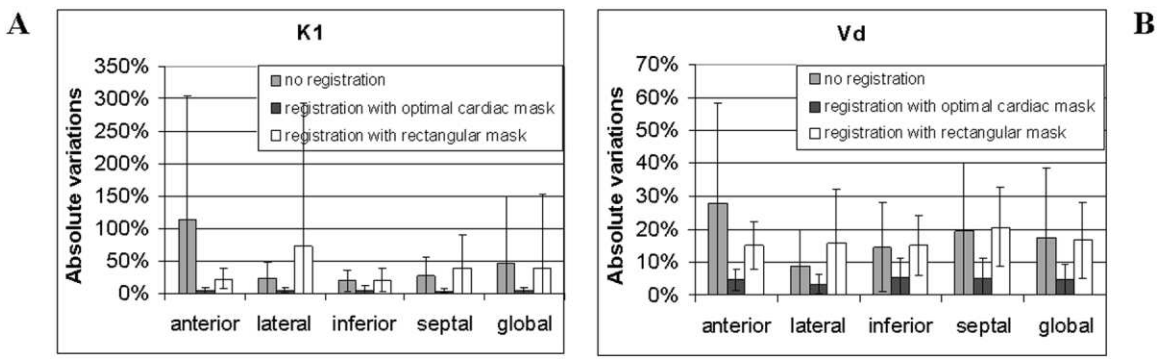

Figure 6. Variability in the determination of the perfusion parameters with or without a registration stage is plotted for *K1* (**A**) and for *Vd* (**B**).

Table 4
Variability of the Model Fit From Eight Patients

Variability (%)	Raw images		Automatic registered images with optimal cardiac mask		Automatic registered images with rectangular mask	
K1	(46 ± 103)%	$P = 0.07$	(5 ± 4)%	$P = 0.58$	(39 ± 113)%	$P = 0.81$
Vd	(18 ± 21) %	$P = 0.01$	(5 ± 5)%	$P = 0.73$	(17 ± 12) %	$P < 0.001$

*(Four Sectors each, *K1, Vd,* See text)
Variability of the model fit (mean ± SD) and value of the *t*-test associated.

On raw images, large variability was obtained in the determination of the perfusion parameters and led to measurements that were statistically different if they were performed on raw images or on the gold standard dataset. Using the optimal cardiac mask for the registration stage led to perfusion values that were very close to the values obtained with the gold standard dataset. Results obtained using the rectangular mask gave perfusion parameters with variability comparable to those obtained directly on raw images.

Finally, on a Pentium III computer (733 MHz) with 512-Mb RAM and with non-optimized coding, total registration time with the algorithm presented in this paper took about 2.5 minutes for 100 frames (256 × 256 pixels). Cardiac perfusion analysis can then be assessed quickly because the manual correction stage is avoided.

DISCUSSION

Usual correction methods for breathing motion are based either on translations only (7), which are easy to implement on interactive imaging platforms (15), or on segmented anatomic features of the heart or landmarks (3,16). The first category was generally tedious to manipulate for numerous frames, and the second one required the extraction of features over all frames. With cardiac perfusion images where large intensity variations exist, this stage was not easy because classic segmentation techniques based on signal intensity are not suited to this kind of image. The technique described in this paper is based on the intensity of the images, not on segmented features such as landmarks or edges. As such, this technique uses all the relevant signal intensity information intrinsically available in the images. Performing the registration stage can also be realized by using an algorithm based on mutual information (MI) (17–19). The cost function for MI is a similarity measure that does not assume any intensity correlation, but relies only on statistical dependence of intensities (20). MI cost function is generally used for registering images from different modalities but is also suited for registering a time series of images.

The registration process used in this work, including rotation, does not include non-rigid transformation. In perfusion analyses, images are acquired in short-axis view at the same phase of the cardiac cycle. Thus, the similarity between the LV appearances along all the images is very high, and a non-rigid transformation is not required. Such a transformation could be of interest when registering various patients or when using an atlas for the definition of the ROIs.

The method used for drawing the optimal cardiac mask is simple and leads to a robust algorithm without including severe constraints. The mask centered on the LV is drawn on the frame where the contrast media is arriving in the LV cavity. Actually, the LV cavity is manually hollowed from the mask but an automatic segmentation based on an intensity threshold can easily be done for removing this cavity.

In the work by Bidaut Vallée (4), to increase the robustness of their iterative technique, boundaries were enforced on all the parameters (translation and rotation) during iteration. These boundaries were chosen to match the most likely range of motion based on the literature (12,13). With these boundaries, absolute translation in every axis was limited to 15 mm and rotation to 15°. The method presented in this work has shown that no artifact was obtained even with translation higher than 25 mm.

Smaller zigzag patterns can still be seen on the time transit curves after registration (Fig. 4). These patterns may be due in part to some remaining motion or uncorrected distortions (such as through-plane motion). It is possible to minimize the effect of the through-plane motion by moving the ROIs placed inside the myocardium independently. But in this work, we preferred to use the same ROIs for performing perfusion analysis on all datasets with or without a registration stage.

In conclusion, the aim of this work was not only to present an efficient registration algorithm but also to use this registration process in order to assess more accurate values of the tissue perfusion inside the LV. This work presents an automated method that significantly improves the ease and accuracy of positioning the ROIs for the refined analysis of perfusion on dynamic cardiac MRI sequences. This registration process, based on a freely available algorithm, corrects most of the motion induced by physiology and free-breathing. This leads to the assessment of more accurate values (*K1* and *Vd*) of the perfusion analysis. Perfusion analyses, which are tedious and time consuming when they are realized by manually shifting the different ROIs over each image, become simpler because the ROIs are defined by only one frame.

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