Published in final edited form as:

Phys Med Biol. 2017 May 21; 62(10): 3944–3957. doi:10.1088/1361-6560/aa6520.

Fully automatic multi-atlas segmentation of CTA for partial volume correction in cardiac SPECT/CT

Qingyi Liu^{1,2}, Hassan Mohy-ud-Din², Nabil E Boutagy³, Mingyan Jiang¹, Silin Ren⁴, John C Stendahl³, Albert J Sinusas^{2,3}, and Chi Liu^{2,4,5}

¹School of Information Science and Engineering, Shandong University, Jinan, Shandong 250100, People's Republic of China

²Department of Radiology and Biomedical Imaging, Yale University, New Haven, CT 06520, United States of America

³Department of Internal Medicine (Cardiology), Yale University, New Haven, CT 06520, United States of America

⁴Department of Biomedical Engineering, Yale University, New Haven, CT 06520, United States of America

Abstract

Anatomical-based partial volume correction (PVC) has been shown to improve image quality and quantitative accuracy in cardiac SPECT/CT. However, this method requires manual segmentation of various organs from contrast-enhanced computed tomography angiography (CTA) data. In order to achieve fully automatic CTA segmentation for clinical translation, we investigated the most common multi-atlas segmentation methods. We also modified the multi-atlas segmentation method by introducing a novel label fusion algorithm for multiple organ segmentation to eliminate overlap and gap voxels. To evaluate our proposed automatic segmentation, eight canine ^{99m}Tc-labeled red blood cell SPECT/CT datasets that incorporated PVC were analyzed, using the leave-one-out approach. The Dice similarity coefficient of each organ was computed. Compared to the conventional label fusion method, our proposed label fusion method effectively eliminated gaps and overlaps and improved the CTA segmentation accuracy. The anatomical-based PVC of cardiac SPECT images with automatic multi-atlas segmentation provided consistent image quality and quantitative estimation of intramyocardial blood volume, as compared to those derived using manual segmentation. In conclusion, our proposed automatic multi-atlas segmentation method of CTAs is feasible, practical, and facilitates anatomical-based PVC of cardiac SPECT/CT images.

Keywords

multi-atlas based segmentation; partial volume correction; cardiac SPECT/CT

⁵Author to whom any correspondence should be addressed. Chi Liu: ude.elay@uill.ihc.

Some figures may appear in colour only in the online journal

1. Introduction

Partial volume effect (PVE) due to limited scanner resolution is a major factor that degrades the image quality and quantitative accuracy in cardiac SPECT and PET imaging. It has been demonstrated that anatomical-based partial volume correction (PVC) methods could effectively correct the PVE for neurology, oncology, and cardiology applications (Erlandsson *et al* 2012). For cardiac SPECT, high-resolution epicardial and endocardial surfaces that are not available in SPECT data are needed to define the organ boundaries as the first step in anatomical-based PVC. Fortunately, there has been an increase in the installation of hybrid SPECT/CT and PET/CT systems with high-end multi-slice CT that are capable of acquiring contrast-enhanced cardiac CT angiograms (CTA). Several studies have demonstrated that the combination of CTA and perfusion SPECT/PET in a single imaging session could further improve the diagnostic accuracy (Di Carli *et al* 2007, Danad *et al* 2013). In addition to providing information on coronary vessel morphology, cardiac CTA also allows for delineation of the epicardial and endocardial surfaces, which are critical to guide anatomical-based PVC.

We have investigated anatomical-based PVC guided by CTA in simulation and *in vivo* studies, in particular for the tracer of Tc^{99m} -red blood cell (RBC) to quantify intramyocardial blood volume (IMBV) using a dedicated cardiac SPECT/CT system with a 64-slice CT (GE Discovery 570c NM/CT) (Liu *et al* 2015). Our published results showed that our PVC methods guided by CTA are capable of achieving accurate quantification of IMBV with low-dose SPECT data. However, this type of PVC requires accurate segmentation of various organs (myocardium, blood pool, lung, liver, background, in our implementation) from CTA data. The current approach for CTA segmentation is based on manual approach, which is very time consuming and impractical for future clinical adoption of CTA-based PVC for cardiac SPECT and PET. For the purpose of PVC, multiple organs need to be segmented without any gap voxels in order to determine both the ‘spill-out’ and ‘spill-in’ effects among all the organs. To address the barrier of practical CTA segmentation for multiple organs, a multi-atlas multi-organ segmentation approach could be a potential solution.

Multi-atlas segmentation methods incorporate prior knowledge of organ spatial location from multiple atlases and results in highly accurate and robust segmentation. In this method, a number of atlas images are first warped to the target image through image registration and then the corresponding manually segmented label images are transformed using the same registration parameters. The final segmentation is obtained by combining all the propagated label images in the label fusion step. It has been successfully applied to the segmentation of various medical images, such as brain, cardiac and abdominal images (Eskildsen *et al* 2012, Bai *et al* 2013, Xu *et al* 2015).

Label fusion is a critical step in multi-atlas segmentation. It is a process to improve the segmentation accuracy in the final result. The original label fusion method is called ‘best label selection’ (Rohlfing *et al* 2004). In this method, a deformed label image was usually selected as the final segmentation result based on the similarity between the registered atlas and the target image. However, this method ignores the potentially useful information in all

other atlases. The most widely used label fusion method is the majority voting (MV) method (Heckemann *et al* 2006). The MV method counts the ‘votes’ from propagated label images for each voxel, and then chooses the label that receives the most votes to produce the final segmentation. The existing multi-atlas segmentation method using the MV method (Kirisli *et al* 2010) or other new label fusion methods (Asman and Landman 2013, Bai *et al* 2015) only consider one ROI at a time without considering the location relationship among different ROIs. The above methods typically combine multiple individual ROI segmentation to generate multiple organs segmentation. They have been successfully applied to the segmentation of myocardium and blood pool from CTA, but not to other organs in a manner that eliminates gap voxels (Kirisli *et al* 2010). Thus, the phenomenon of gaps or overlaps between different ROIs inevitably occurred and will affect the accuracy of SPECT PVC. In most anatomical-based PVC methods, each voxel can only belong to a single organ in order to generate response maps. Thus, in the presence of overlap voxels, it is not practical to perform such PVC. In the presence gap voxels in segmentation, the template response and PVC factor image will have zero values in these voxels, subsequently the PV corrected SPECT images will have zero values for those corresponding voxels. Therefore, neither overlaps nor gaps are permitted in anatomical-based PVC.

In order to eliminate gaps or overlaps, we proposed a new label fusion method, which fused the label images of five ROIs simultaneously by using only one voting process. This method is expected to further improve the segmentation accuracy. We evaluated the accuracy of the improved multi-atlas CTA segmentation and the cardiac SPECT PVC guided by this fully automatic segmentation method in a set of canine cardiac ^{99m}Tc -RBC SPECT/CT images.

2. Materials and methods

2.1. Animal imaging study

Animal SPECT/CT imaging studies were performed with approval of the institutional animal care and use committee. Eight beagle dogs (mean weight of 10.9 ± 1 kg) were initially sedated via peripheral intravenous injection of propofol ($7\text{--}7.5$ mg kg^{-1}), and then intubated, mechanically ventilated, and anesthetized with inhalation of isoflurane (1.5–2%), and oxygen and nitrous oxide (ratio 35%–65%). Anesthetized dogs underwent SPECT/CT imaging for 10 min, after injection of ^{99m}Tc -RBCs (885.6 ± 48.9 Mbq), using a hybrid SPECT/CT system (GE Discovery NM/CT 570c). A dual respiratory-cardiac gating box (Ivy Biomedical Systems, Branford, CT) was used to record the external respiratory motion information through a compressive sensing pillow attached to the dog’s abdomen (Chan *et al* 2014). ECG triggers were injected into the SPECT listmode data from the gating box. The recorded respiratory trace was synchronized with SPECT listmode data.

The contrast CT images were acquired at 120 kVp, 35 mA, with pitch of 0.24:1, slice thickness of 0.625 mm, and rotation speed of 0.35 s per rotation. Iodinated contrast (Omnipaque, GE Healthcare) was administered centrally via a femoral intravenous injection using a power injector (Stellant D; MEDRAD, Warrendale, PA) interfaced with the CT camera and was delivered using a 3-phase injection at a constant flow rate of 3 ml s^{-1} (contrast: 10 ml; 50–50 contrast/0.9% saline mix; 5 ml and 0.9% saline; 10 ml). A timing bolus acquisition (120 kVp, 80 mA) was first performed to determine the optimal timing

delay. By temporarily disconnecting the ventilator, the contrast CT data were acquired at end-expiration phase. The contrast CT images were reconstructed using filtered back projection from the end-diastolic phase (70% RR interval) in our study with a voxel size of $0.625 \times 0.625 \times 0.625 \text{ mm}^3$. The image dimension of reconstructed SPECT images was $150 \times 150 \times 150$, and the voxel volume was $4 \times 4 \times 4 \text{ mm}^3$. As described in section 2.3.2, SPECT listmode data from end-diastolic phase and end-expiration phase were rebinned and reconstructed to match with contrast CT data. A low-dose non-contrast CT was also acquired for each dog for SPECT attenuation correction (AC).

2.2. Multi-atlas segmentation

2.2.1. Overview—An overview of the multi-atlas segmentation method for one of organ ROIs is illustrated in figure 1. First, the multi-atlas based segmentation method requires a set of N atlas images and their corresponding label images, which are binary masks created by manual segmentation. Second, each of the atlas images was registered through non-rigid image registration to the target image that is to be segmented. Third, in the label propagation step, each transformation matrix derived from the non-rigid registration in the previous step was applied to the corresponding labeled image, in order to generate candidate segmentations (deformed label images) that are expected to align with the target image. Finally, the candidate segmentation images were fused into a single final segmentation result through voting algorithms discussed below.

For multiple ROIs' segmentation, the conventional solution applies the second and the last steps to all the ROIs altogether, and then combines the segmentation results of every ROI as the final segmentation result. As discussed in detail below, by using our proposed combined voting algorithm, the last step only needs to be performed once. Compared to the classical MV voting method, which creates voxels that are inside the body but do not belong to any ROI (gap) or belong to more than one ROI (overlap), the proposed algorithm was able to eliminate such gaps and overlaps among different ROIs, and improve the segmentation accuracy for subsequent SPECT PVC. Each of these steps will be described in detail below.

2.2.2. Atlas building—A complete atlas used in the multi-atlas segmentation method includes a set (8 in this study) of atlas images and their corresponding label images. For each of the 8 canine contrast CT angiograms, manual segmentation was performed to generate five ROIs, defining: myocardium, blood pool, liver, lung, and background. The voxels inside the animal's body not belonging to the other four ROIs were assigned into the ROI of background. Special care was taken to assure there was no gap and overlap between different ROIs. The segmentation of each ROI was saved as a binary image. The manual segmentation took about 6 h for each CTA dataset by a postdoctoral fellow with extensive imaging background.

In our study, in order to reduce the computing time needed for registration, we cropped all contrast CT images and their corresponding manual segmentation images to remove the part of scanner bed and other non-relevant space outside the animal's body. The cropped contrast CT images were used as atlas images, and their cropped corresponding manual segmentation images were used as their label images.

2.2.3. Registration—Non-rigid registration was used to spatially align each atlas image with the target image (Hill *et al* 2001). Let I_T be the target image to be segmented. For a set of N atlas images, A_n and L_n respectively denoted the n th atlas image and the corresponding n th label image ($n \in [1, N]$). In the second step of multi-atlas based segmentation method, the atlas image A_n was registered to target image I_T , and the corresponding transformation in the image domain was obtained.

In the process of registering every atlas image to the target image, we applied a two-stage registration approach (Klein *et al* 2010). First, a rigid transformation was applied for initial alignment. Then, the rigid registration result was used as the initialization for a non-rigid registration by using a B-spline transformation model. The B-spline control point spacing was set to 8 mm; the number of multi-resolution levels was set to 4; the number of iterations was set to 15. We employed the sum of squared differences (SSD) as the similarity measure in the registration framework (Kybic and Unser 2003).

2.2.4. Label propagation—After registering each particular atlas image to the target image, the transformation matrices were obtained. Then, the candidate segmentation images were obtained by applying these transformations to the corresponding label images of the five critical organ ROIs, respectively. In our method, we performed this label propagation process for each atlas image respectively to generate all candidate segmentation image sets of five ROIs.

2.2.5. Label fusion—In this step, the candidate segmentations from label propagation were fused to obtain the final segmentation result. In our study, we proposed a new label fusion method for segmentation of multiple objects. The main benefit of this approach is to eliminate the gaps and overlaps, and to improve the segmentation accuracy.

For multi-atlas segmentation of multiple organs instead of a single organ, existing methods typically employ independent label fusion, such as the MV method for each individual organ ROI segmentation (Kirisli *et al* 2010, Dill *et al* 2015). The candidate segmentation images from label propagation are binary maps. Therefore, the conventional MV method for a single organ ROI can be described as:

$$S_F(i) = \begin{cases} 1 & \text{if } \sum_{n=1}^N S_n(i) > \frac{N}{2}; \\ 0 & \text{otherwise.} \end{cases} \quad (1)$$

where n is the n th atlas ($n \in [1, N]$); i is the voxel index. S_F is the final segmentation after voting; S_n is the candidate segmentation derived from the n th atlas. For multi-organ segmentation, the S_F of each organ will simply be fused together as the final segmentation.

However, this approach ignored the crosstalk of ROIs. Our implementation showed that there were some gaps or overlaps between different ROIs, as demonstrated by some voxels near the boundary between different ROIs not belonging to any ROI or assigned into more than one ROIs. This result might be acceptable in some applications. However, in our

research with the end goal of performing SPECT PVC, any gap or overlap voxel will introduce substantial errors in the PVC process. Therefore, it is critical to eliminate gap and overlap voxels through an improved voting methods.

To address this issue, we proposed a novel voting method named ‘combined voting’ (CV), to eliminate the gaps and overlaps between different ROIs. After we obtained the candidate segmentations of five ROIs from each atlas, all the ROIs were used as voting members and were voted together. This means that the final segmentation result of all the ROIs can be obtained by using only one voting process. This process can be described as:

$$S_F(i) = \begin{cases} 0 & \text{if } \sum_{m=1}^{M-1} S_m(i) = 0 \text{ and } \mu S_M(i) < \frac{N}{2}; \\ \arg \max(S_m(i)) & \text{otherwise.} \end{cases} \quad (2)$$

where μ is a weighting constant to enforce boundary smoothness and was set to 1.5 empirically; m is the index of m th ROI ($m \in [1, M]$). In our implementation with $M = 5$, we represented the myocardium ($m = 1$), blood pool ($m = 2$), liver ($m = 3$), lung ($m = 4$), and background ($m = 5$). Regions outside of the animal’s body were not taken into account in the voting process. $S_F(i)$ is the final index value of voxel i after voting. $S_m(i)$ is used to count the votes of voxel i , and defined by the following function:

$$S_m(i) = \sum_{n=1}^N S_{n,m}(i) \quad (3)$$

where $S_{n,m}(i)$ is the vote of voxel i for m th ROI produced by the n th atlas.

By counting the votes of all organ ROIs, the organ that received the most votes was assigned as the organ of each voxel i in the final segmentation. In the case when two organs received the same amount of votes, the voxel was assigned to the organ with a higher priority. In this study, we used an empirical priority of organs, the lower m values have higher priority from high to low of myocardium, blood pool, liver, lung and background, considering our particular application of quantifying intramyocardium blood volume using a blood pool tracer. A different priority list might be needed for other applications. After fusing the candidate segmentations using our novel voting method, the final segmentation became a union of multiple piece-wise templates, each corresponding to an organ. Figure 4 provides an example where each segmented organ is labeled by a unique color.

2.3. Evaluation

2.3.1. Implementation and evaluation of multi-atlas CTA segmentation—In our study, the registration and label propagation steps of multi-atlas segmentation methods were implemented using *BioImage Suite* 3.01, which is an integrated image analysis software suite developed at Yale University (Papademetris *et al* 2006, Scheinost *et al* 2010). All other steps, including label propagation and label fusion, were implemented in the R2010 version of MATLAB.

For each canine dataset, the automatic atlas-based segmentation results (leave-one-out) using both MV and CV were compared with manual segmentation as the gold standard in terms of visual observation along with Dice similarity coefficient for each individual organ ROI. The mean and standard deviation of Dice similarity coefficient were computed through 8 leave-one-out experiments that each used 7 atlases. To investigate the statistical significance, we performed the paired *t*-test between the Dice coefficients associated with the MV and CV label fusion methods.

2.3.2. Evaluation of SPECT partial volume correction—Based on the Ivy dual gating box generated ECG triggers and respiratory wave, all SPECT list mode data were first re-binned into an end-diastolic phase from 8 cardiac phases and end-expiration phase from 5 respiratory phases to correct respiratory and cardiac motion. Images were reconstructed with MLEM algorithm with AC and scatter correction for the cadmium zinc telluride (CZT) detectors of the SPECT/CT system (Fan *et al* 2015). Reconstructed SPECT images were corrected for partial volume effects (PVE) using an iterative Yang approach. While the details for this PVC correction can be found in Chan *et al* (2016), an overview is given here. In each PVC iteration, voxel-wise PVC was performed by scaling the reconstructed SPECT image (*A*) using updated PVC factor image (*F*), i.e. $\lambda_{PVC} = \lambda \cdot F$. The PVC factor image was obtained as a ratio of the template image, *T*, and the reconstructed response image, T_{recon} (Chan *et al* 2016). The template image *T* was constructed using CT as follows: (1) the above described atlas-based segmentation of contrast-enhanced CT was performed to obtain each organ ROI. (2) ROIs were resliced to the SPECT voxel size to obtain tissue fraction maps (Liu *et al* 2015, Chan *et al* 2016), (3) Regional mean values were obtained for the segmented organs using thresholded tissue fraction maps as binary masks, (4) Tissue fraction maps were scaled by the corresponding organ mean values determined by the approaches in Chan *et al* (2016) and additively combined to give template *T*. The template was forward projected and reconstructed using the SPECT system matrix including accurate collimator-detector responses and attenuation map to yield T_{recon} . This process was iterated until the inter-iteration changes of organ mean values are below 1%. In our study, 5 iterations were sufficient to achieve such convergence.

For SPECT/CT images acquired following injection of ^{99m}Tc -RBCs, our interest is to quantify the IMBV, which is defined as the fraction of myocardium that is occupied by blood. IMBV is used as an index of the microvascular bed within the myocardium, which primarily represents the intramyocardial capillary volume. To quantify IMBV, we applied the re-sliced myocardium ($\text{ROI}_{\text{myo rsl}}$) and blood-pool ($\text{ROI}_{\text{LV-blp rsl}}$) masks onto the reconstructed SPECT images to compute the mean activity in the myocardium (C_{myo}) and the left ventricular (LV) blood-pool ($C_{\text{LV-blp}}$). Then IMBV was determined as $\text{IMBV} = C_{\text{myo}}/C_{\text{LV-blp}}$. The IMBV values obtained using manual segmentation and automatic segmentation described above were compared using all the animal studies.

3. Result

3.1. Multi-atlas segmentation study

Figure 2 shows sample transaxial slices of the original 3D contrast CT images for each of the 8 dogs. As can be observed, each dog had different body size, heart anatomy, and positioning within the scanner. The right ventricular (RV) and left ventricular (LV) blood pool contrast ratios were also different between studies, due to differences in physiological status, as well as the volume and timing of the delivery of the CT contrast in relation to the timing of CT acquisition.

We performed the above mentioned segmentation process for each dog using the ‘leave-one-out’ method (Lorenzo-Valdés *et al* 2004, Kirisli *et al* 2010, Bai *et al* 2015), meaning the other seven dog datasets served as atlases for each specific dog as the target image.

Unregistered transaxial contrast CT images of the heart and chest are shown in figure 2. The first dog’s image (with the red box) is taken as the target image, and the other seven images as the atlas images. Figure 3 shows an example of our registration results. The original CTA image in figure 3(a) (in red box) was identical to that shown in figure 2(a). Figures 3(b)–(h) show the results following registration and corresponding transformations from figures 2(b)–(h). The anatomical structures of all images appear visually consistent with the target image in figure 3(a).

Figure 4 shows the final segmentation results of the target image using both the manual and atlas-based automatic methods. In this figure, the different colors indicated the five different ROIs, representing: myocardium (red), blood pool (cyan), liver (yellow), lung (green), and background (blue). The region outside of the dog’s body was displayed as black. As shown in the second row of figure 4, many voxels that should be part of a particular organ are labeled with black color, indicating that the MV methods resulted in gaps among different ROIs. We computed the number of gap voxels and show the percentages in table 1. Across the 8 dogs, on average 3.45% of all voxels inside the dog body are gaps using MV. In contrast, our proposed CV method effectively eliminated all the gap voxels among different ROIs. An example slice of effectiveness of the proposed CV method is shown in the third row of figure 4.

The mean and standard deviation of the Dice similarity coefficient across 8 canine image sets were computed for each of the five ROIs including background, blood pool, lung, liver and myocardium. As shown in table 2, the CV method improved the segmentation accuracy for most ROIs. For the ROIs of liver, lung and background, the differences between CV and MV methods were statistically significant with p -values smaller than 0.05 using dependent t -test.

3.2. partial volume correction with multi-atlas segmentation study

A representative result from one of the dog studies is shown in figure 5. The PVC corrected SPECT images were visually nearly identical using both the manual segmentation and multiatlas segmentation. Both images with PVC showed sharper boundaries and higher contrast than the image without PVC. The crosstalk from the LV and RV blood pools into the septal wall of the myocardium was effectively eliminated with both PVC methods.

Table 3 summarizes the estimation of the IMBV obtained following PVC using the manual and atlas-based segmentation approaches in all 8 dogs. Using the manual segmentation approach as the reference, the PVC following application of the atlas-based segmentation yielded a 9.3% mean relative absolute difference in the estimation of the IMBV. Figure 6 depicts the plot of the correlation between the estimation of the IMBV using both methods. The correlation coefficient of the regression was high and the slope approached unity. Note that the results from Dog 3 were not included in figure 6 and calculation of mean difference, as we found that this dog had significant myocardial hypertrophy on postmortem examination, and the atlas-based segmentation approach did not work well for this dog due to the unusual increase in myocardial wall thickness in this particular heart.

4. Discussion

In this study, we described and validated a framework for automatic multi-atlas segmentation of contrast-enhanced cardiac CT angiograms images relative to manual segmentation to facilitate PVC of ^{99m}Tc -RBC hybrid SPECT/CT heart images. We developed a novel label fusion method to eliminate the gaps among different organ ROIs and improved the segmentation accuracy. Our results showed that PVC with automatic multi-atlas segmentation achieved results consistent with those obtained using manual segmentation.

4.1. Multi-atlas segmentation of contrast CT images

In the multi-atlas segmentation method, the accuracy of final segmentation result was mainly affected by the accuracies of registration and label fusion algorithm. Among the eight dogs evaluated in our study there were apparent differences in anatomical structures, such as the size and orientation of the heart and body, as demonstrated in figure 2. Therefore, it is not realistic to expect perfect registration between every atlas image and the target image. As shown in figures 2 and 3, even though discrepancies between the target image and registered images still occurred in some local regions, combining all candidate segmentations derived from all atlas datasets in the next step, the process of label fusion effectively minimized the impact of such registration errors in the final segmentation, as demonstrated in figure 4. In our study, all the registrations were carried out using the same parameters, which were empirically optimized using a large number of trial-and-error experiments giving satisfactory results for all the datasets. We found such parameters optimized for smaller beagle dogs in this study did not work well for larger dogs, indicating the parameters should be individually optimized for each species and patient populations. For future human studies, the optimal spacing and control points for image registration are likely to be different to account for different body and organ sizes. While such parameter optimization could be time consuming, the emerging use of GPU implementation for fast image registration can facilitate the clinical feasibility of this process. Prior to the registration, in the current implementation we manually cropped out the scanner bed, which does not contain any radioactivity and does not benefit SPECT PVC. This process can also be automatic, as the relative location of the scanner bed in CT volume is fixed for a given bed height. In future studies, we will explore to automatically eliminate the bed using a mask based on bed height recorded during CT data acquisition to further streamline the

segmentation process. Our segmentation approach did not work well for Dog 3 with hypertrophy, because the atlas database did not include cases with abnormal anatomy. In futures studies, we expect expanding the atlas by including a wide range of anatomical variability will further improve the robustness and segmentation accuracy for dogs with abnormal anatomy.

For multi-atlas segmentation of more than three organs, all existing methods typically used the label fusion method independently for each organ one at a time. This often results in some voxels near the organ boundary being segmented into more than one ROI (overlap), or not being segmented into any ROI (gap) (Kirisli *et al* 2010, Sedai *et al* 2015). In our study, we implemented the classical MV method as an example, and independently used this approach for five organ ROIs' segmentation. We demonstrated that multiple gaps occurred between different ROIs using the standard approach. Those gaps meant that those voxels were not classified into any organ in the voting processes for all five organs. In our study, we used seven atlases for each segmentation. Other studies have shown that using even numbers of atlas will result in overlap voxels, in addition to gaps (Kirisli *et al* 2010). Such gaps and overlaps might not affect the calculation of some indices like the ejection fraction using CTA. However, for our application of anatomical-based PVC for SPECT ^{99m}Tc -RBC images, it is not desirable to have segmentation gaps and overlaps, which will propagate into the process of PVC template generation. This will adversely affect the 'spill-in' and 'spill-out' corrections needed for SPECT PVC. Therefore, the existing label fusion methods could not be used in our application.

To address this limitation, we developed a new label fusion method that is capable of eliminating gaps and overlaps and further improving the segmentation accuracy by using a novel CV method. Compared to the independent MV method, we found that the segmentation accuracy of our CV method improved image quality both visually and quantitatively, as shown in figure 4 and table 2, respectively. The improvement was statistically significant for liver, lung, and background, but not significant for myocardium and blood pool, likely because there were only a few gap voxels between blood pool and myocardium and the sample size is small.

The label fusion process involves voxel-by-voxel voting. For a high-resolution CTA image with a large matrix size, this voxel-wise voting is time consuming, particularly for the conventional MV method that has to be executed five times in order to segment 5 organ ROIs. In contrast, our CV method requires only one voting for all 5 organs altogether, and thus substantially reduces the computational cost.

4.2. Partial volume correction of SPECT images

PVC using atlas-based segmentation showed promising results as compared to the time consuming manual segmentation. The IMBV difference between manual segmentation and atlas-based segmentation was within 10% on average. We expect the difference to further reduce with larger atlas database. In the estimation of IMBV from ^{99m}Tc -RBC SPECT images there was strong correlation between manual segmentation and our new atlas-based segmentation. In this study, we used a subset of the image studies as an atlas for each segmentation to demonstrate the initial feasibility of our approach. We expect that using a

larger number of atlas images will further improve the segmentation accuracy and accommodate potential variation in the anatomy of the heart, particularly in the presence of disease.

5. Conclusions

We established the feasibility and potential advantage of an automatic segmentation approach over standard manual segmentation of CTA images using a multi-atlas segmentation method to facilitate PVC of ^{99m}Tc -RBC SPECT/CT images. This segmentation approach requires a new CV method to eliminate gaps and overlap voxels among various organ ROIs required for PVC.

Acknowledgments

This work was supported by NIH Grants R01HL123949, R01HL113352, T32HL098069, 1S10RR02555, and National Natural Science Foundation of China (No. 61471225), Natural Science Foundation of Shandong Province (No. ZR2014FM039), and a China Scholarship Council (CSC) grant.

References

- Asman AJ, Landman BA. Non-local statistical label fusion for multi-atlas segmentation. *Med Image Anal.* 2013; 17:194–208. [PubMed: 23265798]
- Bai W, Shi W, Ledig C, Rueckert D. Multi-atlas segmentation with augmented features for cardiac MR images. *Med Image Anal.* 2015; 19:98–109. [PubMed: 25299433]
- Bai W, Shi W, O'Regan DP, Tong T, Wang H, Jamil-Copley S, Peters NS, Rueckert D. A probabilistic patch-based label fusion model for multi-atlas segmentation with registration refinement: application to cardiac MR images. *IEEE Trans Med Imaging.* 2013; 32:1302–15. [PubMed: 23568495]
- Chan C, Harris M, Le M, Biondi J, Grobstein Y, Liu YH, Sinusas AJ, Liu C. End-expiration respiratory gating for a high-resolution stationary cardiac SPECT system. *Phys Med Biol.* 2014; 59:6267–87. [PubMed: 25256033]
- Chan C, Liu H, Grobstein Y, Stacy MR, Sinusas AJ, Liu C. Noise suppressed partial volume correction for cardiac SPECT/CT. *Med Phys.* 2016; 43:5225. [PubMed: 27587054]
- Danad I, Rajmakers PG, Knaapen P. Diagnosing coronary artery disease with hybrid PET/CT: it takes two to tango. *J Nucl Cardiol.* 2013; 20:874–90. [PubMed: 23842709]
- Di Carli MF, Dorbala S, Meserve J, El Fakhri G, Sitek A, Moore SC. Clinical myocardial perfusion PET/CT. *J Nucl Med.* 2007; 48:783–93. [PubMed: 17475968]
- Dill V, Franco AR, Pinho MS. Automated methods for hippocampus segmentation: the evolution and a review of the state of the art. *Neuroinformatics.* 2015; 13:133–50. [PubMed: 26022748]
- Erlandsson K, Buvat I, Pretorius PH, Thomas BA, Hutton BF. A review of partial volume correction techniques for emission tomography and their applications in neurology, cardiology and oncology. *Phys Med Biol.* 2012; 57:R119–59. [PubMed: 23073343]
- Eskildsen SF, Coupe P, Fonov V, Manjon JV, Leung KK, Guizard N, Wassef SN, Ostergaard LR, Collins DL, Alzheimer's Disease Neuroimaging I. BEaST: brain extraction based on nonlocal segmentation technique. *Neuroimage.* 2012; 59:2362–73. [PubMed: 21945694]
- Fan P, et al. Scatter and crosstalk corrections for $(^{99m}\text{Tc})/(^{123}\text{I})$ dual-radionuclide imaging using a CZT SPECT system with pinhole collimators. *Med Phys.* 2015; 42:6895–911. [PubMed: 26632046]
- Heckemann RA, Hajnal JV, Aljabar P, Rueckert D, Hammers A. Automatic anatomical brain MRI segmentation combining label propagation and decision fusion. *Neuroimage.* 2006; 33:115–26. [PubMed: 16860573]

- Hill DL, Batchelor PG, Holden M, Hawkes DJ. Medical image registration. *Phys Med Biol.* 2001; 46:R1–45. [PubMed: 11277237]
- Kirisli HA, et al. Evaluation of a multi-atlas based method for segmentation of cardiac CTA data: a large-scale, multicenter, and multivendor study. *Med Phys.* 2010; 37:6279–91. [PubMed: 21302784]
- Klein S, Staring M, Murphy K, Viergever MA, Pluim JP. Elastix: a toolbox for intensity-based medical image registration. *IEEE Trans Med Imaging.* 2010; 29:196–205. [PubMed: 19923044]
- Kybic J, Unser M. Fast parametric elastic image registration. *IEEE Trans Image Process.* 2003; 12:1427–42. [PubMed: 18244700]
- Liu H, Chan C, Grobshtein Y, Ma T, Liu Y, Wang S, Stacy MR, Sinusas AJ, Liu C. Anatomical-based partial volume correction for low-dose dedicated cardiac SPECT/CT. *Phys Med Biol.* 2015; 60:6751–73. [PubMed: 26296043]
- Lorenzo-Valdés M, Sanchez-Ortiz GI, Elkington AG, Mohiaddin RH, Rueckert D. Segmentation of 4D cardiac MR images using a probabilistic atlas and the EM algorithm. *Med Image Anal.* 2004; 8:255–65. [PubMed: 15450220]
- Papademetris X, Jackowski MP, Rajeevan N, DiStasio M, Okuda H, Constable RT, Staib LH. BioImage suite: an integrated medical image analysis suite: an update. *Insight J.* 2006; 2006:209. [PubMed: 25364771]
- Rohlfing T, Brandt R, Menzel R, Maurer CR Jr. Evaluation of atlas selection strategies for atlas-based image segmentation with application to confocal microscopy images of bee brains. *NeuroImage.* 2004; 21:1428–42. [PubMed: 15050568]
- Scheinost D, Teisseyre TZ, Distasio M, DeSalvo MN, Papademetris X, Blumenfeld H. New open-source ictal SPECT analysis method implemented in bioimage suite. *Epilepsia.* 2010; 51:703–7. [PubMed: 20074234]
- Sedai, S., Garnavi, R., Roy, P., Liang, X. Multi-atlas label fusion using hybrid of discriminative and generative classifiers for segmentation of cardiac MR images. 37th Annual Int Conf of the IEEE Engineering in Medicine and Biology Society; 2015. p. 2977-80.
- Xu Z, Burke RP, Lee CP, Baucom RB, Poulouse BK, Abramson RG, Landman BA. Efficient multi-atlas abdominal segmentation on clinically acquired CT with SIMPLE context learning. *Med Image Anal.* 2015; 24:18–27. [PubMed: 26046403]

Figure 1. Illustration of the process of multi-atlas segmentation method of the left ventricle (LV) and right ventricle (RV) blood pools for the SPECT cardiac images.

Figure 2.
The original contrast CT images from 8 different dogs prior to registration. (a) is the target image. (b)–(h) are atlas images.

Figure 3.
The contrast CT images after registration. (a) is the target image. (b)–(h) are registration results respectively.

Figure 4.

The segmentation results of the target contrast CT image. The first row shows manual segmentation. The second row shows multi-atlas based segmentation with the MV method. The third row shows multi-atlas based segmentation with the CV method. The fourth row shows the multi-atlas based segmentation with the CV method overlaid on the original contrast CT image. The insets in the second and third row are zoomed to a region consisting of myocardium, blood pool, liver and background, to highlight the improvement of CV in gap elimination.

Figure 5. SPECT images without and with PVC using different segmentation approaches in three views. From top to bottom: (1) original SPECT image without PVC, (2) PVC with manual segmentation, (3) PVC with multi-atlas segmentation, (4) PVC with multi-atlas segmentation overlaid on the contrast CT. The yellow arrow denotes the septal wall of the myocardium.

Figure 6.

Scatter plot of IMBV using PVC with atlas-based segmentation method against manual segmentation method. Dog 3 was not included in this plot due to the abnormal anatomy.

Table 1

The percentages of gap voxels for eight dogs.

	Dog 1	Dog 2	Dog 3	Dog 4	Dog 5	Dog 6	Dog 7	Dog 8
Gap (%)	1.21	4.51	7.52	2.61	3.43	2.26	2.37	3.35

Table 2

Comparison of the accuracy in terms of Dice coefficients over segmentations for each of the 8 dogs (8 leave-one-outs) with two different label fusion algorithms.

	Myocardium	Blood pool	Liver	Lung	Background
MV	0.759 ± 0.046	0.882 ± 0.048	0.725 ± 0.154	0.799 ± 0.049	0.894 ± 0.048
CV	0.786 ± 0.035	0.888 ± 0.041	0.918 ± 0.040	0.897 ± 0.021	0.939 ± 0.023
<i>p</i> -value	0.2196	0.7893	0.0042 ^a	0.0001 ^a	0.0340 ^a

^a *p* < 0.05.

Table 3
Intra-myocardial blood volume (IMBV) obtained with manual segmentation and atlas-based segmentation.

	Dog 1	Dog 2	Dog 3	Dog 4	Dog 5	Dog 6	Dog 7	Dog 8
Manual Segmentation	0.138	0.152	0.144	0.152	0.177	0.168	0.207	0.122
Atlas-based segmentation	0.146	0.168	0.221	0.149	0.194	0.135	0.211	0.103
% change	5.8%	10.5%	53.4%	-2.0%	9.6%	-19.6%	1.9%	-15.6%