Semi-automated Segmentation and Registration of Triggered Three-Dimensional Echocardiographic Images as a Basis for Volumetric Analysis of Myocardial Perfusion

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Abstract

We developed a technique for automated identification of 3D myocardial ROI suitable for translation-free quantification of myocardial videointensity over time, MVI(t), from RT3DE images. Our software was tested on 12 ECG-triggered RT3DE datasets obtained in pigs during transient contrast inflow. Analysis included: (1) semi-automated detection of endo- and epicardial surfaces using level-set techniques to define a 3D myocardial ROI, (2) rigid 3D registration to reduce translation and rotation, (3) elastic 3D registration to compensate for deformation, and (4) quantification of MVI(t) with and without registration to assess its effectiveness. Analysis of myocardial contrast throughout contrast inflow was feasible in all datasets. 3D registration improved MVI(t) curves in terms of both % variability during steady-state enhancement: 2.8±1.8% to 1.5±0.9%, and goodness of fit to the indicator dilution equation MVI(t)=A•(1-exp(-βt)): r^2 from 0.79±0.2 to 0.90±0.1. This is the first study to describe a new technique for semi-automated volumetric quantification of myocardial contrast from RT3DE images that includes registration and thus provides the basis for 3D measurement of myocardial perfusion.

1. Introduction

Despite the potential of contrast-enhanced real-time three-dimensional echocardiography (RT3DE) to assess myocardial perfusion more accurately than 2D imaging, there are no tools for quantitative 3D analysis of perfusion [1]. One of the major difficulties in designing such volumetric analysis tools is that they require the ability to define 3D regions of interest (ROI), in which myocardial videointensity would be measured over time (MVI(t)) during dynamic changes in myocardial contrast. Moreover, even after 3D ROIs are defined, they need to be adjusted frame-by-frame to compensate for cardiac translation and deformation, adding another layer of complexity to the problem. Such adjustments are crucial, since ROIs fixed in space are unlikely to maintain a fixed anatomical position, even when images are acquired at the same phase of the cardiac cycle. Thus, spatially fixed ROIs inevitably result in noisy MVI(t) curves, which limit the reproducibility of quantitative perfusion analysis.

We have recently described a technique for translation-free perfusion analysis from 2D contrast-enhanced images based on frame-by-frame automated detection of LV endocardial boundary, which eliminated the need for manual tracing and frame-by-frame tracking of myocardial ROIs [2]. We hypothesized that a similar approach could be used for frame-by-frame semi-automated definition of 3D ROIs, which in combination with 3D image registration would allow translation-free volumetric analysis of myocardial contrast over time.

Our goal was to develop such volumetric analysis technique and test its applicability to RT3DE images. We used the 3D level-set techniques for detection of the endo- and epicardial boundaries and optical flow analysis for frame-by-frame image registration of the detected myocardium. This technique was tested on contrast-enhanced RT3DE datasets obtained in pigs by measuring MVI(t) during transient contrast inflow [1]. This approach allowed us to study the effects of registration on the stability of myocardial contrast during steady-state enhancement and on the goodness of fit of the transition phase to the indicator dilution equation commonly used to model myocardial contrast replenishment. These two parameters are essential for the ability to obtain low noise MVI(t) curves, a prerequisite for reliable volumetric analysis of myocardial perfusion.

2. Methods

2.1. Animal preparation

Experiments were performed in 5 pigs (20-28kg). Animals were pre-treated with telazol (2.2mg/kg, IM) and atropine sulfate (0.05mg/kg, IM). Following intubation, pigs were mechanically ventilated and anesthetized with isoflurane (0.5-2.5% mixed with oxygen). Electrocardiogram, blood pressure and expiratory gases were monitored (Datex, Cardiocap).

2.2. Ultrasound imaging

RT3DE imaging was performed using a SONOS 7500 system (Philips) equipped with a matrix-array transducer (X4) in the harmonic mode. The spatial aperture was set to be the widest available (58°×29°) for triggered acquisition of series of end-systolic pyramidal datasets. Imaging was performed from the left parasternal approach, resulting in volumetric short-axis datasets containing the mid portion of the left ventricle (figure 1A). Contrast enhancement was achieved by intravenous infusion of Definity (1.3ml in 25ml saline at 150-260ml/hr). To minimize bubble destruction, the minimal mechanical index necessary to visualize myocardial contrast was used (0.4 to 0.8).

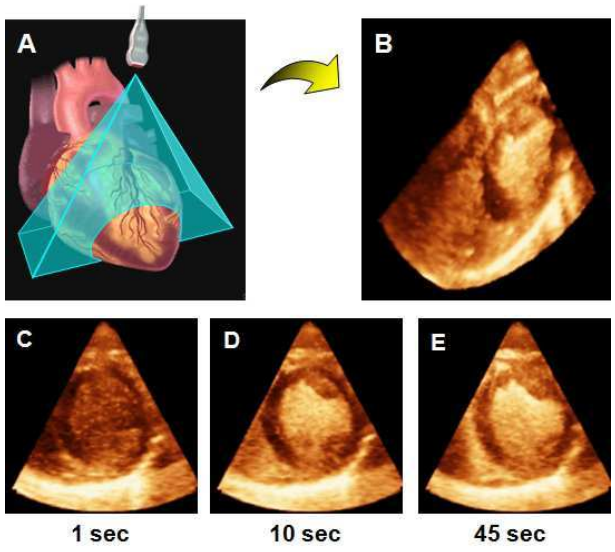

Figure 1. Schematic representation of volumetric parasternal short-axis imaging of the heart (A). Actual RT3DE dataset that contains the mid portion of the left ventricle (B) shown with en-face short-axis views of a mid-papillary 3D slice obtained before the onset of myocardial contrast inflow (C), during (D) and after (E) reinstatement of steady-state enhancement.

Figure 2 shows a schematic representation of the TCI maneuver, which included: (1) optimization of contrast infusion rate and imaging settings during steady-state enhancement; (2) infusion interruption to allow contrast clearance, which was expedited by continuous 2D imaging at high mechanical index; (3) resumption of contrast infusion, resulting in contrast inflow. Image acquisition started approximately 5sec prior to the resumption of infusion to capture the entire transition from non-contrast to reinstated steady-state enhancement. Images were saved digitally for off-line analysis.

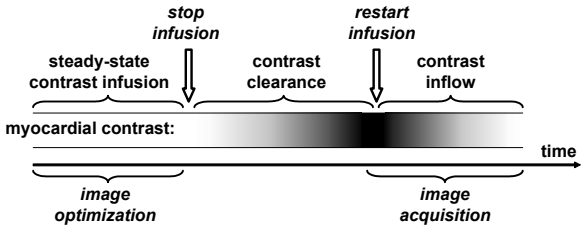

Figure 2. Schematic representation of the transient contrast inflow sequence. The lower portion of the diagram shows the time line of imaging steps that comprise the sequence. The upper portion shows the timing of infusion interruption and resumption (arrows) and their effects on the myocardial contrast with the level of enhancement shown above the time axis.

2.3. Image analysis

Images were analyzed using custom software implemented in Matlab. Initially, semi-automated endocardial surface detection based on the level set approach [3], was performed on a fully contrast-enhanced reference frame selected from the steady state phase. This technique uses an implicit representation of an evolving curve as partial differential equation to identify boundaries, without geometrical assumptions or a priori shape knowledge. The resulting equation of the motion for the level set function is shown in equation:

$$\frac{\partial \varphi}{\partial t} = g\varepsilon K|\nabla\varphi| + \nu\nabla g \cdot \nabla\varphi$$

with the initial condition $\varphi(\mathbf{x},0) = \varphi_0$ and where $\varphi(\mathbf{x},t)$ is the level set function, the first term on the right hand is a curve tension force that depends on the Euclidean curvature K and the second term is a force that attracts the curve towards the boundaries and thus has a stabilizing effect. The edge indicator g is a non-increasing function of the gradient of a smoothed version of the initial image. The parameter ν is used to limit the regularization of the embedding controlled by the parameter ε.

To manually define $\varphi(\mathbf{x},0)=\varphi_0$, four LV short-axis planes were selected from the 3D dataset, and 8 to 12 endocardial boundary points were manually initialized in each plane. The selected points were connected to define a set of polygons. For each polygon, a signed distance function was calculated [4], and a rough surface corresponding to the endocardium was computed using linear interpolation of the signed distance functions. This surface was then used as the initial condition for the level-set partial differential equation, which guided surface evolution within the volumetric dataset towards the endocardium under the constraints of the two terms. When the two forces balance each other, the evolution reaches a steady state and the resultant surface represents the endocardium. This procedure was repeated to detect the LV epicardial surface, and the volume confined between the two surfaces was used as the myocardial ROI.

3D registration included two consecutive steps. First, rigid transformation was performed by shifting and rotating each frame throughout the image sequence for optimal match between the position and spatial orientation of the left ventricle in the current and the reference frames. Matching was achieved by maximizing weighted cross correlation of the pyramidal datasets representing these two frames, while excluding the LV cavity from analysis in order for the changes in contrast intensity not to affect the registration. The goal of this step was to compensate for translation and rotation of the heart relative to the reference frame that predominantly occurs because of respiratory motion. After the dataset was shifted and rotated, it was subjected to an elastic transformation. First, using an algorithm based on optical flow techniques [5], displacement field representing point-wise motion between the two images was computed. Then using this field, the current frame was warped by forcing the endo- and epicardial LV boundaries into their position in the reference frame.

Once the myocardial ROI was defined and 3D registration completed, mean MVI was calculated by averaging pixel intensity in each consecutive frame throughout the sequence to generate MVI(t) curves. This procedure was also performed with the original non-registered image sequence to assess the effects of registration on MVI(t) curves. For each curve, we assumed that myocardial contrast inflow followed the indicator dilution equation:

$$MVI(t)=A\left[1-e^{-\beta t}\right]+C,$$

where C is the initial MVI before contrast inflow, A - maximum contrast-induced increase in MVI, and β - characteristic constant related to tissue blood flow. For both registered and non-registered MVI(t) curves, nonlinear fitting to the indicator dilution equation was performed and the goodness of fit was estimated in terms of r^2. In addition, the post-replenishment steady-state portion of the curve was used to estimate signal variability (in % of its mean value) as 100•SD/mean, with and without registration.

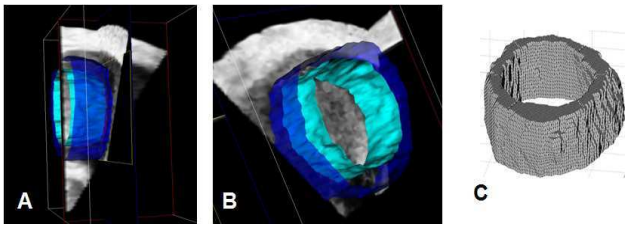

Figure 3. Example of the detected LV endocardial (cyan) and epicardial (blue) surfaces shown in two different orientations (A and B) superimposed on the original RT3DE dataset. The automatically defined myocardial ROI is shown in panel C.

3. Results

Twelve pyramidal datasets were analyzed. Figure 1 shows an example of a dataset that contains the mid portion of the left ventricle (B) and en-face short-axis views of a mid-papillary 3D slice obtained at different phases of the TCI sequence (C-E). Semi-automated detection of LV endo- and epicardial surfaces (figure 3,A-B) was feasible in all datasets and resulted in identification of the myocardial region of interest (figure 3,C) in every one of the 12 datasets. Analysis of one dataset required approximately 10 minutes, including initialization of the endo- and epicardial boundaries in multiple planes, calculation of the 3D endo- and epicardial surfaces and surface adjustments when necessary, and calculation of MVI(t) throughout the TCI image.

The 3D registration required additional time, which ranged between 15 and 25 minutes depending on the number of heart beats included in the TCI image sequence (up to 50 frames). Figure 4 shows the resultant MVI(t) curves obtained from the same dataset with and without 3D registration, which demonstrate the marked decrease in the level of noise during the phase of post-replenishment steady-state contrast enhancement noted with the registration. In the 12 datasets we studied, the use of our 3D registration technique resulted in decreased MVI(t) signal variability (2.8±1.8% to 1.5±0.9%; $p<0.05$) and in increased goodness of fit to the indicator dilution inflow model (r^2 from 0.79±0.2 to 0.90±0.1; $p<0.05$). Importantly, improvement in both parameters was statistically significant, thus proving the effectiveness of the 3D registration algorithm.

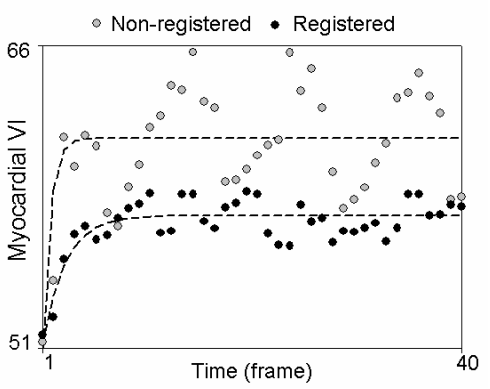

Figure 4. Example of myocardial videointensity over time, MVI(t), curves measured during transient contrast inflow in one animal.

4. Discussion and conclusions

We developed and tested a 3D technique for translation-free quantification of myocardial contrast over time, which is essential for volumetric quantification of myocardial perfusion. The most challenging part of our technique, namely 3D registration, was implemented in two consecutive steps: the rigid registration that addressed the problem of translation and rotation, followed by the elastic registration that modified the shape of the ventricle to resemble the reference frame when necessary. Once the myocardium was forced into its reference position, the 3D myocardial ROI detected in the reference frame was essentially fixed, allowing the generation of translation-free MVI(t) curves throughout the image sequence.

To test the effectiveness of this approach as a potential solution for motion artifacts in 3D space, we compared MVI(t) curves obtained from the same RT3DE datasets with and without registration and calculated for each curve two parameters that are key for robust volumetric quantification of myocardial perfusion: (1) goodness of fit of the MVI(t) curve to the indicator dilution contrast replenishment model, and (2) the noise level in the steady-state post-replenishment portion of the MVI(t) curve, which reflects the quality of information on blood flow dynamics and is crucial for its reliable analysis [6]. Importantly, both parameters were significantly improved by registration, proving the effectiveness of this approach and supporting its applicability to series of ECG-triggered contrast-enhanced RT3DE images obtained during transient contrast inflow, despite the frame-by-frame changes in both contrast characteristics and LV shape.

One limitation of this technique is the subjective choice of a reference frame, which affects the registration process and may thus affect the measured MVI(t) curves. In our experience, selecting a reference frame during the post-replenishment steady-state enhancement period provided more stable curves than those obtained when using a non-enhanced reference frame at the beginning of the image sequence. This is likely due to the fact that endocardial blood-tissue interface is better visualized with contrast enhancement.

In summary, this is the first study to develop and test a new semi-automated technique that allows true 3D quantification of myocardial contrast including effective registration of contrast-enhanced RT3DE images, and thus provides the basis for accurate volumetric quantification of myocardial perfusion. This methodology or its further refined derivatives may prove as a valuable addition to the noninvasive diagnostic cardiac imaging arsenal and become part of the routine cardiology practice.

References

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