Three-dimensional myocardial strain estimation from volumetric ultrasound: experimental validation in an animal model

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***Abstract*—Although real-time three-dimensional echocardiography has the potential to allow for more accurate assessment of global and regional ventricular dynamics compared to the more traditional two-dimensional ultrasound examinations, it still requires rigorous testing and validation against other accepted techniques should it breakthrough as a standard examination in routine clinical practice. Very few studies have looked at a validation of regional functional indices in an in-vivo context. The aim of the present study therefore was to validate a previously proposed 3D strain estimation-method based on elastic registration of subsequent volumes on a segmental level in an animal model. Volumetric images were acquired with a GE Vivid7 ultrasound system in five open-chest sheep instrumented with ultrasonic microcrystals. Radial (ϵ_{RR}), longitudinal (ϵ_{LL}) and circumferential strain (ϵ_{CC}) were estimated during four stages: at rest, during esmolol and dobutamine infusion, and during acute ischemia. Moderate correlations for ϵ_{LL} (r=0.63; p$<$0.01) and ϵ_{CC} (r=0.60; p=0.01) were obtained, whereas no significant radial correlation was found. These findings are comparable to the performance of the current state-of-the-art commercial 3D speckle tracking methods.**

***Index Terms*—Elastic registration, sonomicrometry, cardiac strain assessment, in-vivo setup**

I. Introduction

Although real-time three-dimensional echocardiography (RT3DE) has been available for several years, ongoing advances in both transducer hardware and ultrasound computer software have only recently resulted in a growing research interest, not only within academic circles but also commercially, as many major ultrasound systems currently offer RT3DE solutions as a diagnostic tool for routine medical practice. RT3DE is a promising technique as it has the potential to allow for a faster and more accurate assessment of global and regional ventricular dynamics. As many cardiac pathologies such as coronary heart disease result in regional myocardial dysfunction, investigation of local wall motion and deformation has gained considerable attention over the past decade. Various methods have been developed for this purpose, all differing primarily in their underlying tracking algorithms.

One approach consists in using segmentation techniques to track myocardial borders in time [1]. However, motion is typically obtained only at the borders and estimation of intramural velocity gradients is thus challenging. A second, more popular approach is the use of optical flow methods. In the ultrasound society these are traditionally subdivided into either phase-based techniques applied on the radio-frequency data using correlation, time- or phase-shift techniques to estimate motion [2]; and block-matching techniques on B-mode data [3][4]. A third approach is to use image registration techniques where the cardiac deformation field is parametrized using smooth basis functions [5][6][7].

Our lab has previously presented such a 3D strain estimation method (3DSE-method) based on elastic registration of subsequent volumes [6]. This method was shown to be reliable in extracting *global* LV functional parameters in simulated datasets and in a clinical setting [6]. Very recently, the performance of this approach was tested in tissue mimicking phantoms on a *regional* level [7]. The aim of the present study was to further validate the methodology in an animal model by comparing the estimated strain values with the ones obtained from sonomicrometry.

II. Methods

A. Animal preparation

After approval of the study protocol by the local ethics committee, five Suffolk sheep (39 ± 5 kg) were premedicated with an intragluteal injection of ketamine (10 mg/kg) and piritramide (1 mg/kg). They were placed in a dorsal recumbancy on a surgical table and anesthesia was induced via the cephalic vein with an intravenous infusion of propofol (10 mg/kg) and a bolus of sufentanil (0,5 μg/kg). The trachea was intubated and the sheep were mechanically ventilated throughout the procedure with a mixture of sevoflurane, oxygen and room air to maintain normocapnia and normoxia (tidal volume of 8 ml/kg and respiratory rate of 12 times/minute). A gastric tube was positioned to evacuate excess gas and fluids from the reticulorumen. Anesthesia was maintained by a continuous

infusion of sufentanil (1 μg/kg/h) and an end-tidal sevoflurane concentration of 2.5%.

A bi-lumen catheter was inserted into the left jugular vein to allow measurement of the central venous pressure and administration of drugs. Furthermore, a catheter-tipped pressure transducer (Millar, Houston, Texas, USA) was advanced into the left ventricle (LV) via the right carotid artery for continuous monitoring of the left ventricular pressure and its first temporal derivative (dP/dt). The systemic arterial pressure was measured in the proximal aorta via a fluid-filled side-line of the arterial sheet.

Ten minutes before surgical incision, a bolus of cisatracurium (20 mg) was administered. A sternotomy was then performed, and the heart was suspended in a pericardial cradle to maintain a normal anatomic configuration. Cardiac output was monitored with a flow probe positioned around the pulmonary artery.

In order to have an independent measure of the ventricular wall deformation throughout the cardiac cycle, a Sonometrics Digital Ultrasonic Measurement System (Sonometrics Corporation, London, Ontario, Canada) was used. Reference radial (ϵ_{RR}), longitudinal (ϵ_{LL}) and circumferential (ϵ_{CC}) strain components were obtained using four ultrasonic microcrystals attached in a tetrahedral configuration to the myocardium in the mid-inferolateral (IL) wall (figure 1, panel a). Three crystals were sutured to the epicardium, resulting in two crystal pairs along the circumferential and longitudinal direction, while a fourth crystal was placed subendocardially just radially to the center crystal. The latter was introduced in an oblique way to limit damage to the myocardium under investigation.

B. Data acquisition

A GE Vivid7 ultrasound scanner (GE Vingmed, Horten, Norway) equipped with a 2D matrix transducer (3V probe) was used to acquire volumetric data at a frame rate of 25-32Hz with ECG gating over four cardiac cycles. The left ventricle was scanned from an apical position using a liver as a stand-off. The optimal combination of spatial and temporal resolution was achieved by decreasing the volume size and depth to the smallest setting possible, while keeping the whole LV within the field of view.

After image data collection at rest, the range of strain values was further moderated by reducing the inotropic state by esmolol infusion and subsequently increasing it by dobutamine administration. A physiological target was set to a 50% reduction in dP/dt and a 100% increase in dP/dt relative to baseline for esmolol and dobutamine respectively. Infusion rates were titrated continuously according to this target. In the final stage, acute ischemia was induced by ligating a distal branch of the circumflex coronary artery. Ischemia measurements could not be completed in two animals and esmolol data was lacking in another. Overall, 17 datasets could thus be included for further analysis.

Due to the overlapping frequency bands of the microcrystals and the ultrasound system, both systems could not be operated simultaneously. Therefore, crystal data were acquired immediately before and after each stage, and the system was switched off during ultrasound recordings.

C. Data analysis

All data sets were processed using a previously presented elastic registration approach developed in our lab [6][7]. In this method, inter-frame myocardial displacement is modeled with a three-dimensional third-order B-spline tensor-product. For every pair of images, the optimal displacement field was estimated iteratively using a limited memory Broyden Fletcher Goldfarb Shannon optimization routine with simple bounds while using mutual information to express image similarity between the image pairs. In order to capture small deformations, model complexity was gradually increased in four stages by halving the B-spline grid size in each direction in every stage. The full resolution data set was used in every refinement stage. Regularization was performed during the optimization process by the addition of a bending energy penalty and a volume conservation penalty term in the cost function, yielding a spatially smooth displacement field. All images in the cardiac cycle were then registered to each other in a pair-wise fashion starting from end-diastole (ED).

In order to assess strain, the endo- and epicardial borders were first manually contoured at (ED) using custom-made software (Speqle3D) to indicate the region-of-interest (ROI) for strain estimation. The same software was used for least-square surface fitting using a fifth order spherical harmonic expansion. Subsequently, the ROI was populated with a 3D myocardial mesh of 16000 points, consisting of 5 samples in the radial direction, 80 samples circumferentially, and 40 samples longitudinally from base-to-apex. In each point, the directions corresponding to the directions of a local cardiac coordinate system (radial, longitudinal and circumferential) were calculated, and given a label according to a standard 18-segment model. Finally, the generated mesh was propagated over the cardiac cycle using the recovered inter-frame transformation field.

According to continuum mechanics, strain $\epsilon_{\boldsymbol{N}}$ in every point along a certain direction, represented by its corresponding unit vector N, can be calculated using:

$$\epsilon_{\boldsymbol{N}} = \frac{\|\boldsymbol{dx}\| - \|\boldsymbol{dX}\|}{\|\boldsymbol{dX}\|} = \sqrt{\boldsymbol{N}^T \cdot \boldsymbol{F}^T \cdot \boldsymbol{F} \cdot \boldsymbol{N}} - 1 \qquad (1)$$

where $\boldsymbol{dX}$ is an arbitrary material line segment which is deformed to $\boldsymbol{dx}$, and $\boldsymbol{F}$ is the Jacobian matrix of the transformation field. Since the transformation field is expressed as a tensor-product B-spline, the Jacobian matrix and thus the strain could be calculated analytically. The estimated strain curves were drift compensated to obtain values of zero strain at the end of the cardiac cycle. Finally, strain values were averaged within each segment. ES strain values extracted from the mid IL wall were used for further analysis.

In order to obtain reference strain curves, the recorded crystal traces were further post-processed in custom-made software. By using the speed-of-sound (1530 m/s) and the

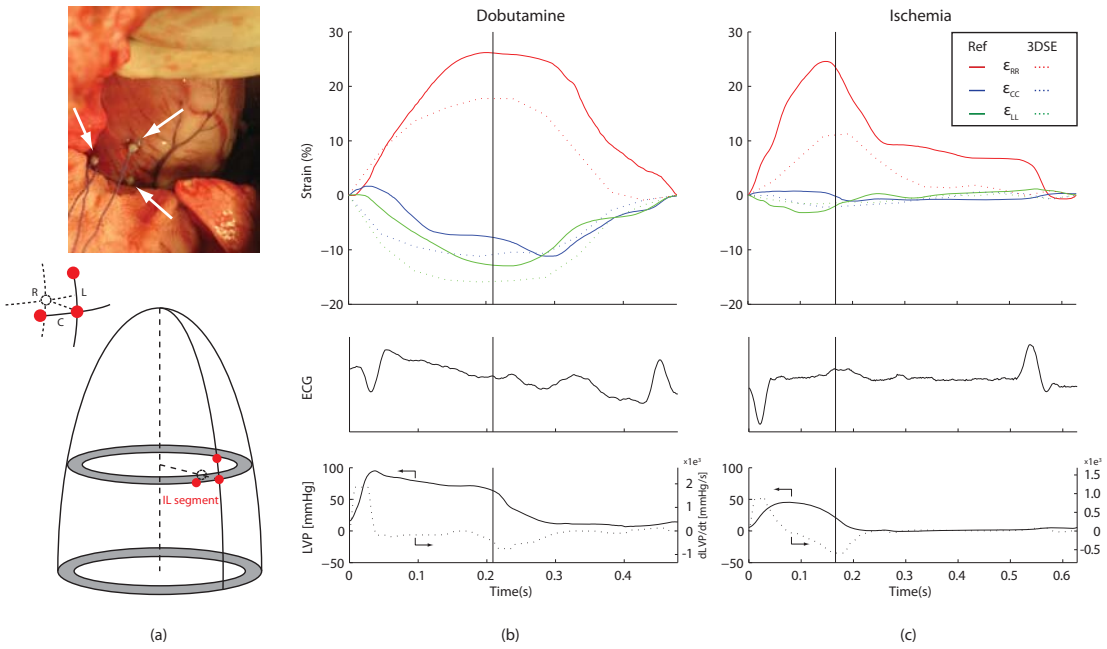

Fig. 1. (a) Sonomicrometry crystal locations to obtain ground-truth myocardial deformation. (b-c) Sample strain curves during dobutamine infusion (b) and acute ischemia (c). Aortic valve closure timing is indicated with a solid vertical line. LVP = left ventricular pressure, 3DSE = 3D strain estimation method.

time-of-flight between ultrasound emission and detection in a neighboring crystal, inter-crystal distance could be calculated continuously at a time resolution of 1 ms and with a spatial resolution of 15.4 μm. The following steps were performed successively for all channels: outliers were removed both automatically and manually, data was median-filtered, the ED of every consecutive cardiac cycle was identified based on the onset of the LV pressure and the reference displacements were averaged over different cycles. Strain was calculated based on:

$$\epsilon_N(t) = \frac{D_N(t) - D_N(0)}{D_N(0)} \tag{2}$$

where $D_N(t)$ is the distance between two adjacent sample points in either the radial or circumferential direction at time point t, and similarly $D_N(0)$ being the respective initial distances (at ED). End-systolic values were defined at the aortic valve closure, determined as $dP/dt_{min} - 20ms$ [8]. Finally, the reference ES strain value before and after each stage were averaged to account for any physiological change during the course of the procedure.

The 3DSE systolic strain values were correlated with the reference ES strain values obtained by sonomicrometry using the Pearson correlation coefficient. P-values lower or equal to 0.05 were considered significant.

III. Results

Example strain curves for the 3DSE-method and sonomicrometry are shown in figure 1 during dobutamine infusion (panel b) and during acute ischemia (panel c). The correlation coefficients between the estimated ES strain and the reference ES strain values was r=0.21 (p=0.42) for ϵ_{RR}, r=0.63 (p<0.01) for ϵ_{LL} and r=0.60 (p=0.01) for ϵ_{CC}.

IV. Discussion

Although RT3DE has the potential to allow for more accurate assessment of global and regional ventricular dynamics, it still requires rigorous testing and validation against other accepted techniques should it breakthrough as a standard examination in routine clinical practice. The superiority of RT3DE over previously used 2D techniques in terms of assessing *global* myocardial function, has already been shown [9]. In contrast, very few studies have looked at a validation of *regional* functional indices in an in-vivo context. The aim of the present study therefore was to validate our previously proposed 3DSE-method on a segmental level in an animal model. To the best of our knowledge, this is the first paper to investigate the performance of a *registration-based* method with a known ground-truth.

We obtained moderate correlations for ϵ_{LL} (r=0.63) and ϵ_{CC} (r=0.60) using our elastic registration approach. On the other hand, radial correlation was poor and non-significant (r=0.21; p=0.42). Mean errors were 11.5%, -2.9% and -5.0% for ϵ_{RR}, ϵ_{LL} and ϵ_{CC} respectively. These observations are consistent with a previous clinical study in which we compared the 3D segmental strain estimates against those obtained with 2D techniques (r=0.63 for ϵ_{LL}, r=0.41 for ϵ_{CC} and no significant correlation for ϵ_{RR})[10]. Myronenko et al. developed a comparable registration method, but they only reported sonomicrometry correlations for global twist and results for strain measurements were lumped for all directions [5].

These findings are also in line with the performance of the current state-of-the-art commercial 3D speckle tracking methods, which typically rely on *block-matching* based algorithms. Regional validation studies are scarcely reported. Seo et al. present regional correlations of r=0.59-0.70 for ϵ_{RR}, r=0.65-

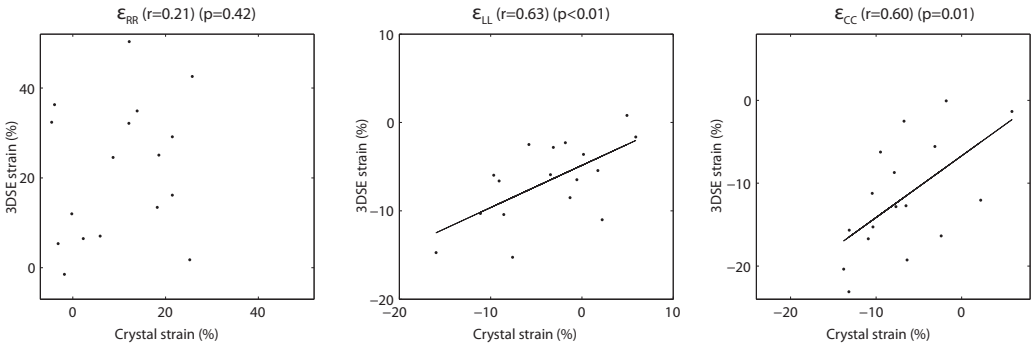

Fig. 2. Estimated ES strain by the 3DSE-method against reference ES strain in the (a) radial, (b) longitudinal and (c) circumferential direction.

0.68 for ϵ_{LL} and r=0.71-0.78 for ϵ_{CC} against microcrystals in an animal population of 10 sheep [4]. Clinically, 3D strain values have been compared to 2D techniques, e.g. by Maffessanti et al. who also found moderate segmental correlations of r=0.49 and r=0.43 for ϵ_{LL} and ϵ_{CC} respectively [11], whereas radial correlation was poor (r=0.24).

These studies all show that current 3D strain estimation approaches can estimate ϵ_{LL} and ϵ_{CC} with acceptable accuracy from volumetric ultrasound datasets, but determining ϵ_{RR} remains difficult. This suboptimal performance could be related to the fact that the spatial motion gradient has to be calculated over a relatively small region due to the limited wall thickness in combination with limited spatial resolution. Due to the orientation of the LV in the image volume, beam density and consecutively spatial resolution in the radial direction is lower then the longitudinal direction. It is also worth mentioning that until the present day, ϵ_{RR} strain estimation has been more difficult and prone to errors even with 2D strain estimation techniques [12]. Currently, the radial component may thus better be estimated from the other two components through conservation of volume.

Whether 3D elastic registration performs better then 3D block-matching based methods remains to be proven. Moreover, as 3D ultrasound typically comes at the expense of temporal resolution with associated de-correlation between subsequent volumes, elastic registration may be more robust.

V. Conclusion

In this study, we demonstrated that ϵ_{LL} and ϵ_{CC} could be estimated with acceptable accuracy from volumetric ultrasound datasets in an animal model. However, estimates of ϵ_{RR} require further improvement. These findings are comparable to the performance of the current state-of-the-art commercial 3D speckle tracking methods.

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