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Left Ventricular Ejection Fraction Assessment: Unraveling the Bias between Area- and Volume-based Estimates

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Abstract:

Calculating left ventricular ejection fraction (LVEF) accurately is crucial for the clinical diagnosis of cardiac disease, patient management, or other therapeutic treatment decisions. The measure of a patient's LVEF often affects their candidacy for cardiovascular intervention. Ultrasound (US) is one of the imaging modalities used to non-invasively assess LVEF, and it is the most common and least expensive. Despite the advances in 3D US transducer technology, only limited US machines are equipped with such transducer to enable true 3D US image acquisition. Thus, 2D US images remain to be widely used by cardiologists to image the heart and their interpretation is inherently based on two dimensional information immediately available in the US images. Past knowledge indicates that visual estimation of the LVEF based on the area changes of the left ventricle blood pool between systole and diastole (as depicted in 2D ultrasound images) may significantly underestimate the ejection fraction, rendering some patients as suitable candidates for potentially unnecessary interventions or implantation of assistive devices. True LVEF should be calculated based on changes in LV volumes, but equipment and time constraint limit the current technique to assess 3D LV geometry. The estimation of the systolic and diastolic blood pool volumes requires additional work beyond a simple visual assessment of the blood pool area changed in the 2D US images. Specifically, following the manual segmentation of the endocardial LV border, 3D volume would be assessed by reconstructing a LV volume from multiple tomographic views. In this work, we leverage on two idealized mathematical models of the left ventricle — a truncated prolate spheroid (TPS) and a paraboloid geometric model to characterize the LV shape according to the range of possible dimensions gathered from our patient-specific multi-plane US imaging data. The objective of this work is to reveal the necessity of calculating LVEFs based on volumes by showing that LVEF estimated using area changes underestimate the LVEF computed using volume changes. Additionally, we present a method to reconstruct the LV volume from 2D blood pool representations identified in the multi-plane 2D US images and use the reconstructed 3D volume throughout the cardiac cycle to estimate the LVEF. Our preliminary results show that the area-based LVEF significantly underestimates the true volume-based LVEF across both the theoretical simulations using idealized geometric models of the LV shape, as well as the patient-specific US imaging data. Specifically, both the TPS and paraboloid model showed an area-based LVEF of $41.3 \pm 4.7\%$ and a volume-based LVEF of $55.4 \pm 5.7\%$, while the US image data showed an area-based LVEF of $34.7 \pm 11.9\%$ and a volume-based LVEF of $48.0 \pm 14.0\%$. In summary, the area-based LVEF estimations using both the idealized TPS and paraboloid models was 14.1% lower than volume-based LVEF calculations using corresponding models. Furthermore, the area-based LVEF based on reconstructed LV volumes are 13.3% lower than volume-based estimates. Evidently, there is a need to further investigate a method to enable practical volume-based LVEF calculations to avoid the need for clinicians to estimate LVEF based on visual, holistic assessment of the blood pool area changes that improperly infer volumetric blood pool changes.

Keywords: ultrasound image analysis; echocardiography; 3D reconstruction; left ventricular ejection fraction

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1. INTRODUCTION AND OBJECTIVES

Despite its simplicity in calculation, LVEF is an essential indicator of cardiac function and serves as a critical biomarker for cardiac diseases. Thus, LVEF is considered one of the most vital measures in the field of cardiology. Other than being an indicator of cardiac health in clinical examinations of patients, LVEF is also a criterion used to determine patient eligibility for various therapeutic management strategies in many hospital systems or participation in various research and clinical trials.

LVEF is defined as the ratio between the stroke volume (i.e. the difference between the left ventricular volumes at end-diastole $V_{diastole}$ and end-systole $V_{systole}$) and the end-diastolic volume as illustrated by the equation below:

$$LVEF = \frac{V_{diastole} - V_{systole}}{V_{diastole}} = \frac{StrokeVolume}{V_{diastole}} \tag{1}$$

In practice, however, cardiologists most often use 2D US imaging to visually estimate ejection fraction based on change in areas of the LV blood pool between end-diastole and end-systole rather than change in volumes. Square-Cube Law explains that the ratio of two volumes will always be greater than the ratio of their surfaces. Consequently, the law infers that an object's change of volume in three-dimensional space is always greater than that of area in two-dimensional space. Therefore, visual assessment of LVEF based on area changes is suspected to produce lower LVEFs than the true volumetric assessments.

Our clinical collaborator's preliminary analysis suggested that the LVEF estimates based on area changes are approximately 16.7% lower than the LVEF estimates based on volume changes using a database of 68 patients. Furthermore, the comparison exposed that there is a bias for the visually estimated LVEF towards the lower values in general. Understandably, the echo-cardiologists tend to aim for safety and, if in doubt, would rather underestimate than overestimate the LVEF, so that patients may be eligible for additional follow-up or potentially implantable assistive devices or other therapies to prevent cardiac malfunction.

Another statistical characteristic of the visually estimated LVEFs is binning. The reported LVEFs based on visual estimations appeared discrete and were typically reported in increments of 5%. Since visual estimation is a rough method to determine LVEF, it is difficult for echo-cardiologists to estimate LVEF in finer increments. Such characteristic is detrimental though. For a healthy person, the LVEF should exceed 55%, while a LVEF below 35% is considered reduced contraction efficiency[1] . Such thresholds are not universal as they vary on a case by case basis. Therefore, when the visual estimations of LVEF are only reported in increments of 5%, estimated LVEF values around the 55% or 35% thresholds will lead to incorrect diagnosis. Due to the lack of precision, the LVEF could fall on either side of these threshold, hence rendering a patient's heart function either normal or abnormal, simply due to the inherent variability of the visually estimated LVEFs. Consequently, people without cardiac disease may be diagnosed with reduced LVEF and vice versa.

Diagnosis of cardiac disease then leads to therapeutic decisions, some of which, such as implantable cardiac defibrillators (ICD), are associated with an initial operation cost between $30,000 to $50,000, and a follow-up treatment on the order of $5,000 to $17,000.[2] In addition to the significant healthcare cost, the patients life changes inevitably. As such, the premise of this work is two-fold: 1) demonstrate, using both mathematical models of the LV geometry, as well as patient-specific data, that 2D area-based LVEF measurements significantly underestimate 3D volume-based measurements and 2) propose a method to reconstruct the 3D LV blood pool in systole and diastole from 2D multi-plane images and assess it against a current method used in the clinic.

2. METHODOLOGY

2.1 LVEFs of Geometric Models

We first used mathematical models of the idealized LV geometry to study the effect of area vs. volume estimates on LVEF. Other researchers proposed several mathematical approximations of the LV geometry: cylindrical[3] , truncated prolate spheroid (TPS)[4] , and paraboloid[5] models were published in prior literature. Of these, the TPS and paraboloid models matched the LV shapes from our US image dataset more closely, so they were used

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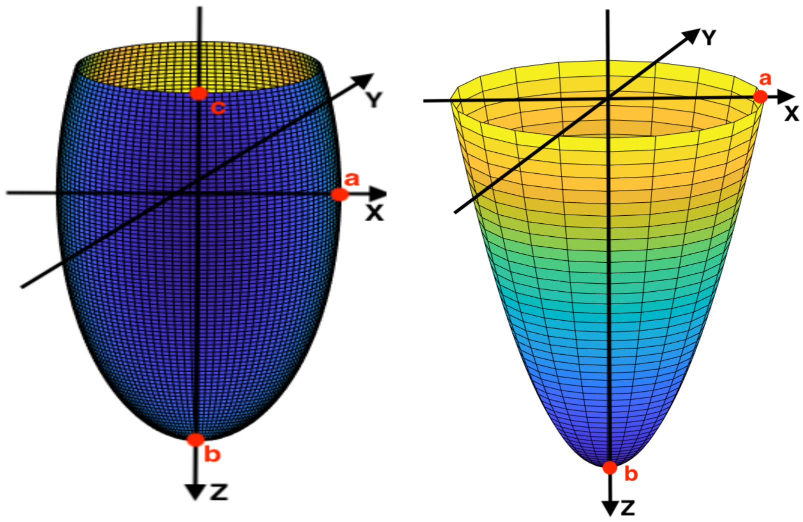
for geometric simulations to characterize and describe the left ventricle. Both models were parametrized based on the length and width of the LV in systole and diastole according to clinical knowledge about the heart size available from our US image dataset.



(a) TPS model of the LV described by three parameters, which measure the overall length, width at base and at the mitral valve region.

(b) A paraboloid model of the LV characterized by two parameters descriptive of the overall length and width at the base of LV.

Figure 1: Mathematical approximations of the LV geometry.

As illustrated by Figure 1a and 1b, the TPS model is characterized by three parameters and the paraboloid model is characterized by two. For the TPS model, parameter **a** defines the overall width of the LV, parameter **b** defines the distance between the widest section of the LV and the LV apex, and parameter **c** defines the distance between the widest section of the LV and the mitral valve. Similarly, the paraboloid model is characterized by the same two parameters **a** and **b** but not **c**. In this model, parameter **b** defines the distance between the mitral valve and apex. The truncated section of the TPS model leads to significantly different cross-sectional areas and internal volumes from those of the paraboloid for any given dimension. Using the information gathered from our image dataset, we ran simulations using both the TPS and paraboloid models to generate shapes that range from thin-elongated LVs to wide-short LVs in order to cover a variety of LV shapes. LVEFs were calculated based on the simulated LV areas and volumes consequently.

2.2 Echocardiography Data

Ultrasound images of 68 de-identified, retrospectively imaged patients were used for this study. The image dataset contains both male and female patients, some of which were previously diagnosed with cardiac disease. Each patient dataset consisted of three US image views: a two-chamber (2C) view, a three-chamber (3C) view and a four-chamber (4C) view, with the exception of several patients for whom the 3C view was replaced with a parasternal long axis (PLEX) view. In addition, each image is accompanied by a endocardial LV trace in both systole and diastole outlined by an experienced cardiologist, as well as several measurements provided by the software employed (GE's EchoPac PC) including the blood pool area enclosed in the traces and estimated volume (computed using the method of discs).

2.3 3D Volume Reconstruction from 2D Multi-plane US Images and LVEF Estimation

In the clinic, the software tool used by the clinicians estimates a LV blood pool volume using the "method of discs" from each of the three views in which the endocardial LV border was traced. In short, the method assumes that the left ventricle is axisymmetric about its long axis and approximates its volume by revolving each

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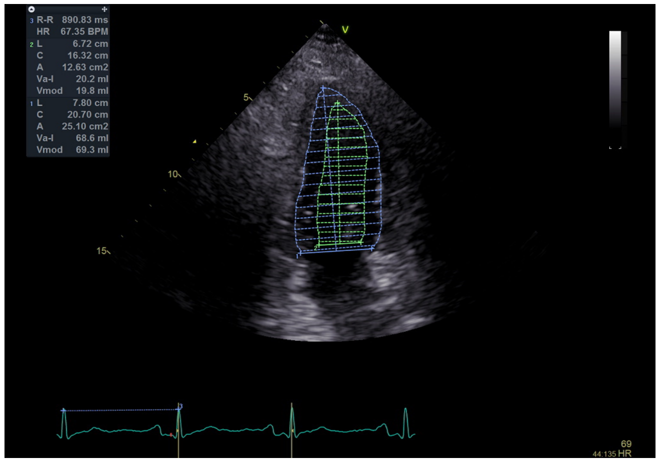

Figure 2: Example of a 2D US image of a patient depicting the LV. Endocardial traces in both systole and diastole outlined by the cardiologist are shown, along with several measurements.

endocardial trace about the normal line connecting the apex to the midpoint of the mitral valve line. Moreover, to account for the fact that the heart was depicted using three views positioned at more or less 60 degrees apart, the same axisymmetric volume is estimated from the other two views in both systole and diastole. Finally, a systolic and diastolic blood pool volume is estimated by averaging the three volumes approximated from each of the three axisymmetrically-assumed views.

As an alternative method, which does not make any assumption about the LV axisymmetry, we proposed a method that leverages the true geometry of the LV depicted by the three 2D multi-plane US images and their relative spatial location. As such, since each patient's heart was imaged in three tomographic views located 60° apart, a 3D LV volume was reconstructed by first co-locating the LV apex from all views, then aligning the apex to mitral valve base line from the three views along the vertical axis, and lastly using using spline interpolation to connect points on the endocardial trace of the LV blood pool from each of the three views at the same elevation from the LV apex. Alternatively, instead of the spline interpolation method, a convex hull fitting algorithm similar to that proposed by Dangi *et al.*[6] could be employed. Both approaches — the spline-based interpolation or convex hull fitting — yielded similar 3D blood pool volumes, with minimal differences in their estimated volumes.

Following the 3D blood pool volume reconstruction, we proceeded to estimate the LVEF using the area measurements from the three views in systole and diastole and compared the area- and volume-based LVEF to one another and to the ground truth LVEF estimates obtained using the GE EchoPac PC clinical software.

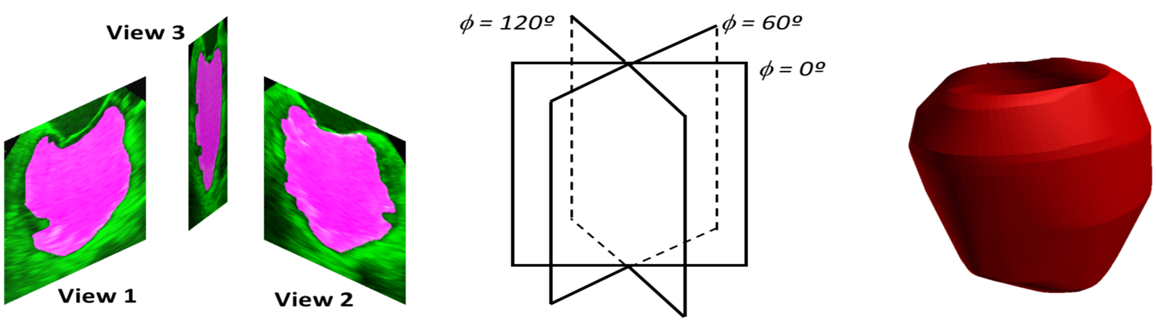

Figure 3: 3D reconstruction workflow: extract LV blood pools in three views; align apices and mitral valve bases; reconstruction by convex hull interpolation between three views.

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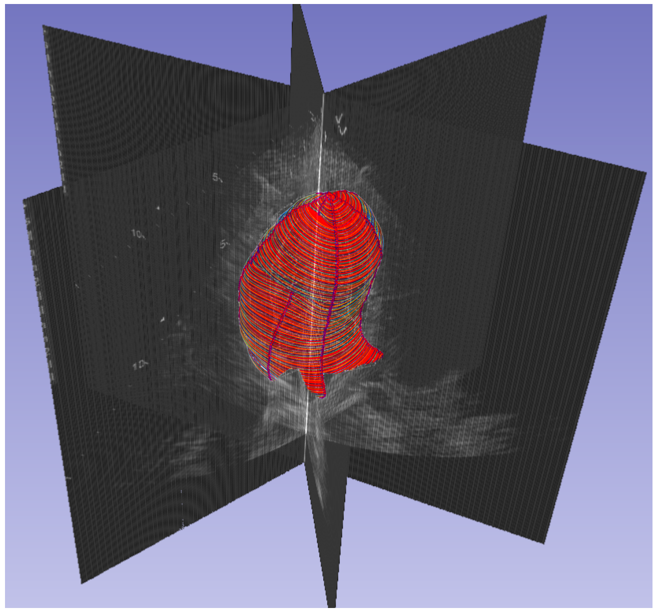

Figure 4: 3D Reconstruction of LV volume using convex hull model.

3. RESULTS

Firstly, we gathered a range of typical LV blood pool dimensions from an image database provided by our cardiology collaborator. The image database consisted of anonymous US images from 68 patients. As observed in the image dataset, diameters of LV blood pool range from 1 cm to 4 cm and the lengths range from 2 cm to 10 cm. For these varying heart sizes and shapes, LV cross-sectional areas and volumes in both systole and diastole, as well as the corresponding EFs, were calculated using both mathematical models. A comparison of the area- vs. volume-based estimates of the LVEF using both TPS and paraboloid models clearly reveal that the area-estimated LVEF is significantly lower than the volume-estimated LVEF by approximately 16% on average.

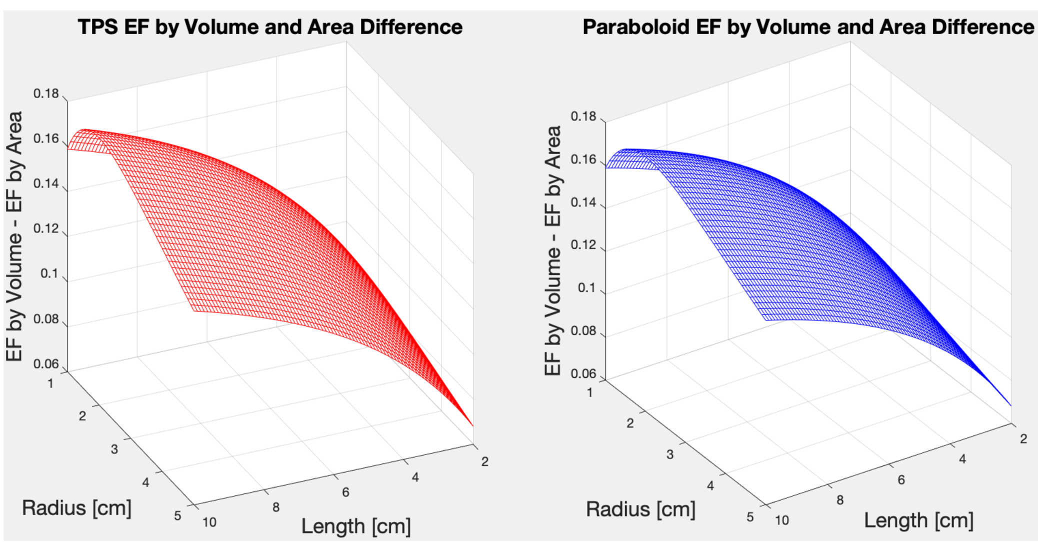

Figure 5: The difference of LVEFs calculated based on volume and area using TPS and parabolid models.

Plotting the difference of LVEF based on volume and area in Figure 5 illustrates that volume-based LVEFs are higher than area-based ones across the lengths and radius of the LVs we used to run the TPS and paraboloid

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model simulations. Further, the difference between volume-based and area-based LVEFs is higher for the thin-elongated LV shapes than for the wide-short LV shapes regardless of the model type. The difference peaks at a radius of approximately 2 cm and length of 10 cm for both TPS and paraboloid models. Performing Student's t test on the LVEF estimated by area and those calculated by volume side by side confirmed that the area-based LEVF estimated are significantly lower than the volume-based LVEF estimates ($p < 0.05$) for all analyzed data.

Table 1: Summary statistics of the LVEF-related quantities based on the TPS model, paraboloid model, 3D blood pool reconstructions from the multi-plane 2D US imaging data, and the clinical data analysized using GE's EchoPac PC clinical software.

Model	Mean±Standard Deviation					
	LVEF		Diastolic		Stroke	
	Area [%]	Volume [%]	Area [cm^2]	Volume [ml]	Area [cm^2]	Volume [ml]
Image Data	41.8 ± 12.7	58.7 ± 15.9	13.9 ± 4.1	67.4 ± 20.0	35.1 ± 9.7	126.8 ± 59.2
TPS	41.3 ± 4.7	55.4 ± 5.7	16.1 ± 2.3	99.5 ± 29.1	40.0 ± 10.1	186.9 ± 73.1
Paraboloid	41.3 ± 4.7	55.4 ± 5.7	17.3 ± 3.8	174.2 ± 35.4	42.67 ± 12.4	316.7 ± 89.0
Reconstruction	34.7 ± 11.9	48.0 ± 14.0	11.5 ± 4.0	62.4 ± 24.5	35.0 ± 10.0	143.1 ± 75.5

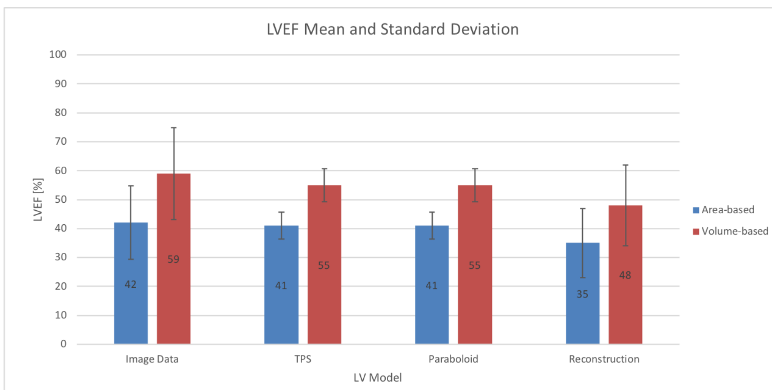

Figure 6: Comparison of the area- and volume-based LVEF estimated using the GE EchoPac PC clinical software, TPS model simulations, paraboloid model simulations, and our proposed 3D blood pool reconstruction method.

In addition, since the proposed 3D blood pool reconstruction volume has not previously been assessed, here we conducted a preliminary study to compare the area- and volume-based blood pool measurements in both systole and diastole, as well as the area- and volume-based LVEF between our proposed method and the clinically utilized EchoPac PC platform. As summarized in **Table 1** and also shown in **Fig. 6**, the blood pool area measurements are similar, the blood pool volume measurements are also similar, and moreover both methods clearly confirm that area-based LVEF calculations underestimate the true volume-based LVEF calculations. Even though the mean and standard deviation of LVEFs based on TPS and paraboloid models were the same, both quantities were produced from significantly different stroke and diastolic areas or volumes as shown in Table 1. Comparing the stroke and diastolic areas and volumes, TPS model matched more closely to our reconstruction results from image dataset. One plausible explanation, which also explains the limitations of using these idealized models to faithfully describe the LV geometry and shape, is their different geometries in the mid to apical range, for which the paraboloid model tends to underestimate the volume relative to the TPS model. Hence, the prolate spheroid model is considered to provide a more faithful approximation of the LV shape. Additionally, due to imperfect extraction of LV blood pools in our ultrasound images, the systolic areas and volumes were higher resulting in reduction in LVEFs. Accounting for the surface variations during volumetric reconstruction also contributes to the slightly lower difference in LVEF based on volume and area.

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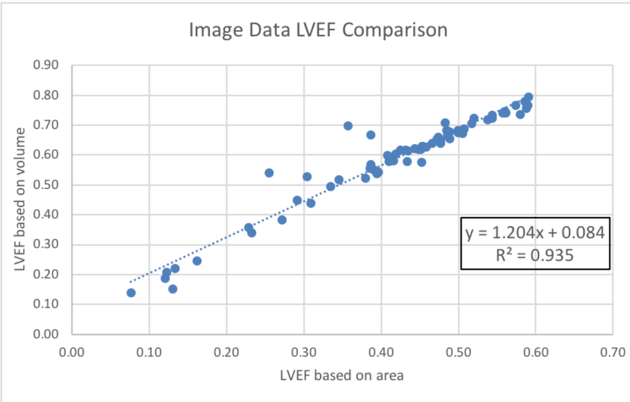
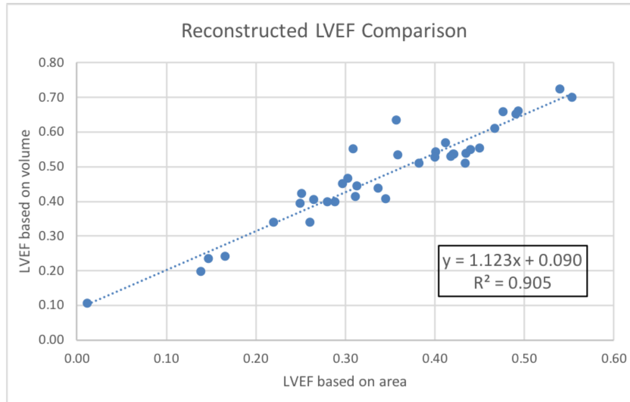
In **Fig. 7**, LVEFs based on volume are plotted against those based on area using both the original image data and our reconstruction method. Linear regression curves generated on both plots yield similar slope and y-intercept for LVEF calculated based on volume and area using the EchoPac PC and the proposed method. Therefore, our propsed method is able to achieve the same difference between the the area- and volume-based LVEF estimates as the current gold standard.



(a) Image dataset results



(b) Reconstructed LV results

Figure 7: Volume-based LVEFs compared to area-based LVEFs.

4. DISCUSSION, CONCLUSION, AND FUTURE WORK

Our attempt to demonstrate the necessity of quantitatively assessing LVEF rather than qualitatively estimate based on visual cues hopefully conveys the message that no shortcuts should be taken to calculating the LVEF. Using both idealized mathematical models of the LV and patient specific ultrasound imaging data, that area-based LVEF estimates underestimate true volume-based LVEF estimates. Thus, relying on area changes as a surrogate for volume changes should not be practiced. Moreover, we also showed a method that utilizes the relative position and orientation of the multi-plane 2D US images to correctly reconstruct a more faithful representation of the LV blood pool than simply averaging three axisymmetric LV shapes.

We will extend this study to a larger patient population and also plan to build a statistical shape model of the LV based on the extended patient population, to enable us to study the effect of the orientation of the cross-sectional areas on the area-based LVEF estimates. Moreover, the statistical shape model will also help reduce the intra- and inter-observer variability associated with the tracing of the LV endocardial border in both systole and diastole and also providing a more straight-forward method to estimate the blood pool volumes to determine the ejection fraction.

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