Robotic Arm Assisted Multiple Apical-View 3D Fusion of Echocardiography for Enhanced Right and Left Ventricular Assessment and Measurement

by

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Abstract

Introduction: Historically, among both ventricles, the right ventricle (RV) has received less attention than the left ventricle (LV) in cardiac research despite its critical impact on cardiovascular disease outcomes. The RV's complex anatomy presents unique challenges for echocardiographic evaluation, often resulting in suboptimal image quality and diagnostic accuracy. LV has a regular, symmetrical shape compared to the RV, which simplifies the quantifications of its volumes. Traditional three-dimensional echocardiography (3DE) encounters challenges such as limited field of view (FOV) and poor signal-to-noise ratio (SNR), which restrict comprehensive assessment. To overcome this, multi-view 3-D echocardiography (M3DFE) has emerged as a solution where multiple 3DE datasets from various acoustic windows are fused, and precise spatial and temporal alignment is crucial.

Robotic technology has been extensively used in different healthcare fields lately. However, researchers have recently suggested integrating a robot to assist in scanning and tracking positions in 3D echocardiography on humans. The use of a robotic arm will have the promise of enhancing the quality of echocardiographic scans by ensuring precise 3D tracking of the transducer's position.

This study explores the integration of a robotic arm to enhance 3DE by providing accurate 3D transducer tracking, aiming to fuse different apical views more effectively and improve RV and LV assessment quality. The proposed approach believed to be the first of its kind, tests the hypothesis that robotic-assisted data fusion can lead to superior RV and LV function and structure evaluations, tested on both volunteers and a select patient group.

Methods: This study utilized datasets from the Mazankowski Alberta Heart Institute, including 20 echocardiographic scans—15 from healthy volunteers and five from patients—approved by the University of Alberta's Health Research Ethics Board. Precision in image acquisition was achieved using the UR10e robotic arm paired with a Philips EPIQ 7C ultrasound scanner for volunteer scans. The protocol incorporated multi-beat acquisition across apical and parasternal 3D views to construct detailed cardiac sub-volumes. We employed the same protocol for patient scans but without the robotic arm. Echocardiographic data were initially exported to Cartesian form and converted to NRRD using 3D Slicer to facilitate postprocessing of spatial and temporal alignment for accurate single-view fusion. Subsequent image fusion employed averaging implemented using a Python script and wavelet-based method implemented using a 3DSlicer module.

The quantitative assessment involved SNR and contrast-to-noise ratio (CNR) calculations for both fused and non-fused images. RV and LV volume measurements were analyzed using TomTec software for non-fused images and 3DSlicer for fused images, with cross-validation for reliability. A user study was conducted to evaluate the fusion's effectiveness qualitatively.

Results: The study demonstrated that image quality improved with better SNR and CNR after using wavelet fusion and averaging techniques. Data from robotic arm echocardiography showed enhancements in SNR and CNR compared to manual methods, demonstrating the precision and repeatability of the robotic arm technology. Although the sample size was small, there were no significant differences in SNR and CNR among the groups, but the trends were positive. Additionally, fused data showed marginal improvements in RV and LV volumes and measurements, and inter-rater assessments confirmed higher image clarity and easier segmentation in post-fusion images, especially with the wavelet method. These findings highlight the potential of using robotic assistance and fusion methods in echocardiography to achieve better image quality and detail, which could improve cardiac diagnostics and patient care.

Conclusion: This study utilized data from a robotic arm to track the transducers and align the 3D echocardiography images on the volunteers and compares its performance with patient scans acquired without robot arm assistance. An apical-to-apical registration was performed, followed by single-view fusion using averaging and wavelet-based methods. The resulting enhancement in the images suggests improved image quality. While there were noticeable improvements in RV and LV quantifications in the small sample size, they were not statistically significant. However, further studies with larger sample sizes could address this limitation and utilize machine learning techniques to provide further improvement in image quality.

Preface

This thesis defines Khalid Alquwaynim's original work, which was done to fulfill the requirements for the Master of Science degree in Translation Medicine. Khalid Alquwaynim completed 100% of the writing. A part of this thesis is based on a manuscript that has been submitted to a peer-reviewed journal. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name “Robot-arm assisted 3D Multiview Fusion Echocardiography,” Principal Investigator: Dr. Harald Becher, Study ID: Pro00109218.

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List of Abbreviations

2DE: 2-Dimensional Echocardiography.

3DE: 3-Dimensional Echocardiography.

AI: Artificial Intelligence.

AMI: Acute Myocardial Infarction.

ANOVA: Analysis of Variance.

AVG: Voxel Averaging.

CI: Confidence Interval.

CML: Cross-Modality Learning.

CMR: Cardiac Magnetic Resonance.

CNR: Contrast-To-Noise Ratio.

CT: Computed Tomography.

DICOM: Digital Imaging and Communications in Medicine.

DL: Deep Learning.

EBD: Endocardial Border.

ECG: Electrocardiographic.

EDA: End-Diastolic Area.

EDV: End-Diastolic Volume.

EF: Ejection Fraction.

EM: Electromagnetic.

ESC: Elevational Spatial Compounding.

ESA: End-systolic Area.

ESV: End-systolic Volume.

FAC: Fractional Area Change.

FOV: Field of view.

HSH: Tukey's Honest Significant Difference.

ICC: Inter-Rater Statistical Analysis.

LOA: Limits of Agreement.

LPS: Left-Posterior-Superior.

LV: Left Ventricle/Ventricular.

LVEF: Left Ventricle Volumes Ejection Fraction.

M3DFE: Multi-View Fusion 3D Echocardiography.

MAV3DE: Multiple Apical Single view 3DE.

ML: Machine Learning.

NRRD: Nearly Raw Raster Data.

PET: Positron Emission Tomographic.

ROI: Region of Interest.

RT3DE: Real-Time 3D Echocardiography.

RTDE: Real-Time Data Exchange.

RV: Right Ventricle.

RVEF: Right Ventricle Ejection Fraction.

RVH: Right Ventricular Hypertrophy.

SNR: Signal-To-Noise Ratio.

TAPSE: Tricuspid Annular Plane Systolic Excursion.

TEE: Transesophageal Echocardiography.

TTE: Transthoracic 2-Dimensional Echocardiography.

WAV: Wavelet-Based.

Chapter One: Background and Literature Review

1. Current Use of Transthoracic 2D Echocardiography and Its Limitations

1.1 Introduction to 2D Echocardiography and Its Limitations

Transthoracic 2D echocardiography (TTE) is a non-invasive imaging modality for evaluating cardiac structure and function. It utilizes high-frequency ultrasound waves to visualize the heart and has several advantages over other imaging modalities, including its wide availability, low cost, and lack of ionizing radiation (1). TTE is widely used in clinical practice for a variety of indications, including the assessment of valvular heart disease (2), coronary artery disease (3), and cardiac function (4). It can be used to visualize the chambers of the heart, the vessels, and the heart valves, and it can provide important information about the heart's size, shape, and function (4).

Despite its widespread use, TTE has several limitations that should be considered. One limitation is the inability to visualize the posterior wall of the heart and specific segments of the LV, which can be difficult to image due to the presence of the spine (4). In these cases, alternative imaging modalities such as transesophageal echocardiography (TEE) or cardiac magnetic resonance imaging (CMR) may be needed (1). Another limitation of TTE is the reliance on operator skill and experience. The quality of the images obtained with TTE can vary significantly depending on the operator's experience (4), and poor image quality can lead to inaccurate interpretation of the images (1).

Additionally, 2D TTE may be limited in accurately assessing certain cardiac conditions, such as myocardial perfusion or cardiac masses (1). In these cases, alternative imaging modalities such as nuclear medicine imaging or cardiac CT may be needed (3). Overall, TTE is a useful and widely available imaging modality for evaluating cardiac structure and function (4), but its limitations should be considered when interpreting the results (1).

1.2 2D Echocardiography Ventricles Assessments

Transthoracic 2D echocardiography is used to assess ventricle volumes and ejection fraction, and several studies evaluated the accuracy of the 2-dimensional echocardiography (2DE) LV volumes ejection fraction (LVEF) (5,6,7). Each study differs in the number of patients included, the cause of the heart disease, and the left ventricular function and volume. These studies show that the transthoracic 2DE consistently underestimated the end-diastolic volume (EDV) and end-systolic volume (ESV) by 2D echocardiography (5,6,7). However, the LVEF measure based on transthoracic 2DE tends to be overestimated according to the studies, which shows a substantial discrepancy. The larger the volume, the larger the underestimation is, but LVEF differences are more significant when LVEF is lower. CMR was used as the reference for these studies.

1.3 2D Echocardiography Compared to CMR

Various studies have compared the accuracy of measurements obtained using CMR and echocardiography in assessing cardiac function and structure in patients with acute myocardial infarction (AMI) and heart failure, showing that CMR is generally more accurate than echocardiography. For instance, in a study by Nowosielski et al. (8), it was found that CMR was significantly more accurate than echocardiography in measuring both wall thickening ($p<0.05$) and ejection fraction ($p<0.05$) in patients with AMI. The study also showed that CMR has better diagnostic accuracy than echocardiography in identifying the infarct-related artery.

Another study compares the results of CMR and TTE in assessing cardiac volumes and regional function in patients who have had a myocardial infarction (6). 47 consecutive patients went into both CMR and TTE. The study found large and systematic differences in absolute measurements, with echocardiography underestimating LV volumes, stroke volumes, and ejection fraction. CMR was found to be much more sensitive in detecting segmental wall motion abnormalities ($p < 0.001$), and when comparisons were made with normal controls, an increase in LV volumes, a decrease in LVEF, and preservation of stroke volume after myocardial infarction were observed. This suggests that CMR provides more detailed and accurate information on cardiac structure and function regarding wall thickening, ejection fraction, cardiac volumes, and regional function compared to echocardiography.

Another study compares the results based on three imaging modalities, namely, echocardiography, radionuclide ventriculography, and CMR in assessing left ventricular ejection fraction and volumes in patients with heart failure (5). Bellenger et al. found that CMR was the most accurate of the three modalities in measuring LVEF with a mean difference of -1.7% (95% CI: -2.9 to -0.5) and LV EDV with a mean difference of -7.7 ml (95% CI: -15.5 to -0.1) when compared to echocardiography. Radionuclide ventriculography has the least accurate measurement in LVEF and LV EDV among the three modalities (5).

Overall, these studies suggest that CMR is a more accurate imaging modality than 2D echocardiography for assessing cardiac function and structure in patients with AMI and heart failure. CMR provides more detailed and accurate information on cardiac structure and function in terms of wall thickening, ejection fraction, cardiac volumes, and regional function. It can be said that 2D echocardiography has certain limitations while assessing ventricular function, mainly due to its single-plane imaging.

1.4 2DE: Right ventricle

The RV assessment is vital in the assessment of many cardiovascular diseases. With advancements in echocardiography, new opportunities have arisen for studying RV physiology, function, and dysfunction. Accurate evaluation of RV dimensions and function is critical for clinical management and determining prognosis. This review aims to provide a guidelines-based approach for the echocardiographic assessment of the RV, focusing on the latest methods for quantifying and predicting RV function.

1.4.1 Quantitative Evaluation of Right Ventricular Size by 2D Echocardiography

Estimating the size of the RV can be challenging due to its complex geometry. Assessment of RV dimensions enhances inter-rater reliability (9). However, 2DE echo measurements can be difficult to perform. RV dimensions and areas can vary greatly with small changes in transducer position in the conventional apical four-chamber view. The RV may appear enlarged when viewed in the RV-modified apical four-chamber view, especially if the peak of the sector is not centered over the RV apex. Therefore, quantitative RV measurements should not be performed in this view, and qualitative judgment should be used with caution. The best way to measure RV dimensions is to use an RV-focused apical four-chamber view, where the LV apex is at the center of the scanning sector while simultaneously displaying the largest basal RV diameter (9).

1.4.2 Volumes and ejection fraction

It is important to note that there are two main methods of quantification of RV volume using 2DE, the area-length method and the disk summation method. The area-length method is based on the assumption of modified pyramidal or ellipsoid models for RV geometry approximation, however, this method has been shown to underestimate RV volume when compared to 3DE-

derived volumes (10, 11). Additionally, studies have found that the disk summation method, which primarily calculates RV "body" volume, also underestimates true RV volume as it does not include the inflow and outflow parts during quantification.

In addition, the pooled studies of these 2DE methods derived RVEF have a lower reference value of 44% with a 95% confidence interval (CI) of 38–50%. It is, however, noteworthy that the American Society of Echocardiography does not recommend the calculation of RV ejection fraction (RVEF) in 2D at this point in time. This is due to the limitations of 2D RV volume quantification methods which can lead to inaccurate results (12).

It is also important to consider that these limitations may impact the overall clinical utility of 2D RV volume quantification. In addition, the use of other imaging echocardiography techniques and modalities, such as 3D echocardiography or CMR can provide more accurate and detailed information on RV structure and function. Generally speaking, RV function parameters determined using 2DE do not represent the global function of the RV, and estimating the RVEF and volumes precisely is almost impossible with only 2DE views (13).

1.4.3 Endocardial border

Endocardial border (EBD) echocardiography, also known as EBD tracking, is a valuable tool for measuring heart chamber size and function. It is a technique that uses 2D echocardiography to visualize, measure, and track the size and movement of the EBD. Due to the highly variable shape of EBDs, determining the location of the border within each image is an essential first step in the application of these measures. However, it is possible to perform this manually, and this is laborious, time-consuming, subjective, and not a satisfactory method (14). This concludes that 2DE is not accurately applicable in measuring the EBD.

2. Current Application of Right Ventricular Three-dimensional Echocardiography

2.1. Overview of RV using 3DE

3DE is a medical imaging technique that provides an advanced and comprehensive evaluation of the heart and its chambers in a three-dimensional approach (15). In the past few decades, this technique has been widely used for the assessment of LV anatomy, function, and dynamics. Yet, assessing the RV was quite limited in the beginning, and the available data on its reliability and accuracy in assessing its function and volume are limited.

The RV is considered a complex and dynamic chamber that plays an integral role in the systemic circulation of the heart. There are two main reasons for making the acquisition of the RV and its function using 2D or 3D echocardiography challenging. The first challenge is the overall shape of the RV, which can be described as a shell covering part of the LV and a relatively thin free wall. The second challenge is the location of the RV, which may be obscured in the apical window by the ribs or sternum, especially if the image is focused on the LV, and acquiring a good apical view for the RV requires more optimization from the user focused on the RV (16).

As 3DE offers a more thorough and precise study of RV anatomy, volume, and function, it has opened up new possibilities for RV assessment. By offering more precise and comprehensive data on RV structure and function, the technique offers the potential to enhance the diagnosis and treatment of cardiovascular illnesses connected to the RV. Overall, assessing the RV via 3DE is critical for prognosis and understanding the impact of various cardiovascular illnesses on heart function. In many congenital and pediatric heart disorders, indicators of RV size and function can be used for prognosis (17). The accuracy and reliability of 3DE in assessing RV volume and function have been extensively explored and validated, making it a helpful tool in the clinical environment.

2.2 Current Limitation of 3D Echocardiography

Real-time 3D echocardiography (RT3DE) is a valuable imaging modality in the evaluation of cardiac function, but it also has several limitations that need to be considered. Regarding cardiac function analysis, EDV or ESV is affected by the reduction of the temporal resolution compared to 2DE. As a result, chamber volume and function measurements may be inaccurate. The poor image quality and the inability to visualize specific structures during specific phases may also result in measurement errors (18). To maintain optimal image quality, the FOV is often reduced to avoid image artifacts and blurriness of the image owing to the decrease in the temporal and partial resolution (4).

Despite its prevalence and wide use, image quality is still a major shortcoming of RT3DE. A major concern is a dependence on the angle, as some of the waves may not reflect back to the transducer, which may result in weaker signals and reduced image quality (19). The RV has a variable shape angle. Consequently, RV quantification can be difficult when the ultrasound beam is not perpendicular to the RV wall, and the reflected signals are weaker.

A number of studies have demonstrated the challenges associated with RV imaging using RT3DE. A study conducted in 2010 found that RV volume measurements obtained using RT3DE may add some value but are still challenging and different from those acquired from the gold standard CMR imaging (20).

2.3 Quantitative Evaluation of Right Ventricular Size by 3D Echocardiography

An accurate assessment of the size and function of the RV is essential for the management of various cardiac conditions. 3DE utilizes a matrix array transducer that enables the acquisition of multiple image planes and the construction of 3D volumetric data as well as the manipulation of the data in real time in order to quantify cardiac size (21). An important advantage of 3D is that accurate measurements of RV can be made without the need for geometric assumptions.

2.3.1 3DE RV: Tricuspid Annular Plane Systolic Excursion and FAC

The measurement of ejection fraction in the assessment of LV in clinical cardiology is standard practice. Unlike the RV, the non-volumetric parameters are mostly used in the assessment (22). A common parameter used to assess RV function is the tricuspid annular plane systolic excursion (TAPSE). It has been found that TAPSE has excellent reproducibility and practicality because it does not assume geometric assumptions or RV endocardial definition (23). Also, a number of studies indicated that a lower TAPSE rate is related to a poor prognosis of some cardiac pathologies (23,24,25). Another non-volumetric measure is the Fractional Area Change (FAC). It is also considered a representative indicator of RVEF since it is measured similarly to LVEF, having a positive correlation with cardiac mortality and cardiac mortality morbidity (26). Regarding the RV, besides the non-volumetric parameters, ejection fraction and volume measurement together could be the standard RV echocardiography evaluation if they could be obtained accurately.

2.3.2 3DE RV evaluation: compared to CMR

It has been demonstrated that CMR is a very reliable method of measuring both LV and RV size and function (27). As a state-of-the-art method, a study in 2011 compared CMR with 3DE in 25 patients with heart failure. 3D echocardiography showed an underestimation of RVEDV and RVESV compared to CMR. According to the authors, 3DE is not yet suitable for routine clinical use to assess RV dilatation in patients with more than mild dilatation (21). Another study was conducted on 88 patients, and according to the results, RT3DE imaging had slightly lower volumes than MRI, but there was no significant difference in ejection fraction between the two methods. The correlation coefficients of both methods were high, suggesting that the two methods are in good agreement (28). It appears that RT3DE imaging can provide a cost-effective and time-efficient alternative to MRI when assessing the size and function of the RV.

3. Addressing the Limitations of Transthoracic 3D Echocardiography

3.1 Automated techniques for 3D RV assessment.

The use of machine learning (ML) and automation to reduce manual input and minimize human error is becoming increasingly important when it comes to quantifying the size and function of the RV using 3DE. Measurements can be more accurate and efficient when ML and automation are implemented. Using 3DE, a new ML-based software tool was tested for accuracy and reproducibility (29). According to the results of the study, the automatic approach was accurate in 32% of cases, with an analysis time of 15 seconds and a reproducibility rate of 100%. Unlike the other 68%, a minimal manual interaction was needed which increased the analysis time to 114 seconds. However, the measurements of RV volumes and EF were accurate and highly reproducible.

Another study compared the accuracy and feasibility of a fully automated 3DE software with semi-automated software for the quantification of RV volumes and RVEF in 100 patients. Results showed that the new software had a 91% feasibility rate, underestimated the RV EDV compared with CMR, but offered good correlations with CMR and reasonable correlations with RVEF (30). Moreover, the automated technique had a shorter analysis time than the semi-automated software. Accordingly, full automation approaches are a promising option for clinical practice due to their rapidity and reproducibility.

3.2 Semi-automated techniques for 3D RV assessment.

In recent years, several technological advances have helped minimize some of the limitations of RV 3DE. A semi-automated approach for assessing the RV measurement showed good reliability and good correlation with manual methods for all measures, Speckle tracking was used to track one EBD in the software and perform all quantitative measurements. (31). Another study evaluated the accuracy of semi-automated software to analyze apical RV-focused views. In patients with suboptimal acoustic windows, the software requires manual tracing of the RV boundaries simultaneously in the cardiac cycle, which is dependent on image quality (32). These are methods that can be applied to improve the accuracy of the assessment for the RV.

3.3 Fusion techniques

Among the advancements in imaging techniques being made recently to improve the assessment of the ventricles is the "fusion" method, which can be applied in echocardiography as a way to investigate improvements to 2DE and 3DE. This method was also used in noncardiac applications such as breast image registration and prostate biopsy (33, 34). It is possible to fuse echocardiography images with another modality, such as MRI, to provide additional information on anatomical structures that can't be seen on the basis of echocardiography alone, thus improving the quality of the image (35, 36).

The limited FOV is considered a major drawback in the image quality of the 3DE. It has been found that combining (fusion) multiple datasets of echocardiography along with tracking breath-holding position will result in higher quality images and a wider FOV (37). An improved diagnosis and treatment of cardiovascular diseases may be possible through this approach to overcome the limited FOV in 3DE.

3.4 2D fusion approaches

Fusion techniques were first studied with two-dimensional echocardiography. Two major methods, known as temporal compounding and elevational spatial compounding (ESC), were used to improve image quality and overcome the limitations of individual acquisition processes (38, 39).

3.4.1 Elevational Spatial Compounding

This technique is referred to as elevational spatial compounding, which involves the acquisition of multiple 2DE datasets from slightly different angles in the elevation of a region of interest (ROI) (38). As a post-processing step, a single 2DE dataset is created by fusing datasets collected during the same part of the cardiac cycle. Therefore, the quality of the image can be improved by reducing the occurrence of artifacts and noise (38,40).

It is important to note that ESC has one important limitation: it is susceptible to tissue boundary blurring when the arc of elevation is large during the compounding process. It is difficult to distinguish between different structures when the transducer is angled through large arcs due to the capturing of more tissue volumes. The blurring phenomenon may result in misleading results of cardiac quantifications (38). applying an edge enhancement algorithm is one way to reduce the effect of this limitation.

3.4.2 Temporal Compounding

In ultrasound imaging, temporal compounding is a technique that is used to minimize image noise and to compensate for differences in the image that result from changes in blood movement or tissue during a cardiac cycle, which can affect the image quality. Two methods can be used to fuse datasets from unmoving transducers. It can either be multiple frames from the same cardiac cycle or a similar timed frame from a different cycle (39, 41).

Fusing images taken during the same cardiac cycle may result in a reduced temporal resolution and blurring of the tissue boundaries due to the fact the heart is in motion (42). Despite this method's improvements, it tends to be more useful with stationary or slow-moving objects (42).

Alternatively, fusing images from different cardiac cycles preserves temporal resolution since the movement of the heart is captured over time. This method can also blur borders if there is a slight shift in the transducer's position, thereby reducing image quality (41, 42). As part of the acquisition process, breath-hold maneuvers must be used, and a regular heart rhythm must be maintained to ensure a high-quality image for diagnostics (42).

4. Multi-view 3D Fusion Echocardiography

4.1 Introduction to multi-view 3D fusion echocardiography

In echocardiography, the single-view fusion transducer position remains constant during the acquisition, in contrast to M3DFE, which acquires images from multiple positions (43.44). A more comprehensive and complementary image is obtained by fusing two or more datasets from multiple views.

Fusion concepts involve combining overlapping datasets that contain valuable information for enhancing the image. A good representation of the RV, which is known to be a complex structure, can however be achieved by combining multiple perspectives and acquiring datasets from multiple views. Echocardiography allows visualization of the RV from several windows, including the parasternal, subcostal, and apical views. Similar to the LV, the apical window provides an excellent view of the RV's EBD, ensuring that the border is demonstrated clearly. A subcostal approach allows for visualization of the RV's base and apex in a more direct, perpendicular manner. In the parasternal window, the RV outflow tract and tricuspid valve can be seen from an oblique perspective. The overall resulting image with the use of M3DFE can display an enhanced and more detailed RV.

Image fusion can optimize FOV without affecting resolution, which is one of many potential benefits. In addition, it is challenging to acquire and quantify an image of a patient with right ventricular hypertrophy (RVH) even though it is recommended to use the subcostal 4-chamber view in these cases (45). Also, this method will play a major role in minimizing the need for contrast agents, which is unsuitable for all patients considering the allergic ones, and the chance of repeating the procedure to obtain better results (46). M3DFE datasets must be processed in several steps to ensure diagnostic quality. To accomplish this, the steps are: 1) spatial alignment, 2) temporal alignment, and 3) image fusion and optimization (43, 46).

4.2 Spatial Alignment

During the fusion phase, multiple echocardiographic images are combined to create a better and more accurate demonstration of the heart in a single dataset, and alignment of the multiple datasets is a crucial step for achieving better results. There are two types of spatial alignment to be performed, either by image registration or transducer tracking.

4.2.1 Spatial Alignment by Image Registration

A spatial alignment by image registration utilizes computer algorithms in order to determine the best spatial alignment between two or more datasets to achieve consistent results (47, 48). Not only echocardiography but this method has also been applied in the fusion of several imaging modalities such as MRI and positron emission tomography (PET) (35, 49).

Every method is always limited, regardless of how effective it is. A significant factor affecting the degree of spatial alignment by image registration is the level of similarity or overlap between the datasets that are aligned. As an example, datasets that were obtained from a similar window are easy to align due to the similarity of the structures between them (43). Nevertheless, the challenge in aligning different datasets - such as obtaining apical and subcostal images - is when the datasets are from different acoustic windows. The resolution of the datasets, artifacts, and noise also can limit image registration (50). There are however some limitations to the registration techniques that are being addressed by the current studies (51, 52), and there is no doubt that their effectiveness will continue to improve in the future as more and more studies are conducted.

4.2.2 Spatial Alignment by Transducer Tracking

Another approach is spatial alignment by transducer tracking, which tracks and records the position and orientation of the transducers during the acquisition of images. These recorded data are then used to align or merge datasets acquired at different times. As opposed to image registration, transducer tracking does not rely on the visual similarity of datasets. The ideal M3DFE study based on transducer tracking requires less movement of the heart within the 3D spatial position during the scan. These movements may be due to the effect of the diaphragm and the chest wall on respiratory movement (53). To date, researchers have explored two major approaches for transducer tracking, namely, electromagnetic (EM) tracking and optical tracking.

4.3 Temporal Alignment

The cardiac cycle and breathing are highly related to the heart position and morphology changes. Moreover, when merging or fusing two datasets, we need to consider these changes. The first consideration when fusing the data is the synchronization of the datasets according to the cardiac cycle, which can be monitored commonly using electrocardiographic (ECG) gating. However, an algorithm for ECG-independent temporal registration can be used (37, 52).

When imaging the heart, cross-sectional modalities such as MRI and CT can produce better and fewer motion artifacts images due to the direct observation of the diaphragm movement (54,55). In echocardiography, it is common for the sonographer to ask the patient to hold their breath, whether during the end-inspiration or end-expiration phase, to record images (37). By developing a respiratory gating technique where the acquisition of images is breath-free, the potential benefits of M3DFE could be maximized.

4.4 Fusion of 3DE datasets

As a final step, the individual 3DE recordings are processed and combined to create the final M3DFE dataset. Essentially, the overlapping portions of the recordings must be processed to determine the final intensity of each voxel and the smooth transition between recordings. Several methods exist for fusing multiple datasets in M3DFE, yet they often result in reduced SNR and contrast (37,56). Additionally, a computer algorithm called wavelet decomposition has been shown by some researchers to be able to give a better ratio of signal to noise and contrast. Wavelets filter images according to their frequencies. While high frequencies contain artifacts and noise, low frequencies carry signals representing the image. Suppressing high frequencies will enhance the visualization of the low frequency, resulting in a clear image (37,57). It is, however, difficult to identify which fusion method will yield the best results for M3DFE.

5. Current RV echocardiography fusion results and challenges

5.1 Results of M3FDE on RV

To date, there have been no publications demonstrating the feasibility of M3DFE for assessing the RV. In the context of the LV, M3DFE shows promising results in image quality and FOV improvements. As part of a study, the M3DFE was investigated to enhance the visibility of the lateral border of the LV, which also resulted in enhancing the medial wall of the RV (58). Accordingly, M3FDE can be applied to the RV, giving the likely benefits of improving image quality and extending FOV. Studies conducted by LV indicate that chamber quantification accuracy is not compromised by the M3DFE (43).

5.2 Challenges of 3D Fusion Echocardiography

M3DFE is still a new technology, and the majority of the studies have been done on healthy volunteers, which cannot validate the feasibility of the technology in clinical use. Despite its effectiveness in laboratories, applying this technique to daily use in clinics with different patient conditions may be challenging. More studies on patients and the validation of the results with state-of-the-art CMR are needed for accuracy and reliability before M3DFE can be widely used in hospitals. Furthermore, the aligning and fusion process needs both time and expertise, which may affect the workflow of clinics. In a positive light, new techniques are being developed to make the fusion of acoustic datasets from different windows possible. Over the years, these techniques are expected to continue to progress.

6. Integration of Robotic Arm Assistance in Medical Imaging

6. 1 Overview of Robotic Assistance in Medical Fields

Over the past few years, humans and cobots (collaborative robots) working in a shared workspace have emerged intelligently in the medical field. They are designed to work as an assistant to the medical practitioner, using their precision, endurance, and precision to improve the accuracy and effectiveness of medical interventions and reduce human error (59). More importantly, integrating robotic technology in the fields means more automating and optimizing processes. Human-robot cooperation must be in a safe environment to prevent any incident or collision, as using the robot should provide advantages in reducing work-related injuries.

6.1 Robotic Assistance in Echocardiography

Echocardiography started with tele-echocardiography, where the sonographer remotely controls the examinations, as several studies have shown (60,61). The focus was on training the experienced sonographer to remote-control the ultrasound system. Yet, the applications of cobots in echocardiography are still new. Future research in robotics for ultrasound involves advancements in autonomous image capture, therapy guidance, and diagnostics. Artificial intelligence (AI) is currently the future direction for the use of robotics, as it has the potential to enhance performance in medical imaging, and it's important for increasing the autonomy of the robotics systems in ultrasound (62).

6.2 Current Applications and Benefits of Robotics Arm in Echocardiography

One current benefit of using a robotic arm for echocardiography is its ability to conduct examinations remotely. In a study, an ultrasound probe is attached to a robotic arm via an internet connection controlled by an expert sonographer. Their findings presented promising results, indicating a minimal decline in image quality and consistent measurements in over 90% of cases (60). These results highlight the opportunity to explore and improve robotic integration in echocardiography to elevate image quality.

3-D echocardiography has an FOV limitation; a study addressed that by using a robotic arm-based multi-view echocardiography fusion system (63). This system can acquire images from different angles and fuse them together by tracking the transducer. The initial findings from 3 volunteers indicated significant enhancements in the alignment accuracy of multiple scans through the utilization of tracking data. Moreover, work-related injuries are common among sonographers, especially in their wrist and lower back, so one more benefit of robotic technology is to reduce and address this issue (61).

7. Thesis Contribution

In this thesis, we propose a novel approach that uses robotic arm assistance 3D echocardiographic datasets with apical-to-apical 3D fusion echocardiography to enhance the assessment of the right and left ventricles. The entire study is divided into three parts:

1. The first part of the study was to recruit volunteers for the robotic arm scan and acquire high-quality echocardiographic images. Fifteen of the volunteers were carefully selected with the optimal image quality of both ventricles in the apical views. A trained sonographer did the procedure. The acquired images were combined and saved in DICOM format and then converted into a Cartesian coordinate system for alignment and post-processing.
2. The second part of the thesis focuses on the implementation of the apical-to-apical 3D fusion method into a single fused 3D echocardiographic image. Two fusion methods were proposed: the fusion by averaging and wavelet-based fusion techniques. The comparison between both techniques demonstrated that the wavelet-based method significantly improved the SNR and CNR in both volunteer and patient images.
3. The third part highlights the analysis of the fused 3D images for the right and left ventricles. With the promising results of the image quality (SNR and CNR) for post-fusion, the reliability and reproducibility of the EF were valid with the Bland-Altman test. However, the improvements were noticeable in the ventricle’s evaluation, but they did not show statistical significance. The thesis recognizes the promising outcomes and suggests that addressing the study's limitations can lead to further improvement.

8. Conclusion

A promising result was found when fusing multiple views in comparison to 3DE datasets when assessing the LV. However, its potential application in the RV remains unexplored. No other study used echocardiography data obtained from a robotic arm assistant to evaluate the RV volumes and measurements. The novelty of this study remains in the use of robotics data to fuse multiple apical views using two different fusion methods – fusing by averaging and fusing by wavelet-based – and evaluate the RV quantification. The feasibility, accuracy, and robustness of multi-view fusion have improved over the past few years. Therefore, we believe that further research and combining robotic technology with fusion techniques could become an important tool for RV assessment and evaluation, leading to advancements in clinical practice and patient care.

9. Chapter 1 Tables and Figures

Table 1: Summary of Recent Key Studies Utilizing Robotic Arms in Echocardiography.

Author, Year of Publication	Study Subjects	Robotic Method	Findings
Arbeille et al., (2014)	41 Cardiac patients	Tele-operated echocardiography with a robotic arm and internet connection.	The quality of cardiac views was slightly lower than reference echocardiography, but measurements were similar in 93%-100% of cases. The system detected 86% of valve leaks or aortic stenoses, indicating reliable diagnoses and acceptable measurements.
Kumar et al., 2023	3 subjects	Robotic arm-based multiview echocardiography fusion system	Significantly improved alignment accuracy of 3D echocardiography images using tracking information, addressing field-of-view limitations.
Wang et al., 2016	Phantom experiments	Robotic transesophageal echocardiography (TEE) system	High accuracy in maintaining desired anatomies in the FAC, improved probe positioning accuracy with feedback adjustments, potential for remote and automated ultrasound acquisitions.
Rubin et al., 2023	154 patients with embolic cerebrovascular ischemia	Robot-assisted transcranial Doppler (raTCD)	raTCD detected RLS in 64% of patients compared to 20% with TTE, identified large RLS in 27% of patients versus 10% with TTE, and had no serious adverse events.

Table 2: Summary of Recent Key Studies Utilizing Fusion in 3D Echocardiography.

Author, Year of Publication	Study Subjects	Fusion Method	Findings
Carminati et al., (2014)	17 patients	Multiview compounding of 3-D TEE aortic data sets	Feasibility and accuracy of reconstructing the descending thoracic aorta, enabling extended field-of-view visualization and quantitative assessment of aortic plaque burden from 3-D TEE images.
Augustine et al., (2016)	60 patients	Fusion of multiple, sequential RT3D volume datasets	Improved segmental image quality and CNR, approaching 2D contrast echocardiography
Punithakumar et al., (2016)	6 healthy volunteers	Multiview 3-D echocardiography fusion with breath-hold position tracking using optical tracking.	Improved FOV by 35.4%, significant improvement in contrast, CNR, SNR, and feature count with wavelet-based fusion technique.
Danudibroto et al., (2016)	10 healthy subjects	Spatiotemporal registration of multiple 3D echocardiographic recordings.	Enhanced FAC imaging through accurate registration; validation showed significant improvements in temporal and spatial registration.
Bersvendsen et al., (2016)	16 clinical cases	Spatio-temporal registration of 4D cardiac ultrasound sequences.	Enhanced FAC imaging, accurate temporal and spatial alignment, mean distance between landmarks: 4.3 ± 1.2 mm compared to 2.9 ± 0.7 mm with manual registration, and temporal alignment errors within clinically acceptable values.
Punithakumar et al., 92023)	3 healthy volunteers	Multiview 3D echocardiography fusion	Significant improvement in alignment accuracy using tracking information from a robotic arm; focus on addressing alignment issues due to movement.

Punithakumar et al., (2024)	Heart phantom	Robot-assisted multiview fusion of 3D echocardiography	Improved FAC by 24%, significant enhancement in alignment accuracy using robotic arm for tracking, reduced sonographer strain.

Figure 1 The overall system showing the robotic arm components for the multi-view echocardiography fusion. The cardiac structures of the participants are scanned from different positions and aligned using the tracking information obtained from the robotic arm. Credits: Integration of Robotic Technology for Combining Multiple Views in Three-Dimensional Echocardiography (63).

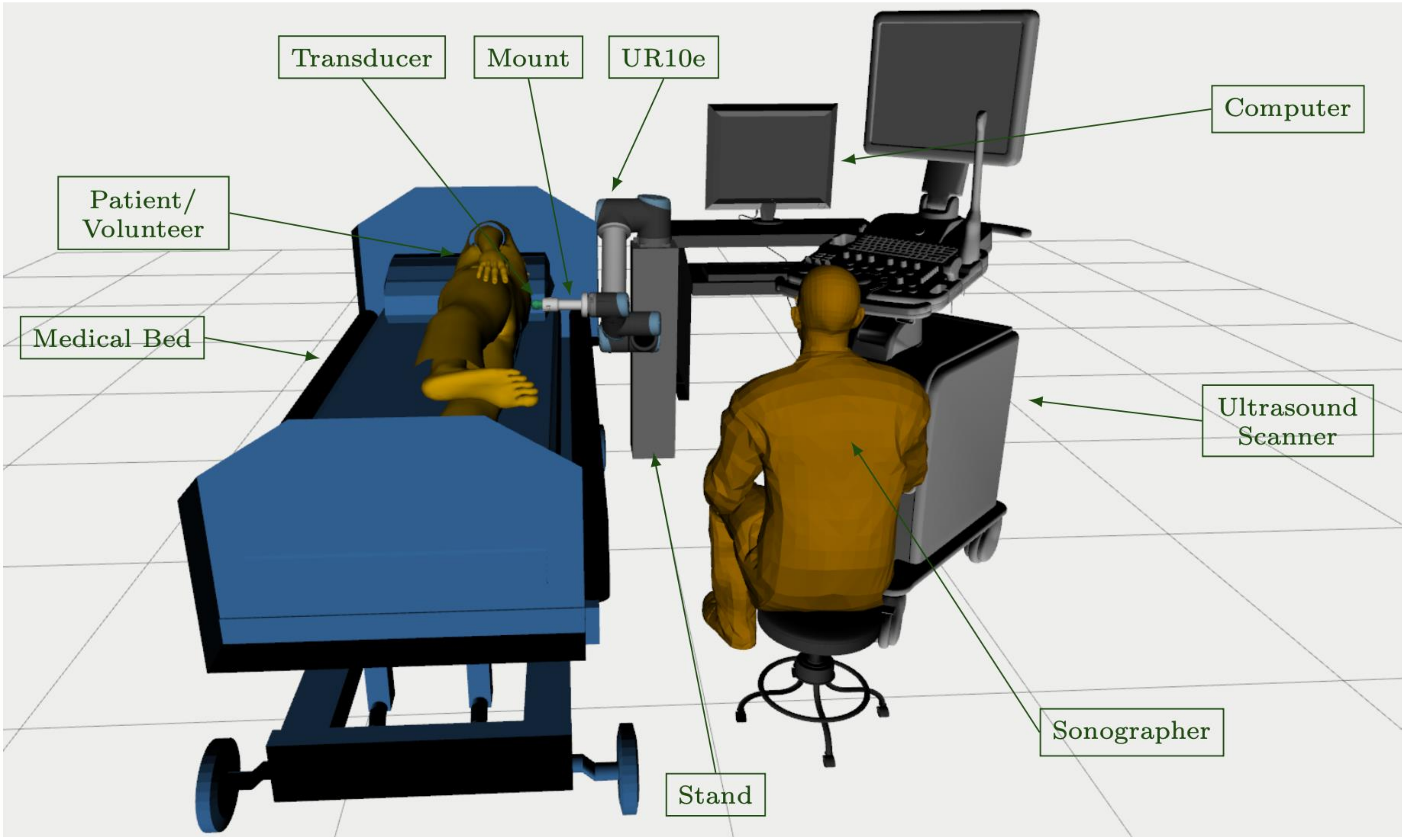


Figure 2 Illustration of the 3D echocardiography data fusion process. The image starts with two apical views, followed by the steps of spatial and temporal alignment, and concludes with the final fused images obtained through averaging and wavelet fusion methods.

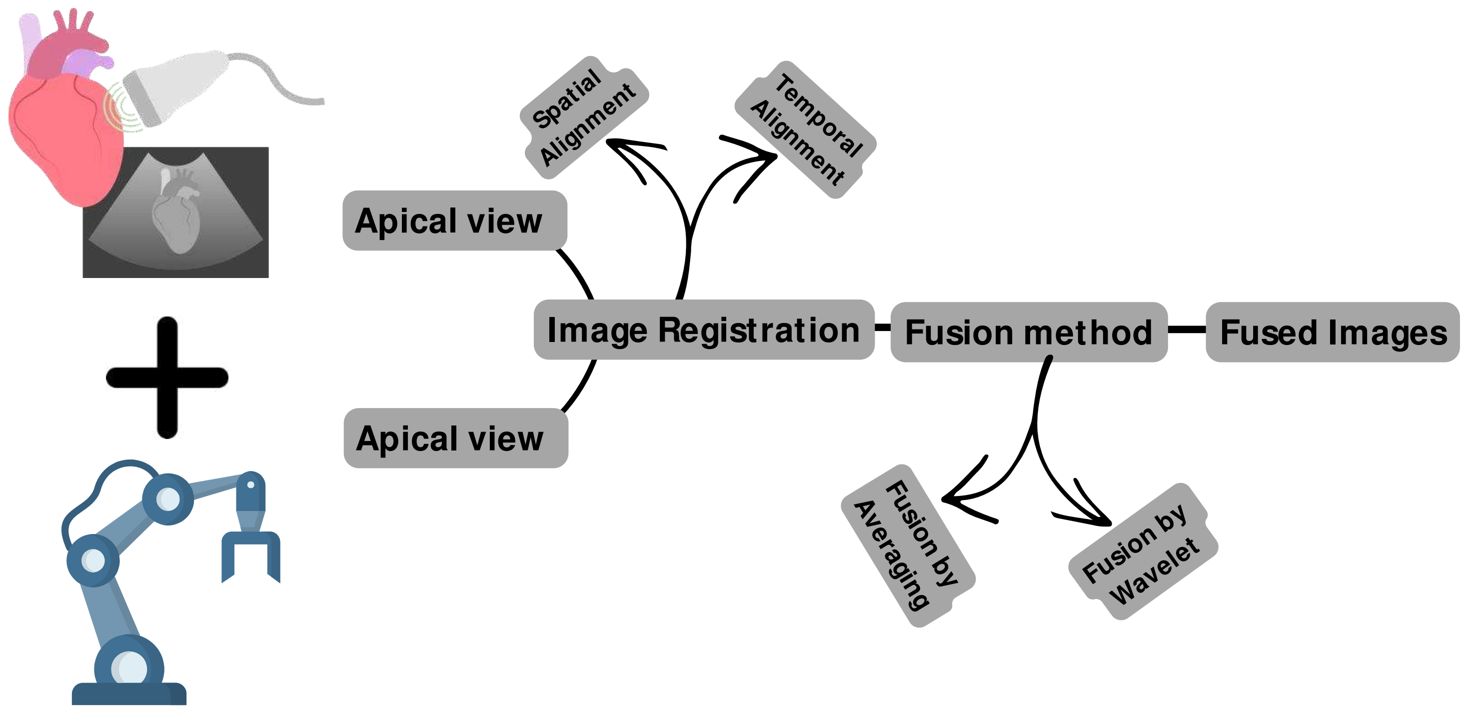


Figure 3 Illustration of ensuring the spatial and temporal alignment of the apical 3D echocardiography data using the matrix module in 3D Slicer before fusion.

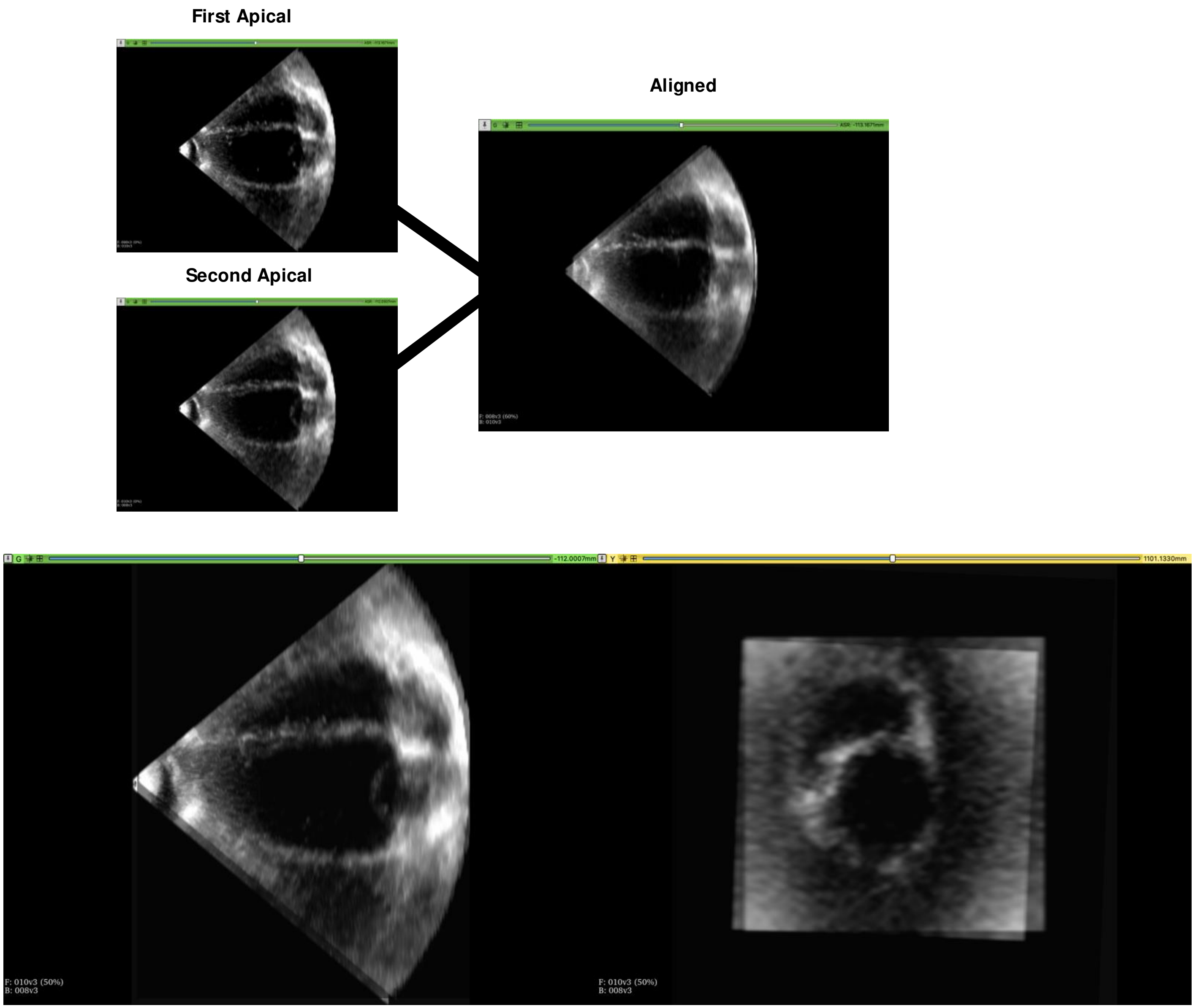
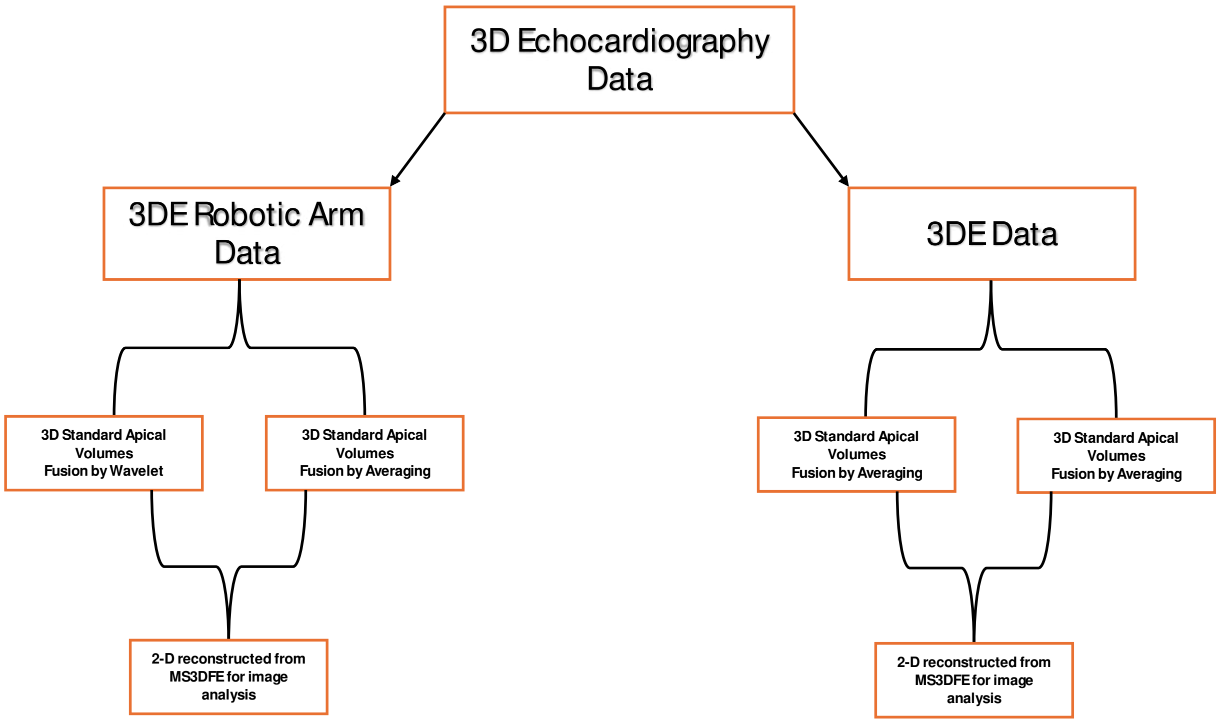


Figure 4 Data study design. 3DE = 3-Dimensional echocardiography; MA3DFE= Multiple single view 3-dimensional fusion echocardiography.



Chapter Two: Robotic-Arm Assisted Multiple Apical-View 3D Fusion of Echocardiography for Enhanced Right Ventricular Assessment and Measurement.

1. Introduction

1.2 Background – Right and Left Ventricle Assessment and Its Limitation in 3DE

Over the years, the RV has garnered less consideration in cardiac diseases than the LV and has been studied less historically. The attention to the LV is mainly due to its high susceptibility to myocardial infarction, a leading cause of mortality from an epidemiological perspective. More importantly, LV is easier to image in all modalities due to its uniform shape, wall thickness, and location in the anterior chest, making it more accessible for ultrasound waves. However, the significant role of the right side of the heart, particularly the RV, has been widely recognizable lately, including various cardiovascular conditions and their relation to mortality and morbidity. CMR, the state-of-the-art in cardiac imaging, has led to a new understanding of RV geometry and function through its advancements. Even though CMR is the optimal modality for demonstrating RV and LV volumes and functions, its limitations regarding daily clinical practice still require better alternatives (64,65).

With recent advancements in echocardiographic technology, the capability of echocardiography to evaluate the RV and LV quantitatively and qualitatively has improved. Echocardiography is widely used as the first-line tool for evaluating RV function and measurement due to its widespread availability, ease of use, and cost-effectiveness. The complexity of the RV shape, position, and anatomical features makes it challenging for comprehensive and accurate evaluation of echocardiographic imaging (65,66). The RV is crescent-shaped in cross-section, triangular in longitudinal view, and more complex in three dimensions. This asymmetry results in non-standard RV volume estimations, and the lack of standardization among echocardiographic protocols limits the availability of normal values for the RV. Also, while advances in 3DE are made, issues like the limited FOV, poor SNR, and EBD definition are magnified in 3DE (67,37).

1.2 Multi-View 3D Fusion Echocardiography

To overcome these limitations, generating a higher quality 3DE can be achieved by fusing multiple 3DE datasets from different or the same acoustics windows together. Along With having a precise spatial alignment between the individual sequences, this method is called multi-view 3-D echocardiography (M3DFE) (4). The M3DFE method has been presented in multiple papers with varying protocols, improving cardiac parameters, especially the FOV (37,76,68). Taking certain steps before performing M3DFE is important to achieve the best fusion results. Each 3D dataset volume must be accurately aligned with the others to ensure successful fusion. This alignment involves both spatial and temporal synchronization between the frames in the sequences. Misalignments, even if minor, can significantly reduce diagnostic accuracy and reliability.

In the literature, preclinical studies on M3DFE have demonstrated improvements in several parameters, such as SNR, CNR, FOV, and EBD. Despite the advancements, there are some limitations when it comes to capturing images from different windows (46,47,68,69). The transducer's position tracking is missing, and there are no automated references to align the images accurately, as is the case with MRI and computed tomography (CT) (70).

1.3 Robotic Arm Assistant in Echocardiography

Robotic technology has experienced widespread adoption in various healthcare sectors, including patient rehabilitation and remote surgical procedures (71). The use of robotic-assisted echocardiography is valuable due to the limited availability of skilled sonographers or physicians and the potential to alleviate work-related injuries, and because of the possibility of remote scanning. Scanning the heart in echocardiography requires grip strength and consistent scanning, which can lead to musculoskeletal issues (72). Thus, a robotic arm system can minimize human interaction during the scan. A recent innovation in research has suggested integrating a robot into scanning and tracking positions in 3DE on humans. The researchers believe using a robotic arm will enhance the overall quality of echocardiographic scans by ensuring precise 3D tracking of the transducer's position (63). This will enable fusing multiple echocardiographic windows and result in better-quality scans. For more information on the technical functioning and benefits of the robotics system, please refer to (60,62,63,73).

1.4 Hypothesis

In this study, we hypothesize that using multiple apical views data from the robotic arm and fusing it using two fusion methods will improve the image quality and the assessment of the RV and LV volumes and measurements; the study will be tested on volunteers' data captured using robotic arm assistance. To the best of our knowledge, this is the first study to use cobot data to fuse multiple apical views for evaluating the cardiac ventricle functions and measurements.

2. Methods

2.1 Subject Enrollment

This study is based on datasets previously collected and processed at the Mazankowski Alberta Heart Institute, as detailed in (63). After receiving approval from the Health Research Ethics Board at the University of Alberta, consent was obtained from all study volunteers, and the procedures were explained to them. Any healthy adult volunteer with no history of cardiac disease was eligible to participate. No financial incentives were given. A total of 20 echocardiography scans were used in this study; 15 scans were acquired from volunteers using the robotic arm, while the remaining five were obtained from adult patients with no cardiac diseases enrolled in another ongoing study. The volunteer's image dimensions were 272 × 176 × 208 with a resolution of 0.775 mm × 1.209 mm × 0.778 mm in the x, y, and z-coordinate directions, respectively (63).

2.2 System Components and Setup

The study consists of a UR10e robotic arm (Universal Robots, Odense, Denmark) securely attached to the Philips EPIQ 7C ultrasound scanner probe using a custom 3D-printed mount, and for stability, it is fixed to a stationary pedestal (63) (Fig 1). The robotic arm is controlled via a Real-Time Data Exchange (RTDE) interface with a 500 Hz frequency for communication with the robotic arm. This setup enables accurate movement and placement of the transducer and the robot arm is connected to a laptop for real-time control and data transfer. Our study adapts the images acquired from this system to apply the fusion method aiming to enhance RV assessment. Volunteers were positioned in the left lateral decubitus position during scanning. Scans were performed on a Philips EPIQ 7C ultrasound scanner with regular echocardiography scanning protocols.

2.3 Scanning Protocol and Data Processing

The volunteer scanning protocol focuses on apical and parasternal 3D echocardiographic views. It utilizes a multi-beat acquisition technique to obtain a comprehensive cardiac sub-volume from participating volunteers during breath-holding. The same protocol was applied to patient scans but without the integration of the robotic arm. The sonographer is trained to guide the robotic arm to the preferred window. A force mode is applied with minimum pressure to keep the transducer in contact with the volunteers, and it can be controlled via a wireless keyboard for different commands and positions. While lying in their lateral decubitus, the volunteers are instructed to hold their breath during the multiple acquisitions. The acquired images were initially combined and saved in Digital Imaging and Communications in Medicine (DICOM) format and then converted into a Cartesian coordinate system for alignment and post-processing (60,63).

2.4 Image processing: 3-D fusion

2.4.1 Image Transformation and Alignments

After the data had been converted into cartesian DICOM, the images were transformed further into nearly raw raster data (NRRD) format using a module in 3D Slicer, as NRRD files are more flexible and can store both image data and metadata. This step is crucial to ensure proper alignment in both spatial and temporal dimensions. The robotic arm echocardiographic data provided as a transformed NRRD were aligned spatially as a part of the post-processing after exporting the images (62,63,74,75). The multi-beat acquisition ensures a rich, consistent cardiac phase across beats, enhancing temporal alignment. Despite simultaneous acquisition, temporal alignment is crucial for fusing multiple single-view datasets. When integrating two sequences from the same scanning session, it is essential to ensure precise temporal alignment between them for fusion and analysis. The first diastolic cycle of each sequence was used as the starting point to test the temporal alignment; the data overlayed on one another using a 3D slicer to test the alignment and synchronization of the data, to exclude or realign any misalignment, as shown in (Fig 2.) When handling the patient's data, the images were not initially acquired for fusion purposes, unlike the volunteer data. Thus, the two sequences were not aligned and shifted. As a result, some adjustments were necessary to align them accurately. The patient's data was properly aligned using an image registration approach in 3D Slicer (75). During registration, one image is chosen as the fixed image to serve as the reference, and the other is the moving image adjusted to align with the fixed one. Apical view volumes with the best quality and optimum RV view were selected as the fixed image; all other images were transformed through the image registration process. The module used in the 3D Slicer for the registration is known as general registration (ANTs), which employs rigid and non-rigid registration approaches. Once the registration is completed, an output transform and a fixed volume are produced, followed by a visual assessment to look for artifacts or misalignment. The transform module in the 3D slicer can also be used to check for rotations in the x, y, and z-axes and translations in the x, y, and z-directions.

2.4.2 3D Fusion

Upon aligning the 3DE data, we proceeded to apply voxel averaging (AVG) and wavelet-based (WAV) fusion approaches to both volunteer and patient sequences. In the fusion-by-averaging approach, the voxel intensities from corresponding locations in each sequence in 3DE are averaged on a voxel-by-voxel basis. This method ensures that the final image preserves the median intensity level, thereby mitigating noise and maintaining anatomical details. The AVG method is most effective when both 3DE volumes display strong signals for all regions. For instance, if the first sequence exhibits strong signals in the tricuspid valve while the other shows weak signals in the same region, the dominant signal will be reduced due to averaging with the weak signal.

A module was built and employed for the advanced fusion wavelet-based approach in the 3D Slicer that works on decomposing the images into high- and low-frequency components through wavelet transform (58). The high-frequency components consist of noise and artifacts. In contrast, the low-frequency ones represent the signal of interest, which is the anatomical structure, such as the tricuspid valve. Both are fused by selecting the maximum value to ensure the preservation of anatomical details. The chosen fused component is then reconstructed into a single fused image using the inverse wavelet transform, leading to improvement in the low-frequency component, thus enhancing the CNR and SNR. These two approaches were constantly used for all of our data. More details of the wavelet-based fusion methods can be found in (67).

2.5 Image analysis

In the fusion process, multiple apical standard views are integrated together, successfully fusing twenty MA3DFE. For each MA3DFE, the end-diastolic and end-systolic volumes are reconstructed into 2-D planes corresponding with the 3DE (non-fused) for analysis. The data that showed misalignment during the analysis process were excluded and replaced with another volunteer scan. The image analysis involves assessing the following parameters: 1- SNR and CNR for the image quality of the robotic data after fusion. 2- Quantification of right and LV volumes and measurements, including EDV, ESV, Ejection Fraction (EF), TAPSE, and FAC. 3- Inter-rater qualitative assessment of the fused images.

To quantitatively assess the image quality of the Multiple Apical single view 3DE (MAV3DE) images, we calculated the SNR and CNR for each of the 2-D volumes. In 3DSlicer, we predetermined the coordinates to directly identify the background and ROI from the images using left-posterior-superior (LPS) orientation. The same coordinates were applied in both the fused and non-fused images for direct comparison between the values, ensuring the precision of the image quality assessment. In the SNR and CNR calculations, the myocardial served as the ROI, while the blood pool area was the background. Showing in the formula below:

$$SNR = \frac{\mu\, ROI}{\sigma\, BG}$$

$$CNR = \frac{\mu\, ROI - \mu\, BG}{\sigma\, BG}$$

The original (non-fused) 3DE data are imported to TomTec, a software for advanced cardiac analysis, for RV evaluation using the 4D RV-FUNCTION tool. This tool allows for a comprehensive evaluation of the RV volumes and measurement for both 2D or 3D echocardiography, such as EDV, ESV, EF, FAC and TAPSE. Also, a 4D LV-ANALYSIS tool is used for LV volume quantification in TomTec. Meanwhile, a 3D slicer was used to evaluate the volumetric measurements, such as EDV and ESV, in the post-fusion LV and RV analysis. The ventricles in the constructed 2-D plane were traced and segmented through a segmentation module in the 3D slicer to measure the volumetrics of the EDV and ESV. Based on that, the EF for both ventricles is calculated as (EDV x ESV)/EDV. The FAC works by measuring the End-Diastolic Area (EDA) and End-systolic Area (ESA) for the RV and then calculating it as (EDA-ESA/EDA x 100). TAPSE measurement is straightforward and involves identifying the tricuspid annulus and manually placing markers at the lateral tricuspid annulus in both end-diastolic (ED) and end-systolic (ES) frames rather than mearing the longitudinal displacement between these two frames. FAC was assessed by segmenting the EBD of the RV at ED and ES and then calculating the RV area for both baes on FAC = [(EDA – ESA) / EDA] × 100, where EDA and ESA represent the End Diastolic Area and End Systolic Area, respectively. All of the assessments were conducted using recommendations from the American Society of Echocardiography Guidelines.

2.6 Statistical analysis

2.6.1 Statistical Analysis for Comparing Single 3DE vs MA3DFE AVG vs MA3DFE wav:

The appropriate statistical methods were employed to analyze the echocardiographic data acquired from manual and robotic arm scans for both volunteers and patients. The main goal was to compare the RV and LV volumes, measurements, and image quality before and after the fusion of the robotic arm echocardiographic data. Descriptive statistics provided an overview of the key measurements, including the means and standard deviations.

Since the fused and single 3DE datasets data analysis was obtained from two different software (3D Slicer and TomTec), and to determine the level of agreement between the image analysis methods, all 20 3DE data, including the volunteers and patients, had their RV volumes and measurements evaluated via TomTec and 3D Slicer. The reliability and consistency of the measurements across both software were assessed quantitatively using the intraclass correlation coefficient (ICC), which ensures the level of agreement between TomTec and 3D Slicer based on the RV measures (76).

To compare the image quality between single and fused 3D datasets, we conducted an analysis-of-variance test (ANOVA) among three groups (3DE, MSV3DE AVG, MSV3DE WAV) to calculate the mean value. Additionally, we will perform ANOVA specifically for volunteers to compare TAPSE, FAC, and EF for the RV among the three groups. Following this, we will conduct Tukey's Honest Significant Difference (HSD) test for post-hoc comparisons.

The LVEF and RVEF measurements were performed twice by the rater, and then Bland-Altman analysis was conducted to evaluate the agreement and reliability of EF measurement for both LV and RV pre- and post-fusion for volunteers. This method quantifies the bias and limits of agreement (LOA) of the RVEF among the three protocols.

2.6.2 Inter-rater Agreement Analysis:

In the user study, two echocardiographers were presented with a scaling form as part of the user study. The form used a scale of 0 to 2, where 0 indicates no difference between the two images, 1 indicates that the first image was better, and 2 indicates that the second image was better. The echocardiographers were presented with two images blindly, one representing the single 3DE and the other representing the MA3DFE. The same form is applied to both AVG and WAV fusion methods. Cohen's kappa test was used to assess the agreement between the two readers' responses.

3. Results

3.1 Study Subjects

Among the volunteers recruited for the robotic arm project, 15 healthy volunteers and five patients with no history of cardiovascular diseases were selected for the study. All of the volunteers and patients were male. They demonstrated 3-D echocardiographic apical views with as optimal an RV window as possible.

Fig 3 shows an example of the volunteer scan done using the robotic arm assistant, showcasing the multiple 3D apical view fusion by both voxel averaging and wavelet decomposition methods. In Fig 4, a similar approach is applied to the 3DE patient's data.

3.2 Image Quality

An assessment of the SNR and CNR for the 2D plane at the end-diastolic cycle was carried out using 20 volumes from single and fused images. The mean SNR value in the MA3DFE WAV group was 15.51 ± 17.69, indicating an improvement compared to other groups, including MA3DFE AVG. Even among patients, MA3DFE WAV had a higher SNR. The volunteer data had better SNR than the patients in all the groups. WAV was better in both patients and volunteers in CNR, with an 8.98 ± 9.72 CNR mean value (Table 1).

The analysis of Variance (ANOVA) performed among the volunteer datasets only— 3DE, MA3DFE WAV, and MA3DFE AVG — to assess the variation in SNR and CNR indicated no significant differences between the groups, as the Tukey HSD post hoc test showed in the p-values presented in Table 2. There was a positive difference in the WAV-AVG +6.05 (p=0.45) +4.41 (p=0.27) in the WAV-3DE groups, yet these differences did not reach statistical significance. Overall, the two fusion methods show a noticeable improvement in the image quality for both volunteers and patient data over the 3DE, but still not enough to be significant due to the small sample size.

3.3 RV and LV Volumes and Measurements

The volumes and measurements of the RV were assessed in three groups: volunteers, patients, and fused data. The mean RVEDV and ESV were slightly lower in the fused volunteer data and higher in the fused patient data compared to 3D echocardiography (3DE) (Table 3). Similarly, the LV Volumes in MA3DFE WAV were lower than single 3DE (Table 4). The RV TAPSE and FAC measured in the MA3DFE wave in both volunteers and patients were higher than the 3DE and MA3DFE average. The RVEF for volunteers in the MA3DFE wave in both AVG and WAV methods showed an increased along with the LVEF in WAV, but the difference was not statistically significant as the p-value was higher than $p>0.05$ (Table 3).

In Bland-Altman analyses, 3DE robotic arm data RVEF and LVEF, the bias among the ratings was 0.29% and 0.24%, respectively, indicating a high level of consistency. In the MA3DFE WAV ratings, both RVEF and LVEF also show high reliability, while AVG showed moderate reliability bias with 1.03% (figure 3). Between WAV and AVG, a minimal bias of 0.33% was observed for the WAV. As shown in Table 4, the ANOVA test performed in volunteers only showed significantly different results in RV FAC between 3DE-WAV ($p < 0.01$). RV TAPSE in MA3DFE WAV was positive but not significant ($p < 0.26$). The ICC test in Table 5 delineates the level of agreement in assessing the RV between TomTec and the 3D slicer, with a total of 0.98 on average, representing robust significant consistency between all measured variables across the platforms.

3.5 Inter-rater Agreement Analysis

In a study of 15 MA3DFE images, two sonographers evaluated image quality using 3DE technology. They assessed image clarity, RV anatomy, and ease of segmentation. The inter-rater agreement and Cohen's Kappa coefficients were calculated across these criteria. A Kappa coefficient of 0 indicates no agreement, 1 indicates agreement before fusion, and 2 indicates agreement after fusion.

For image clarity, both raters showed perfect agreement in both fusion methods, with $\kappa=0.85$ for WAV and $\kappa=0.7$ for AVG. The percentage of agreement with no differences in image clarity was higher (66.67%) in the WAV method. In 20% of the images, both raters agreed that post-fusion images had better quality in both methods. RV depiction showed considerable agreement in kappa values, with 80% showing no differences between WAV-3DE ratings and 26.67% among all AVG-3DE ratings. Regarding ease of segmentation and tracking, both raters had a high agreement ($\kappa=0.8$), with 80% showing no differences in tracking between WAV-3DE data. All details are shown in Table 6.

4. Discussion

4.1 Implication of Robotic-Assisted 3D Fusion

The significant role of RV function in several cardiac diseases has become continuous, and the limitation of 2DE due to the morphology and complexity of the RV is apparent (77,78). Therefore, to our knowledge, this is the first study of the robotic arm's involvement in acquiring 3DE images and integrating these images for ventricle assessment. The robotic arm's assistance in medical diagnostics has proved its effectiveness (79). Thus, addressing this critical gap in RV and LV imaging with the advancement of technology's assistance and fusion methods is promising.

The registration of echocardiography images has to be successfully applied before the 3-D fusion (51,68). Therefore, the registered apical views in our study were relatively successful, even if there were small shifts in the probe movements. A higher degree of overlap and similar acoustic windows result in better alignment and registration, which matches our data. Unlike multi-view fusion, pre-aligning methods such as optical tracking are crucial for successful fusion (58,80).

The apical 2-D planes reconstructed from the fused images are used for cardiac assessment and image quality. The feasibility of contrast media in 3-D echocardiographic assessment of the RV is not well-researched (81). Contrast media is routinely used in LV with suboptimal images to enhance the delineation (82). However, a previous study suggests a potential for more accurate RV volume measurements when using contrast-enhanced images (32). Compared to 2-D Contrast Echocardiography, 3DE fusion showed a significant improvement in LV image quality, reducing the need for contrast media in clinical practice (46). The fusion approach would be ideal in patients for whom the contrast media may not be suitable, such as those with chronic kidney disease.

We conducted a comparative analysis between the fused and non-fused versions of the data. Initially, before performing the fusion, the robotic arm 3DE showed better SNR but less CNR than the regular 3DE. The higher SNR in the volunteer’s scans indicates that robotic-assisted scans can enhance the clarity of the image. After the fusion, in the WAV method, the volunteer’s scans demonstrated better CNR than patients, owing to the combination of robotic advancements and fusion methods. Despite the non-significant improvement in image quality metrics due to the sample size, which will be discussed in the limitation section, the fusion process and the assisted robotic arm reveal the potential to overcome 3DE. The fusion methods also yielded good results in patient data acquired from 3DE.

In RV function assessment, RVEF tends to become an important diagnostic measurement, and studies have revealed that RVEF in 3D echocardiography shows more reproducible and precise measurements compared with 2D echocardiography surrogate measurements (32,83). Our results for RVEF and LVEF in the volunteer MA3DFE established constant and reliable measures, especially with wavelet proving its superiority over other fusion methods. Moreover, the mean value for TAPSE and RVEF in the robotic arm results both correlated and increased after the fusion, which agrees with the strong correlation between both measures (10). FAC, considered a surrogate to the RVEF and TASPE, increased by 2% during WAV fusion (84). These correlated increases suggest that post-fusion images capture an improvement in the cardiac volumetric and measurement output.

The ventricles EDV measured in MA3DFE AVG and WAV showed smaller mean values than the single 3-D echocardiography data. The results correspond with a study comparing the non-enchanted 3-D echocardiography to the enhanced-contrast 3-D echocardiography, and the RV EDVs were smaller (81). Even along LV, the fusion method showed smaller EDVs than contrast studies (58). Smaller EDVs in both RV and LV after fusion might indicate the precise capturing of the EBD.

4.2 Inter-rater

Assessing the RV and LV volumes and measurements for single and fused images was done using TomTec and 3Dslicer; the agreement between the two platforms was 0.98, which indicates a high inter-rater statistical analysis (ICC) value confirming solid reliability in the comparative evaluation of cardiac function and measurements. ICC is commonly used to measure agreement for continuous variables (76, 85). ICC revealed a significant agreement for post-fusion, especially with the wavelet method, which outperformed fusion by averaging in terms of LV and RV anatomy and clarity of the images. However, 0 is the highest percentage score among all the criteria, which indicates no difference. Besides that, a high Cohen's Kappa value - $\kappa=0.85$ for wavelet in clarity and $\kappa=0.77$ in RV anatomy depiction – implies a substantial agreement between the sonographers, highlighting the fusion methods' reliability in optimizing image interpretation among sonographers. However, different echocardiographers might have preferences; some prefer sharper images, and others favour soft images.

Overall, the wavelet method shows a higher potential for improved effectiveness in routine clinical practice when applied to robotic arm data. According to the raters, fusion by averaging data resulted in softer and blurrier outcomes, indicating that the wavelet method can be more effective with additional work and validation. Sonographers are highly prone to musculoskeletal injuries, especially in the upper body extremities (86). Consequently, the assistance of the robotic arm during the scan will reduce some of the sonographer's movement, reducing the prevalence of work-related musculoskeletal injuries.

4.3 Limitations and Future Directions

The study, while focusing on the application of robotic arm-assisted 3-D echocardiography fusion for evaluation of the ventricles and considered a pilot study, still has some limitations to acknowledge. The innovative source of this research was the use of robotic arm technology in echocardiography (15). Due to that, our sample size was relatively small, owing to the selective process of choosing the optimal data with acceptable image quality. Also, this led us to include patient data in the study to compare with the robotic data after the fusion. Thus, expanding the sample size and investigating RV or other chambers with the robotic arm assistant could broaden and validate the benefit of this technology. The RV-free wall in some images was difficult to trace and fuzzy due to the imaging protocol not being specifically designed for RV assessment. A specific protocol for the robotic arm could be adjusted to capture an RV-focused view, which could be addressed in further research. After fusion, the image format was incompatible with TomTec, leading to the analysis of the images in two different software, which limited the use of different measurements, such as LV and RV strain in TomTec. Developing a plugin or modifying existing software to handle various image formats is crucial. As there is no other study that used the robotic arm to integrate the RV and LV, there was an absence of a gold standard to compare our results. With the expansion of the robotic arm project, recruiting volunteers into CMR will act as a strong reference for the validation of robotic data. The study was only conducted at one center, which may limit the generalization of the results. Future studies among different centers, volunteers, and patient groups are recommended. Addressing these limitations is important since this path is new, and further research can improve and enhance robotic arm technology's involvement in medical imaging.

5. Conclusion

This pilot study used robotic arm-assisted data to track the transducers and align the 3-D echocardiography images. Averaging and wavelet-based methods performed an apical-to-apical registration followed by single-view fusion. The enhancement in the images after fusion suggests an increase in image quality. Although the small sample size improvements are noted in the RV and LV quantifications, they are still not significant. Nevertheless, conducting additional studies with larger groups and applying ML to automate RV and LV integration could enhance cardiac diagnostics and sonographer well-being.

6. Chapter 2 Tables and Figures

Figure 1 A comparison of three types of 3D echocardiography (3DE) taken from a robotic: (top) a single non-fused standard apical 3DE volume; (middle) a multi-single apical view fused volumes by averaging; (bottom) a multi-single apical view fused volume.

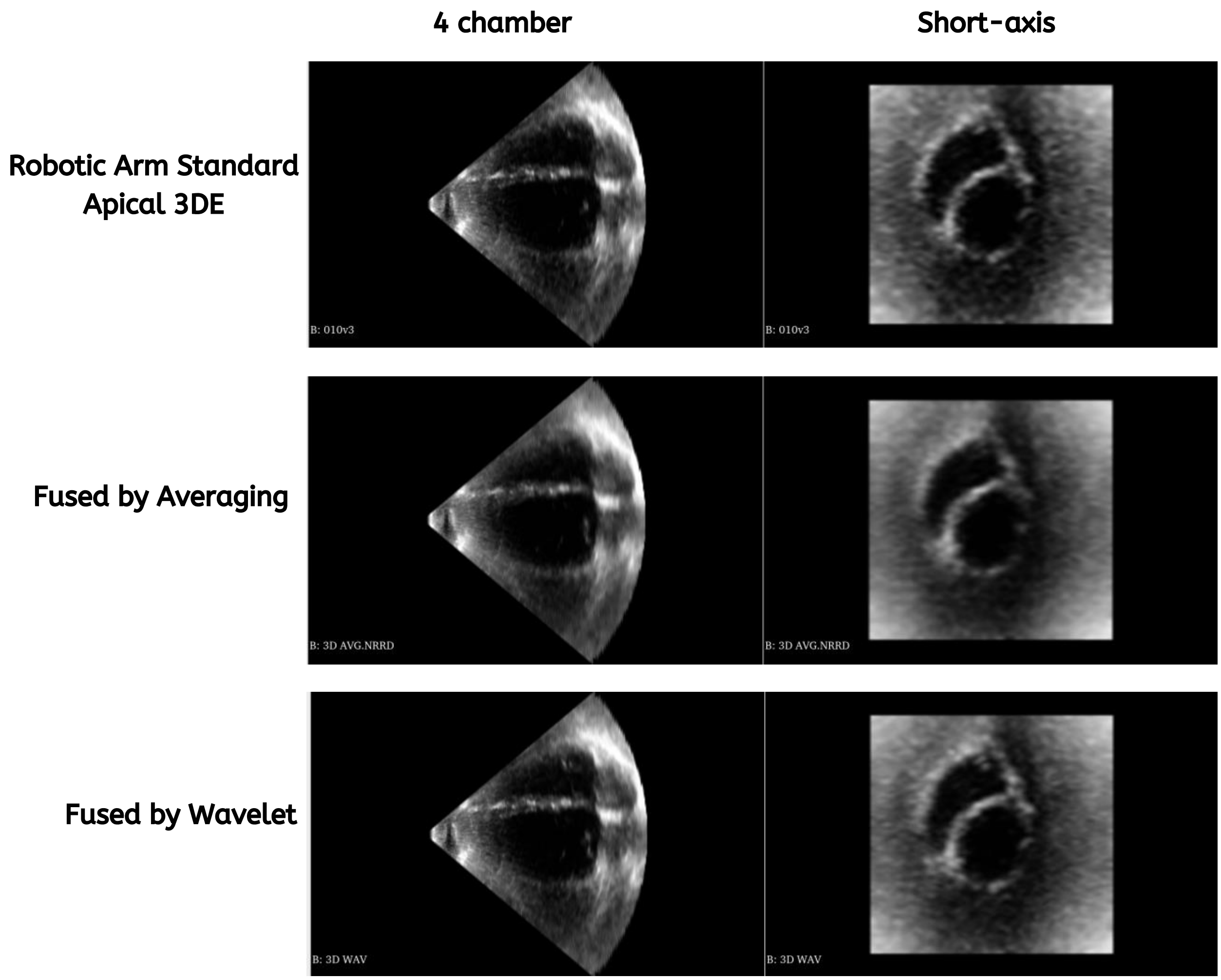


Figure 2 A comparison of three types of 3D echocardiography (3DE) taken from patients: (top) a single non-fused standard apical 3DE volume; (middle) a multi-single apical view fused volume by averaging; (bottom) a multi-single apical view fused volume by wavelet.

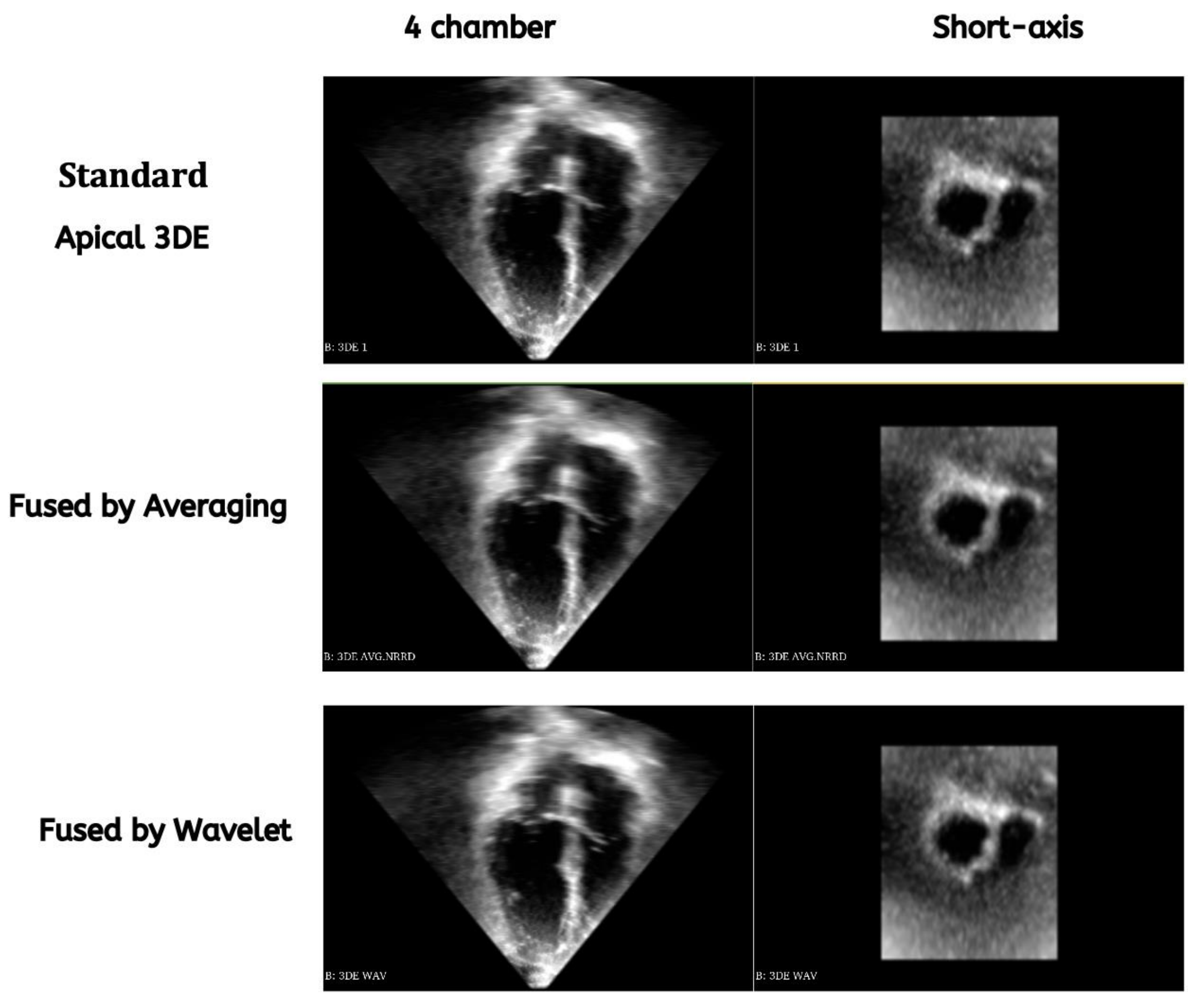


Table 1 Comparative SNR and CNR for Robotic Arm and Manual Echo Before and After Fusion.

Variables	3DE (n=20)		MA3DFE WAV (n=20)		MA3DFE AVG (n=20)	
	Vo (n=15)	Pt (n=5)	Vo (n=15)	Pt (n=5)	Vo (n=15)	Pt (n=5)
SNR	11.02 ± 12.52	7.64 ± 7.69	15.51 ± 17.69	11.94 ± 7.91	14.54 ± 15.26	9.54 ± 7.80
CNR	4.99 ± 4.47	8.16 ± 6.53	8.98 ± 9.72	8.38 ± 7.37	5.88 ± 5.52	6.13 ± 5.62

Values are given as mean ± SD.

3DE= Three-Dimensional Echocardiography; MA3DFE= Multiple Apical Single-View Three-Dimensional Fusion Echocardiography; SNR= Signal to Noise Ratio; CNR= Contrast to Noise Ratio; WAV= Wavelet Fusion; AVG= Averaging Fusion; Vo= Volunteers scan (robotic arm); Pt= Patients scans (non-robotic).

Table 2 Measurements of image quality in volunteers: analysis of variance with Tukey honest significant difference post hoc correction.

	CNR	**SNR**
AVG – 3DE	-1.64 (p = 0.62)	+7.68 (p = 0.51)
WAV – 3DE	+4.41 (p = 0.27)	+9.56 (p=0.43)
WAV – AVG	+6.05 (p = 0.10)	+1.45 (p = 0.87)

SNR= Signal to Noise Ratio; CNR= Contrast to Noise Ratio.

Table 3 Right ventricle volumes and measurements for MA3DFE.

Variables	3DE (n=20)		MA3DFE WAV (n=20)		MA3DFE AVG (n=20)	
	Vo (n=15)	Pt (n=5)	Vo (n=15)	Pt (n=5)	Vo (n=15)	Pt (n=5)
EDV (mL)	122.5 ± 9.80	115.4 ± 11.72	121.92 ± 11.05	115.5 ± 11.42	120.58 ± 10.24	116.82 ± 10.18
ESV (mL)	61.4 ± 7.42	55.82 ± 9.86	59.64 ± 9.28	55.1 ± 9.56	59.16 ± 8.89	55.56 ± 10.45
EF (%)	49.97 ± 3.47	52.15 ± 4.43	51.47 ± 4.12	52.57 ± 4.47	51.12 ± 4.05	51.15 ± 3.88
TAPSE (mm)	18.49 ± 1.02	18.2 ± 0.43	19.06 ± 1.11	18.46 ± 0.711	18.5 ± 1.15	18.2 ± 0.89
FAC (%)	42.11 ± 2.35	44.11 ± 3.79	44.29 ± 2.70	44.85 ± 3.49	42.7 ± 3.22	42.59 ± 5.12

Values are given as mean ± SD.

3DE= Three-Dimensional Echocardiography; MA3DFE= Multiple Apiacl-View Three-Dimensional Fusion Echocardiography EDV=End-Diastolic Volume; ESV= End-Systolic Volume; TAPSE= Tricuspid annular plane systolic excursion; FAC= Fractional Area Change; EF= Ejection Fraction; WAV= Wavelet Fusion; AVG= Averaging Fusion; Vo= Volunteers scan (Robotic arm); Pt= Patients scans.

Table 4 Left ventricle volumes for Robotic Arm (volunteer) MA3DFE.

Variables	3DE (n=15)	MA3DFE WAV (n=15)
EDV (mL)	86.7±14.7	85.9±14.3
ESV (mL)	35.5±5.5	34.4±5.6
EF (%)	58.8±5.0	59.4±3.2

Values are given as mean ± SD.

3DE= Three-Dimensional Echocardiography; MA3DFE= Multiple Apical Single-View Three-Dimensional Fusion Echocardiography EDV=End-Diastolic Volume; ESV= End-Systolic Volume; EF= Ejection Fraction; WAV= Wavelet Fusion.

Table 5 Measurements of TAPSE, FAC, RVEF, and LVEF in volunteers: analysis of variance with Tukey honest significant difference post hoc correction.

	TAPSE	**FAC**	**RVEF**	**LVEF**
3DE - AVG	+0.014 (p < 0.99)	+0.86 (p< 0.64)	+1.16 (p<0.69)	-
3DE - WAV	+0.620 (p < 0.26)	**+2.37 (p < 0.01)**	+1.50 (p < 0.54)	+1.34 (p < 0.54)

TAPSE= Tricuspid annular plane systolic excursion; FAC= Fractional Area Change; RVEF= Right ventricle ejection fraction; LVEF= Left ventricle ejection fraction.

Figure 3 Bland-Altman plots for various echocardiographic measurement methods of ventricles ejection fraction (EF). Robotic Arm 3DE RV (Upper Right), fusion by wavelet-based RV (Upper Left), fusion by averaging RV (Middle Left), fusion by wavelet-based LV (Middle Right), Robotic Arm 3DE LV (Lower Middle).

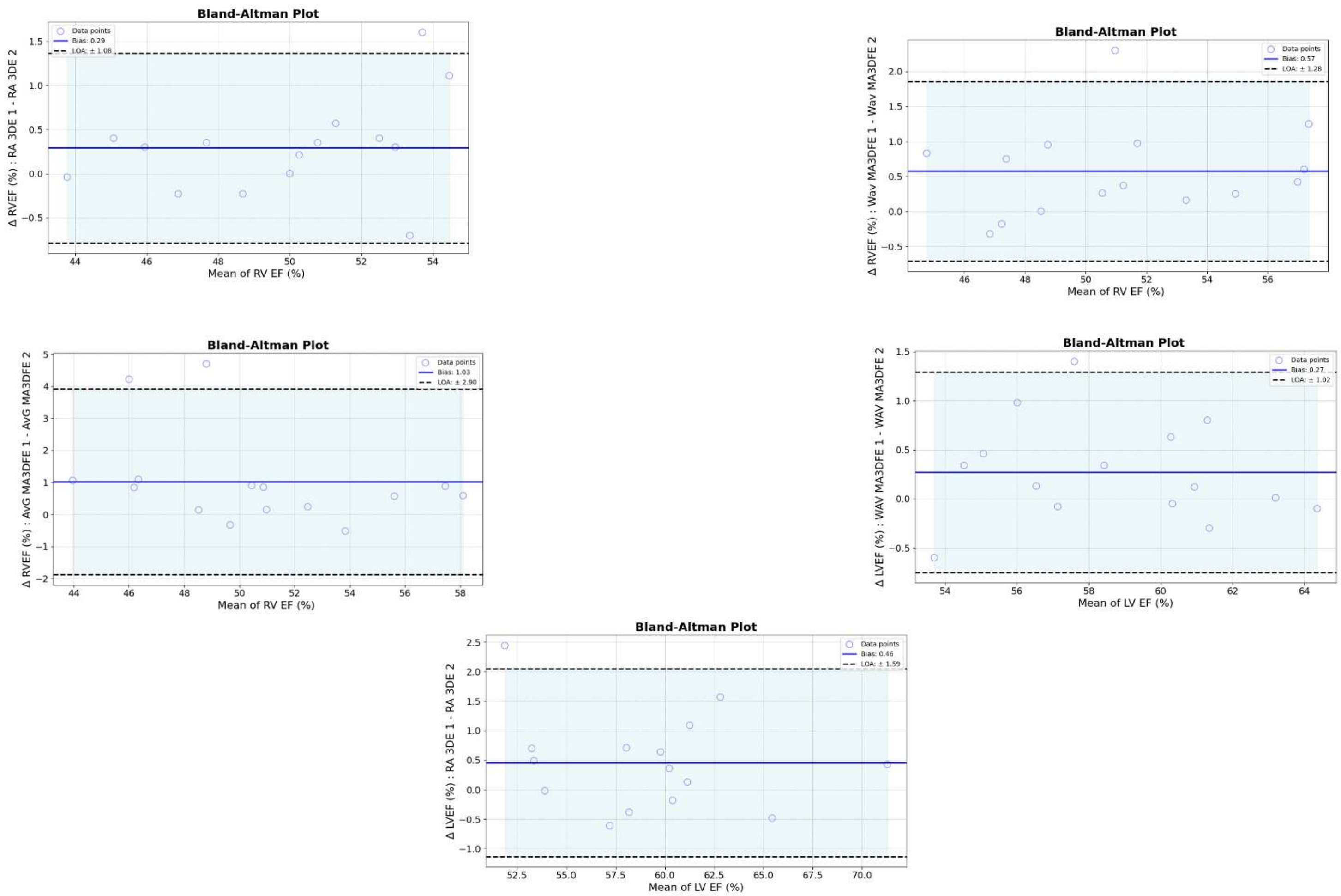


Figure 6 Intraclass Correlation Coefficients (ICCs) for Agreement Between RV Volumes and Measurements from 3D Slicer and TomTec.

Variables	**ICC-Average Measures**		
	Values	95% CI	P Value
EDV	0.998	0.995, 0.999	<0.001
ESV	0.997	0.994, 0.999	<0.001
EF	0.968	0.924, 0.982	<0.001
TAPSE	0.980	0.950, 0.986	<0.001
FAC	0.990	0.975, 0.994	<0.001
Total	**0.987**		

ICC: Intraclass Correlation Coefficient; EDV=End-Diastolic Volume; ESV= End-Systolic Volume; TAPSE= Tricuspid annular plane systolic excursion; FAC= Fractional Area Change; EF= Ejection Fraction.

Table 7 Inter-rater percentage of agreement and Cohen's k coefficient between raters of MA3DFE and single robotic arm 3DE data sets in the visual quality assessment of the MA3DFE images.

	AVG-3DE **n=15** **Rater 1 Rater 2**	**% of the rating**	**WAV-3DE** **n=15** **Rater 1 Rater 2**	**% of the rating**
Image Clarity	80% κ=0.7	0=40% 1=13.33% 2=20%	93.33% κ=0.85	0=66.67% 1=6.67% 2=20%
Accuracy in Depicting Ventricles Anatomy	80% κ=0.7	0=26.67% 1=26.67% 2=26.67%	93.33% κ=0.77	0=80% 1=6.67% 2=6.67%
Ease of interpretation (Segmentation)	86.67% κ=0.6	0=73.33% 1=6.67% 2=6.67%	93.33% κ=0.8	0=80% 1=0% 2=13.33%

0= No differences; 1= Before fusion; 2= After fusion; MA3DF3= Multiple Apical 3-Dimensional fusion echocardiography; 3DE= 3-Dimensional echocardiography

Chapter Three: Future Directions and Conclusions

1. Future Directions

1.1 Using Multi-Views for RV Assessment

The RV is challenging to image by echocardiography, and it is not well shown in most of the standard echocardiography protocols except for the RV-focused view. To maximize the benefits of multi-view 3D fusion echocardiography (M3DFE) for the RV, fusing the RV from different acoustics windows could provide significant enhancements. For instance, integrating the parasternal long axis with an RV-focused view might provide a clear view of the RV-free wall and outflow tract. Similarly, an apical 4-chamber view with an RV focus may improve the visualization of the RV-free wall, inflow tract, and apex. These examples will focus on increasing the chance of a comprehensive covering of the RV anatomical features.

One study assessed the LV from different acoustic windows—parasternal and apical—using the M3DFE approach, resulting in enhanced EBD definition and increased FOV (58). Future studies should, therefore, aim to refine protocols for capturing the RV from different views and fusing these acquisitions to further enhance the RV image quality and assessments.

1.2 Automation of the 3D fusion

Nowadays, deep learning (DL) has become an important tool in medical research, and it has shown promising results in measuring and analyzing echocardiography images (87). In the post-processing context, the DL role in echocardiography has been investigated (88,89). However, incorporating DL and ML algorithms in the M3DFE can greatly improve fusion automation. While no study has yet directly applied DL or ML in multi-view 3D echocardiography fusion, a recent study used a novel transformer-based multimodal fusion algorithm. This algorithm, when applied to detect amyloidosis using echocardiography images – Parasternal long-axis and Apical 4 chambers – along with patient demographics, lab tests, and cardiac metrics, demonstrated high accuracy results (90). This proves that there is a potential for the DL and ML to have a role in improving the accuracy of complex fusion methods. Exploring these advanced computational approaches to streamline the M3DFE process to enhance the reliability of cardiac imaging should be investigated further.

1.3 Cross-Modality Learning for Improved RV Visualization

In medical imaging, DL approaches demonstrated superiority in performance compared to traditional methods. This leads to cross-modality learning (CML), which can be invaluable. CML involves gathering data from different medical imaging modalities, such as CT, Magnetic Resonance imaging (MRI), and echocardiography. Each modality has its advantages, and combining these pros makes it possible to create a more comprehensive representation of RV anatomy. For example, MRI provides a high-resolution and detailed anatomical view, leading to the creation of precise RV contours. Moreover, the contour later can be applied to the M3DFE data to improve the segmentation of the RV. A study using annotated ultrasound from CT images showed an improvement in the segmentation performance in the Left Ventricular (LV) (91). Therefore, further studies can adapt the enhancement of the RV annotation by using MRI-derived contours.

1.4 Increasing Automation and Reducing Work-Related Injuries

The implementation of the robotic arm in echocardiography proved its ability to increase the accuracy of the alignment when the robotic arm tracking information was used (63). Currently, the robotic arm is moved semi-automatically, with the sonographer's guidance, into the scanning location. This will reduce work-related injuries among the sonographers; grabbing the probe with the wrist movement during the scan can last 20 minutes and can lead to stains or stiffness (86). By automating probe positioning and ensuring optimal pressure and patient contact, manual interaction with the robotic arm will be reduced.

Further studies should explore the impact of assisted robotic arm echocardiography on sonographers' work-related injuries. Studies that gather surveys or conduct interviews with sonographers who operate the robotic arm can offer valuable insights. Moreover, a comparison of traditional and robotic-assisted echocardiography in clinical trials can demonstrate the benefits of automation, improving workflow and reducing physical strains.

1.5 Enhancing the Robotic Arm for Echocardiography

It is feasible to create a low-cost and commercially available robotic arm system for ultrasound (74). However, the robotic assistant must be user-friendly and ergonomically designed to be adopted in clinical practice. Focusing on the design of lighter and more maneuverable robotic arms should be considered in the future to make it easier for the sonographer to control and adjust the robotic arm movement. Many current robotics systems are powered by cables, which can limit their range of motion. Future wireless technology will enhance the practicality of robotics in clinical practice and tele-operation.

While the robotic arm we used in our study was tested on volunteers, we aim to expand this innovation to patients and investigate further gaps. Considering the scope is new, other post-processing approaches can be applied and tested for the robotics arm data, such as image registration and segmentation with different DL or ML algorithms.

2. Conclusion

Cardiac imaging now has the potential for improvements in its volume assessment and measurement quantifications with the appearance of technology such as the robotics arm assistant, followed by the fusion of different 3DE volumes. This has been accomplished by using a semi-automatically robotic arm assistant to capture different 3D echocardiographic apical views and fuse them together using fusing by averaging and wavelet-based methods. The robotics integration in echocardiography proved its benefits in alleging the data, which helped with the overall image quality enhancements and the successful fusion.

The future directions for M3DFE with robotic assistants are promising and include several innovative approaches to improving LV and RV capturing and overall cardiac imaging. Considering DL and ML algorithms for post-processing, fusing the RV from different designated windows for compressive view, and leveraging cross-modality learning can add valuable contributions to the scope, along with refining the use of robotic arms and increasing automation in favour of reducing work-related injuries. These advancements can be seen in their way to clinical practice with previous literature support, the promising results in this thesis, further studies, and validations, leading to better patient care.

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