Multi-view Three-Dimensional Fusion Echocardiography System:
First Pilot Study in Patients

by

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A thesis submitted in partial fulfillment of the requirements for the degree of

Master of Science

in

Translational Medicine

Department of Medicine

University of Alberta

Abstract

Background: Multi-view three-dimensional fusion echocardiography (M3DFE) has been shown to improve image quality compared to standard three-dimensional echocardiography (3DE). The clinical application however has been limited due to the fact that suitable recordings require longer breath holds and very stable patient positioning which is not applicable to many patients. To address these limitations, an advanced Three-Dimensional (3D) fusion system has been developed. This thesis examines the hypothesis that this advanced M3DFE system can be successfully applied for the measurement of left ventricular (LV) function in patients with heart failure treated with cardiac resynchronization therapy (CRT) devices.

Methods: Patients with heart failure treated with CRT devices were approached for study enrollment during their standard two-dimensional contrast echocardiography (2DCE) visit. The M3DFE protocol was applied after the standard 2DCE protocol and consisted of 3 phases: recording, alignment and fusion. Participants' datasets were classified into three different groups: single-view three-dimensional echocardiography (S3DE), M3DFE, and standard 2DCE. The percentage of participants undergoing successfully each phase of the protocol was evaluated. Visual LV endocardial border definition (EBD) of M3DFE and S3DE datasets was graded by 2 independent readers. Each reader's M3DFE EBD score was compared to S3DE EBD score. The global and regional LV systolic function of M3DFE datasets was evaluated by 2 readers and compared to standard 2DCE.

Results: Twelve heart failure patients treated with CRT devices were enrolled in the study. 11/12 (91.7%) participants successfully underwent the recording phase of the M3DFE protocol. 99/108 (91.7%) S3DE datasets could be successfully recorded. The alignment and fusion software could be successfully applied in 96/108 (88.9%) of S3DE datasets. The mean improvements in EBD score by the 2 independent readers in the

M3DFE group were as follows: 24.0±3.3 (95% CI, 19 and 27) and 24.3±3.8 (95% CI, 17 and 28). The corresponding values in the S3DE group were 11.7 ±6.0 (95% CI, 3 and 24) and 10.5 ±5.6 (95% CI, 2 and 24), $p<0.01$). The mean and standard deviation of the LV ejection fraction (EF) was 39.5±14.8 by reader 1 in M3DFE group, 37.7±13.1 by reader 2 in M3DFE group, and 40.30±15.7 by the reader of the standard 2DCE. The EF measured on M3DFE datasets was not significantly different from that measured by standard 2DCE ($p > 0.05$). The percentage of agreement in assessing the degree of consistency among the 2 readers in evaluating the regional LV systolic function was 83.3% between the 2 readers of the M3DFE group, 76.5% between reader 1 of the M3DFE group and the reader of the standard 2DCE group, and 74.2 % between reader 2 of the M3DFE group and the reader of the standard 2DCE group.

Conclusion: The M3DFE protocol is feasible in patients with heart failure treated with CRT devices. The LV EBD score in M3DFE datasets is superior to S3DE and the assessment of LV systolic function in M3DFE group is comparable to 2DCE group.

Preface

This thesis is an original work by Victoria Sarban as part of the requirements for Master of Science in Translational Medicine at the University of Alberta. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Health Research Ethics Board, Project Name " Multi-view 3D fusion echocardiography in patients with cardiac resynchronization therapy (CRT) devices - pilot study ", Principal Investigator: Dr. Harald Becher, Study ID: MS1_Pro00084288 originally approved on October 23, 2018, renewed on October 1, 2019, expires on October 1, 2020.

Acknowledgements

This thesis is a product of a wonderful team I was fortunate to be part of. I would like to genuinely thank my academic role-model and mentor, Dr. Harald Becher, for introducing me to the rich and profound field of fusion echocardiography, which integrates a vast knowledge and expertise from cardiac ultrasound physics to cardiac physiology to cardiac image processing and post-processing. I would like to thank him for his confidence and trust in me to take on this challenging topic and for providing me with the intellectual freedom to explore, to learn, and to solve problems. His expertise and guidance have made my graduate studies a fascinating journey, and his support and enthusiasm have made it an unforgettable experience. It has been an honor to have him be the defining part of my academic career, and I could not have asked for a greater mentor.

I am deeply thankful to my research supervisors, Dr. Miriam Shanks and Dr. Kumar Punithakumar for sharing their passion and expertise with me. I am grateful for their continuous guidance and encouragement. It is hard to imagine how I could have completed my research without their valuable support. My gratitude also goes to Dr. Soori Sivakumaran for his willingness to participate as a member of the supervisory committee and to Dr. Surita Sidhu for her willingness to participate as an external examiner. I will always remember your contribution to my education.

I would very much like to acknowledge Eila Mirhadi, ABACUS Echo Research Lab, Adult Clinical Echo Lab and the Mazankowski Alberta Heart Institute for creating a supportive and wonderful environment to conduct my research. I feel blessed to be a part of this delightful team. I would like to acknowledge the statistical support received from Dr. Hayrapet Kalashyan and Consultation and Research Services Platform at The Alberta' SPOR Support Unit. I would like to extend my gratitude to the Canadian Foundation of Innovation and Canadian Institutes of Health Research and the Heart and Stroke Foundation for funding the 3D Fusion project.

I would like to take the opportunity to thank my children, Beatrice and Nick, for their unconditional love, patience, understanding and support. I feel blessed to have such wonderful kids. Last, but not least, I would like to thank my parents, siblings and friends for their love and support in overcoming all the challenges encountered in my life. I am grateful for their continuous encouragement in pursuing further and higher goals. I would not be who I am, without them.

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List of Abbreviations

2DCE	Two-Dimensional Contrast Echocardiography
3DE	Three-Dimensional Echocardiography
AHA	American Heart Association
ASE	American Society of Echocardiography
Ap	Apical view
ApSt	Apical Standard View
ApNSt	Apical Non-Standard View
Ap4Ch	Apical 4 Chamber View
Ap2Ch	Apical 2 Chamber View
CNR	Contrast-to-Noise Ratio
DICOM	Digital Imaging and Communications in Medicine
EBD	Endocardial Border Definition
ECG	Electrocardiogram
EDV	End-Diastolic Volume
EF	Ejection Fraction
ESV	End-Systolic Volume
EW	Equal Weighting
FB	Feature-Based
FOV	Field of View
HDR	High Dynamic Range
IB	Intensity-Based
IQ	Image Quality
LV	Left Ventricle
MAZ	Mazankowski Alberta Heart Institute
MeSH	Medical Subject Headings
M3DFE	Multi-view Three-Dimensional Fusion Echocardiography
MW	Multi-Window
NRRD	Nearly Raw Raster Data

PC	Personal Computer
PSLA	Parasternal Long Axis View
PSA	Parasternal Short Axis
ROI	Region of Interest
S3DE	Single-view Three-Dimensional Echocardiography
SOC	Standard of Care
SNR	Signal-to-Noise ratio
SVV	Siemens Volume Viewer
SW	Single-Window
VOV	Volume of View
WB	Wavelet-Based
WMA	Wall Motion Assessment

Chapter One: Background and Literature Review

1. Current Use and Limitations of Two-Dimensional Echocardiography in LV systolic function assessment

Two-Dimensional Echocardiography (2DE) refers to a "flat" tomographic technique that uses horizontal (X) and vertical (Y) dimensions in a computer space. It is the most commonly used method due to its availability, safety, non-invasiveness, portability, versatility and less costly. However, the quantitative assessment of systolic function with 2DE is limited by geometrical assumptions about left ventricular (LV) shape, foreshortening, malrotation, angulation and spatial interpolation among available views (1-7). Another limitation is suboptimal 2DE image quality in patients with poor acoustic windows (8-9). Because of geometrical assumptions, LV volumetric measurements may be inaccurate and not reproducible (1, 4-7, 10). Currently, the two-dimensional contrast echocardiography (2DCE) is the preferred method at our institute for assessing LV systolic function in patients with heart failure treated with cardiac resynchronization therapy (CRT) devices (4-7, 11). This method involves an intravenous (IV) ultrasound contrast injection to enhance the signal intensity of the blood in the LV cavity, however it is subject to similar limitation as 2DE and the endocardial border definition (EBD) is often poor in the basal segments in particular at the mitral annulus (12, 13). Even though the 2DCE method seems to provide more accurate and reproducible LV volumes compared to 2DE, its use is limited due to the invasiveness and costs related to the IV ultrasound contrast injection.

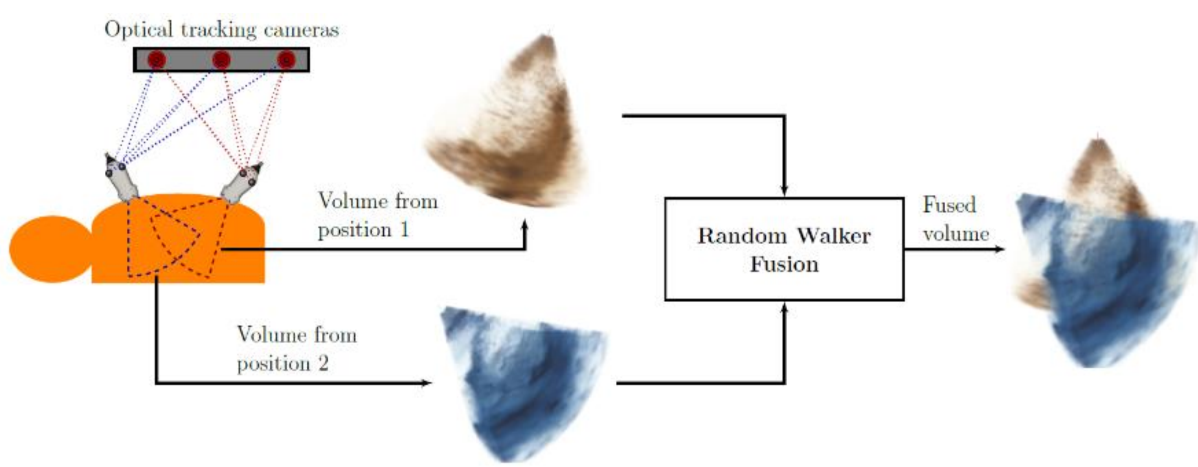
2. Current Use and Limitations of Three-Dimensional Echocardiography in LV systolic function assessment

According to the American Society of Echocardiography (ASE), Three-Dimensional Echocardiography (3DE) is currently the method of choice for left ventricular systolic function evaluation (4-7). 3DE is a real-time volumetric technique that adds the depth (Z) dimension to the 2DE method. This third dimension allows acquisition, visualization and quantification of volumetric datasets. A major advantage of 3DE is the improvement in the accuracy and reproducibility of LV volume measurement by eliminating geometric assumptions and errors caused by foreshortened views (4-7, 14). One of the challenges 3DE faces at the moment is poor image quality. Poor image quality is characterized by poor image contrast, increased image noise and increased ultrasound attenuation which limits visualization of well-defined LV endocardial border and therefore introduces errors into assessing LV systolic function. One reason is due to weakly reflected signals from important interfaces. A second reason is lower line density and therefore lower spatial resolution than 2DE. In order to accurately assess LV systolic function, end-diastolic volumes (EDV) and end-systolic volumes (ESV) need to be measured. However, the limited temporal resolution can result in failure to record true EDV and ESV. The temporal resolution can be improved by narrowing the 3D sector and stitching multiple subvolumes, although this could lead to stitching artifact. Another limitation is the inability to visualize the entire enlarged heart often present in patients treated with CRT due to narrow field of view (FOV). The reason for reduced FOV is part of trade-off to maintain a balance between temporal and special resolution. All of these limitations can introduce errors into LV systolic function assessment.

3. Addressing the Limitations of Three-Dimensional Echocardiography in LV systolic function assessment

There have been efforts in overcoming 3DE limitations (3, 15-25), however no feasible system has been used in patients. A multi-view fusion echocardiography (M3DFE) prototype for aligning and fusing single-view 3D echocardiography (S3DE) datasets from different complementary acoustic windows has been developed and tested in healthy volunteers (16, 19-23). The M3DFE concept is displayed in Chapter 1, Figure 1 (15). For simplicity only one parasternal and one apical dataset are displayed.

Chapter 1, Figure 1: M3DFE Concept: Optical tracking and image dataset processing



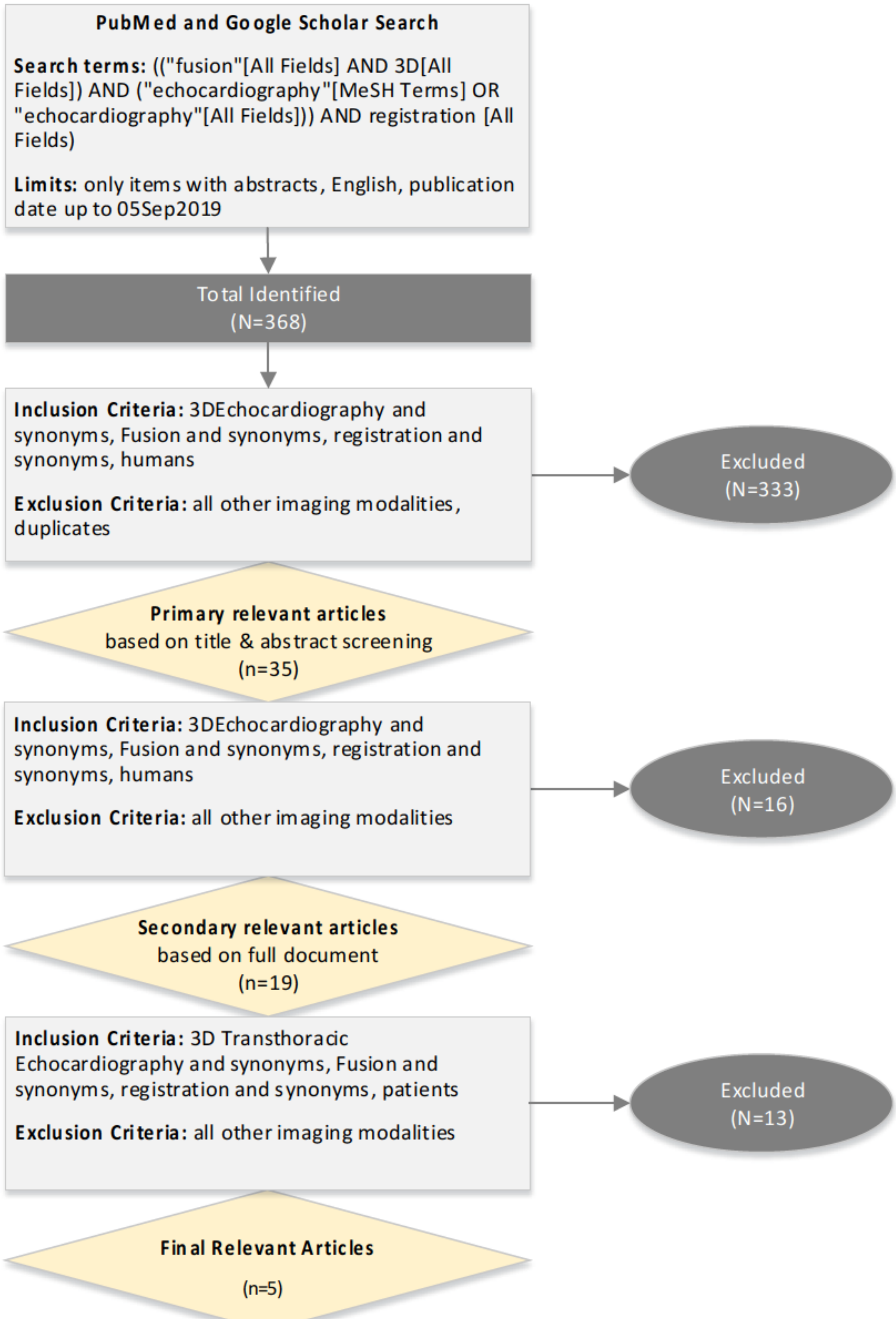
This project addresses the next step of the M3DFE program, assessing the feasibility of M3DFE protocol in patients with heart failure treated with CRT devices.

4. Review of the Literature

This section reviews the currently available literature related to the M3DFE application in patients.

A PubMed and Google Scholar search for articles relevant to M3DFE was performed. Searches included the keywords and corresponding MeSH for fusion, 3D echocardiography and registration. The search was limited to only items with abstracts, English, publication date up to 05Sep2019. A total of five relevant articles reported studies in patients. Although there were several articles on the studies in phantom and volunteers, of these articles, only one paper reported 3D fusion from distant apical and parasternal windows (26). No volumetric analysis was performed on M3DFE datasets. Only data on image quality was revealed in 2 patients. The other 4 studies were all performed using multiple views from an apical window (18, 27-29). The visual image quality and SNR of fused datasets were compared to non-fused datasets. (Chapter 1, Figure 2 and Chapter 1, Table 1).

Chapter 1, Figure 2: Literature Search process for studies on M3DFE



Chapter 1, Table 1: Relevant articles on M3DFE identified through literature search process

Author (s)	Year	Population	US system used	Alignment by					Fusion		End Points		Pertinent findings
				breath hold	ECG gating	patient movement tracking	transducer tracking	image registration	Fusion rule	Acoustic windows/ views	Image quality	LV Volumes	
D. Augustine et al.	2015	24 patients referred to DSE	Philips IE33/X 5-1	+	-	-	-	+	WB	SW/ ApSt	+	-	Improved CNR, EBD & WMA in fused vs non-fused datasets; no sign diff in 2DCE
G. Piella et al.	2013	1 CRT patient	Philips IE33/X 3-1	+	-	-	-	+	FB	SW/ ApSt	-	-	Improved consistency of strain quantification in fused vs non-fused datasets
C. Yao et al.	2011	2 patients	Philips IE33/X 3-1	+	-	-	-	+	FB	MW/ ApSt PSLA	+	-	Improved visual IQ, CNR in fused vs non-fused datasets
C. Szmigielski et al.	2010	16 patients referred to 2DE	Philips IE33/X 3-1	+	-	-	-	+	EW	SW/ ApSt	+	+	Improved EBD, CNR & completeness of fused vs non-fused datasets
P. Soler et al.	2005	8 patients	Philips Sonos 7500/ X3-1	-	-	-	-	+	IB	SW/ ApSt	+	-	Improved Contrast, SNR, FOV in fused vs non-fused datasets

2DCE: two-dimensional contrast echo, Ap: apical view, CNR: contrast-to-noise ratio, EBD: Endocardial border definition, EDV: end diastolic volume, ESV: end systolic volume, EF: ejection fraction, EW: equal weighting, FB: feature-based, FOV: field of view, IB: intensity-based, IQ: visual image quality,, LV: left ventricle, M3DFE: multi-view three-dimensional fusion echocardiography, MW: multi-window, PSLA: parasternal long axis view, SNR: signal-to-noise ratio, SW: single-window, WB: wavelet-based, WMA: wall motion assessment, "-" not described, "+" described

Chapter Two: Multi-view Three-Dimensional Fusion Echocardiography System: First Pilot Study in Patients

1. Study Hypothesis

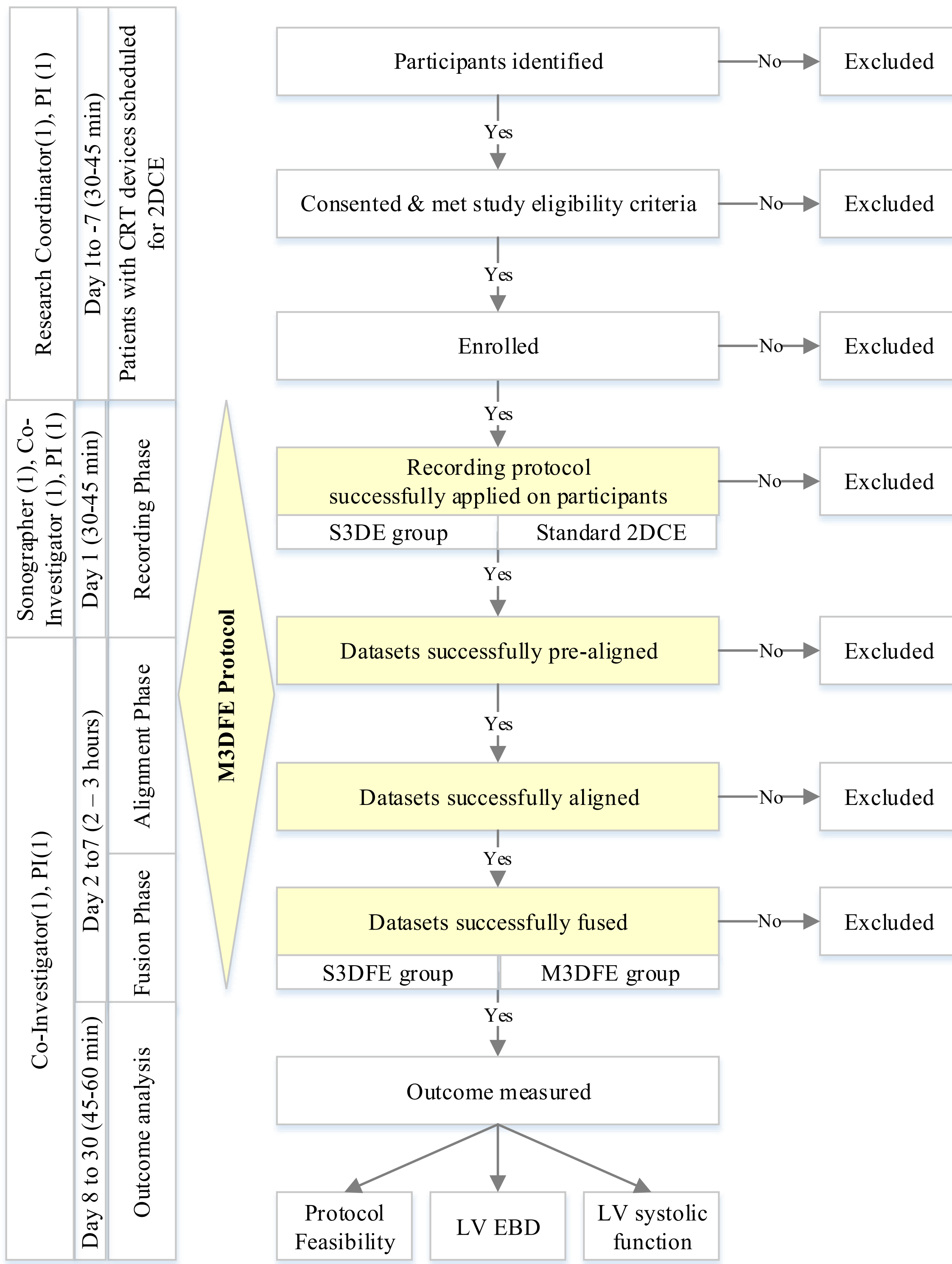
The primary hypothesis is that the multi-view three-dimensional fusion echocardiography (M3DFE) recording phase of the protocol can be successfully applied in >90% of the study patients and that the M3DFE alignment and fusion software can be successfully applied in >80% of the study datasets. The secondary hypothesis is that the left ventricular (LV) endocardial border definition (EBD) score in M3DFE group is superior to single-view three-dimensional echocardiography (S3DE) group. We also hypothesize that the LV systolic function assessment in M3DFE group is comparable to standard two-dimensional contrast echocardiography (2DCE) group.

2. Methods

2. 1 Study design

The study was conducted at the Mazankowski Alberta Heart Institute in Edmonton, AB, Canada from January to September 2019. This study was approved by the University of Alberta Health Research Ethics Board. This was an observational prospective pilot study with the primary aim to demonstrate that M3DFE protocol application in heart failure patients treated with CRT devices is feasible (Chapter 2, Figure 1).

Chapter 2, Figure 1: M3DFE study design per participant



2. 2 Participant identification and recruitment procedure

Patients with heart failure treated with CRT devices were identified before or during their standard of care (SOC) 2DCE visit at the Mazankowski Alberta Heart Institute (MAZ) by a member of the medical/technical staff involved in their care. The staff involved in their care asked participants if they were interested in learning about an ongoing research study and possibly participating in it. If the participant agreed, then the medical/technical staff involved in their care notified the research staff. The researchers then obtained written informed consent. A copy of the consent information sheet was given to the participant. The original signed informed consent form (ICF) was retained at the study site. Participants consenting and meeting all inclusion and none of the exclusion criteria were enrolled in the study (Chapter 2, Table 1).

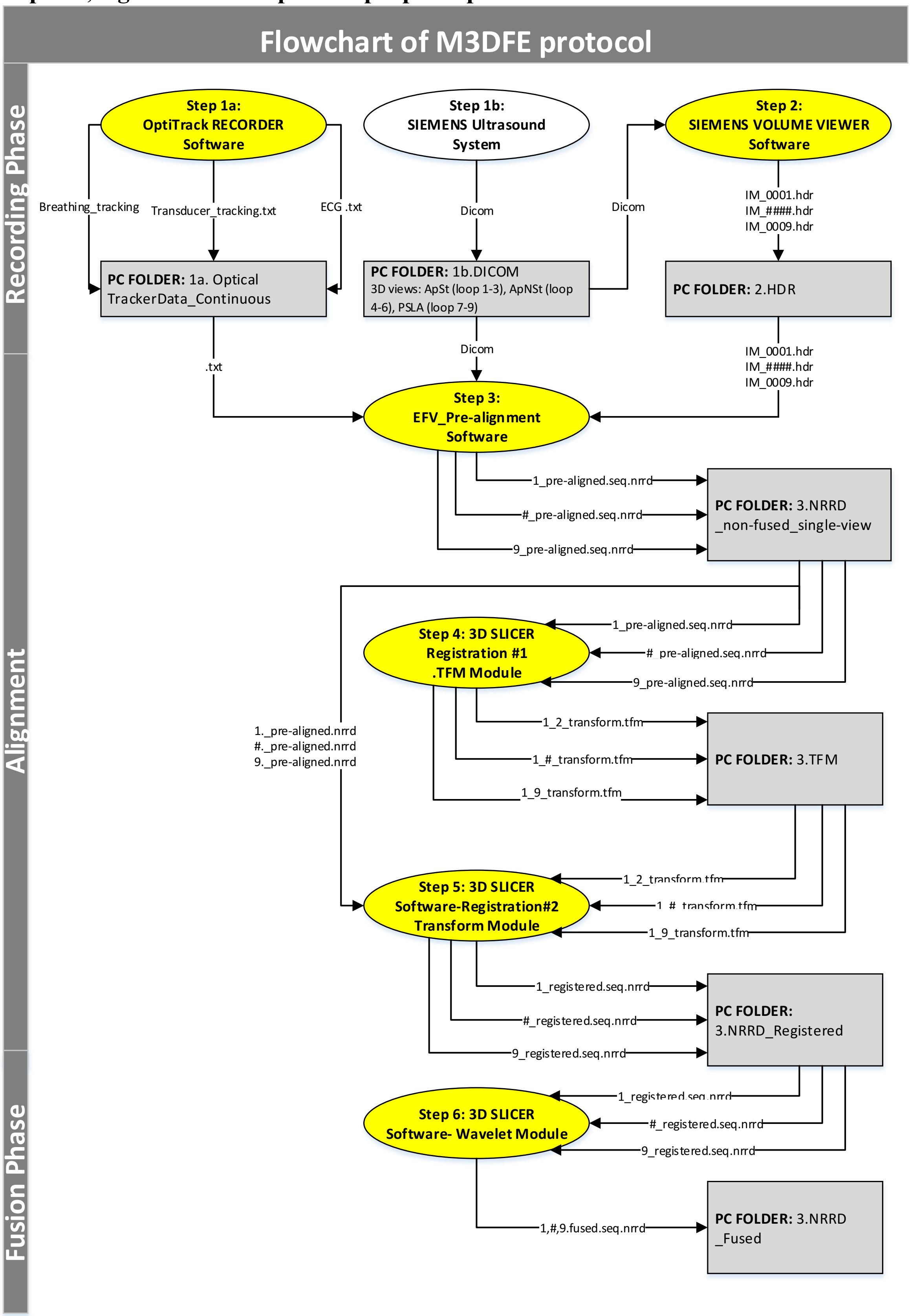
Chapter 2, Table 1: Study eligibility criteria

Inclusion Criteria	Exclusion Criteria
Patients with heart failure treated with a pacemaker CRT device and referred for a 2DCE assessment of LV function at the MAZ	Clinical condition preventing breath holding for the time of study acquisition
At least 18 years of age	Arrhythmia
Stable sinus rhythm	Unstable life-threatening or severe medical conditions
Participant has provided written informed consent	Skin reaction to medical adhesives
	Refuse to be involved in the study or unable to give valid consent

2. 3 Investigation of subjects

After enrollment, all participants, in addition to their standard 2DCE test, underwent the recording phase of the M3DFE research protocol. The M3DFE research protocol is depicted in Chapter 2, Figure 2.

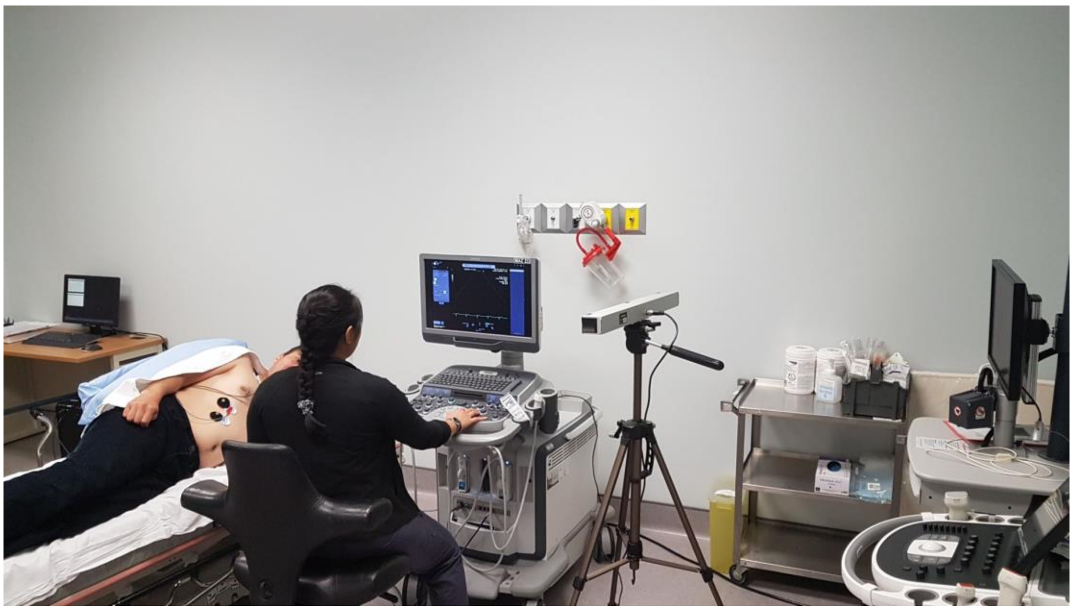
Chapter 2, Figure 2: M3DFE protocol per participant



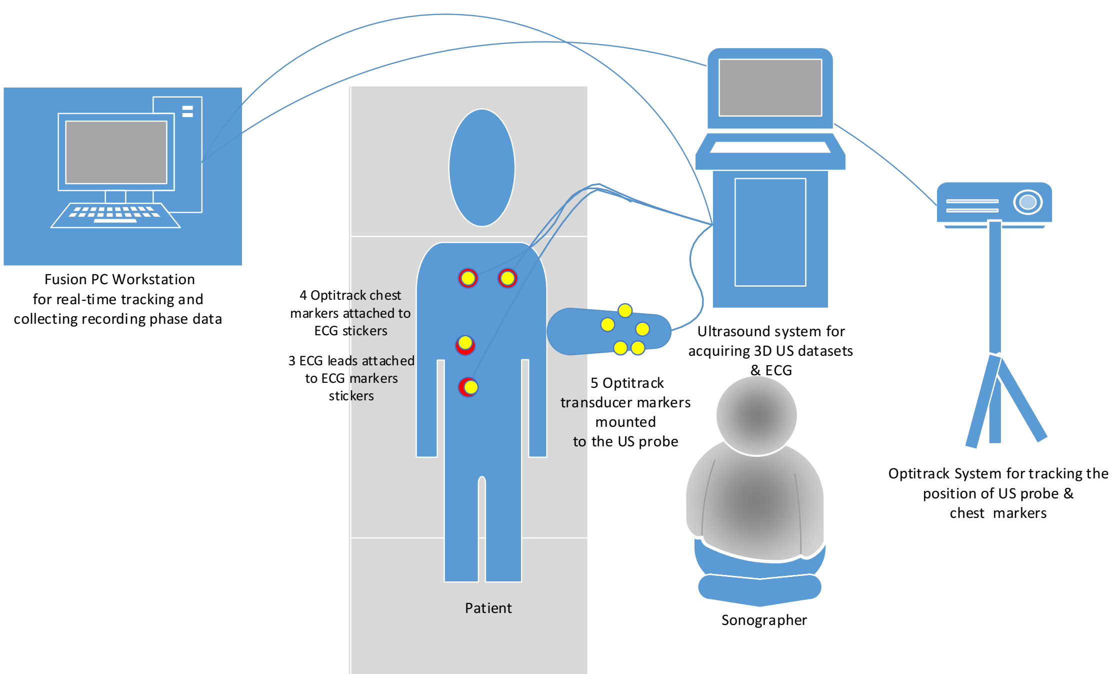
Recording Phase

Chapter 2, Figures 3 and 4 display the overall set up for the proposed M3DFE recording system where the optical cameras allowed for continuous tracking of the transducer and an ECG connection allowed for synchronization between ultrasound scans and optical recordings.

Chapter 2, Figure 3: Overall set up for the proposed M3DFE recording system



Chapter 2, Figure 4: Schematic diagram showing the components of the M3DFE recording system.



The recording phase included 2 steps.

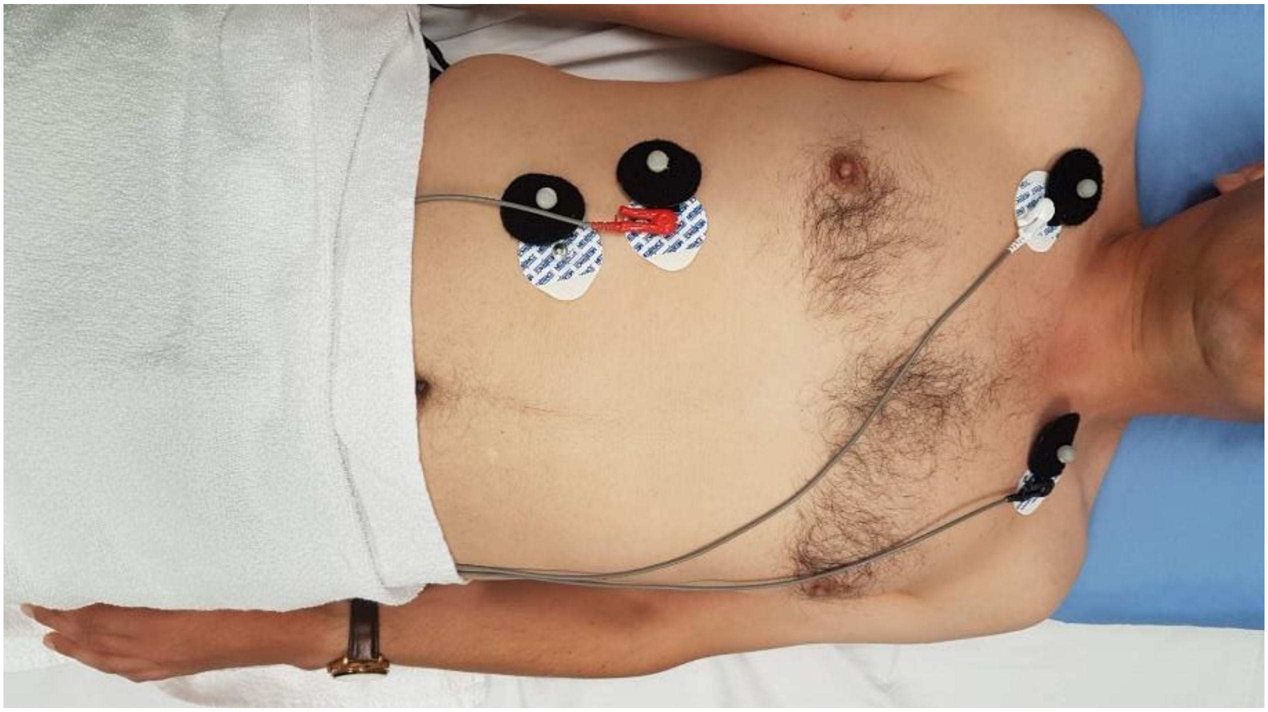
Step 1a: Optical Tracking Protocol

A software module developed in-house was used to record the position and orientation of the transducer by tracking markers attached to the probe using a commercially available OptiTrack optical tracking system, Model V120:Trio (NaturalPoint, Corvallis, OR, USA) (Chapter 2, Figure 5).

Chapter 2, Figure 5: The set up for tracking ultrasound transducer.

In contrast to the previous approach (21), the proposed study utilized Siemens 4Z1c matrix array transducer with five markers (in grey) attached to the mount (in black) to track the ultrasound probe. This change allowed us to track the 3D position and orientation of the transducer during the entire duration of the scanning procedure. Patient's breathing was also tracked by attaching an additional four markers on the chest area (Chapter 2 Figure 6).

Chapter 2, Figure 6: Chest markers attached to the ECG stickers. They reflect infrared light and patient breathing is tracked real-time by the Optitrack system.



The markers were placed on the ECG stickers. In contrast to the previous study (16), this study utilized five markers attached to the ultrasound probe for more reliable tracking of the probe during the entire duration of the scanning. In addition, the recording was performed continuously whereas in the previous volunteer-based study the recording was performed by dedicated personnel who started and stopped the optical recording based on the signal from sonographer. This removed the need for additional personnel other than the sonographer and made the system more practical for clinical use. The markers allowed us to track the position and orientation of the transducer in order to obtain an initial alignment of ultrasound scans acquired from different locations. The primary advantage of using an external tracking approach proposed in this study is that the accuracy of the alignment does not depend on the image quality which is sub-optimal in many cardiac patients.

Step 1b: Imaging Protocol and Data Processing

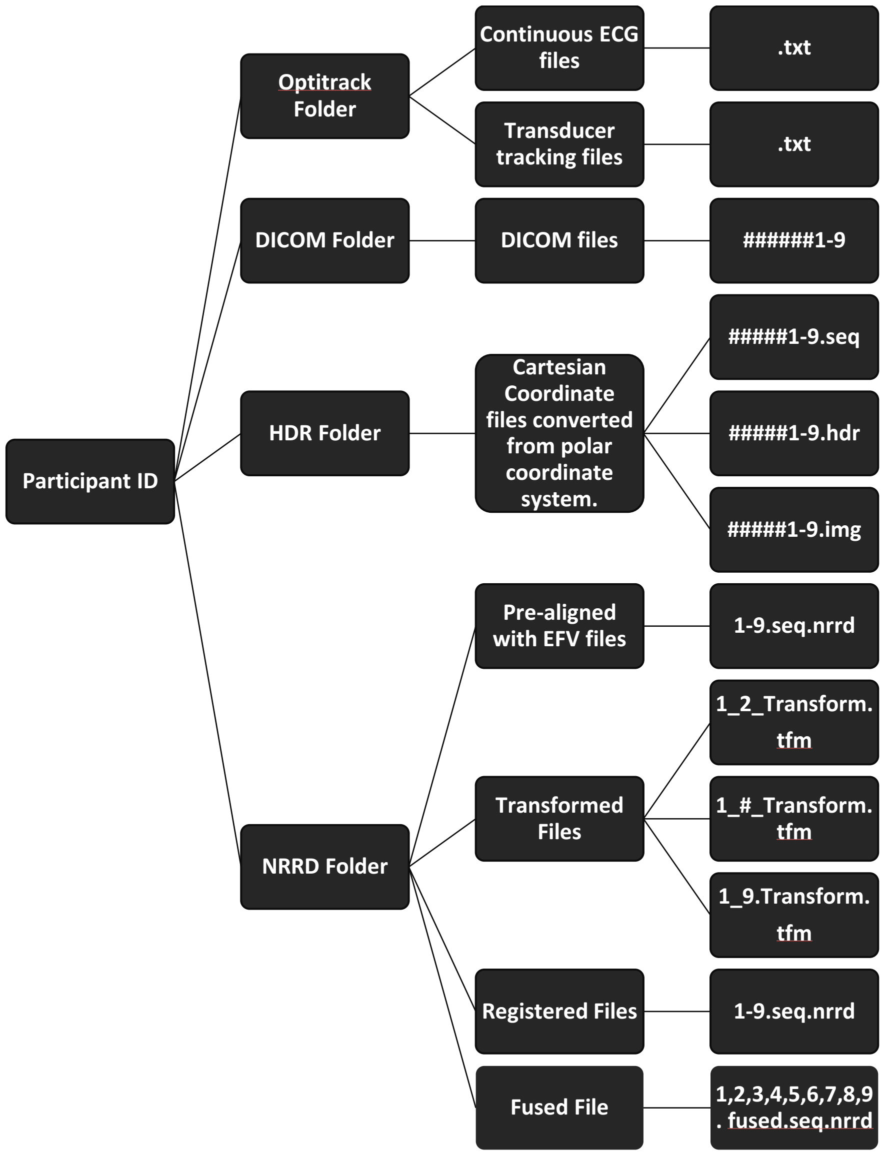
A commercially available ultrasound system (Acuson/Siemens SC 2000 scanner and 4Z1C matrix array transducer) was used to acquire 3D datasets. The ultrasound digital data was coded at the time of scanning. The ECG stickers and breathing markers were applied on participant's chest. Participants were examined in the lateral decubitus position and advised to kept the same during the entire scanning time. 3D recordings were performed from different transducer positions and acoustic windows on the chest. In total, between 9 and 14 loops per participant were acquired. Each loop had a duration of 1 beat. The transducer footprint was kept in the same place until all apical views were acquired. Then, the probe was tilted up, down or laterally to display the apical non-standard views. The following views were acquired: apical standard (ApSt), apical non-standard (ApNSt) and parasternal long axis (PSLA). The same acquisition depth was used to capture all views in order to maintain comparable frame rates. The volume rate ranged from 18 to 25 volumes per cardiac cycle. The dimensions of the acquired volumes (Length x Height x Width) ranged from 164 x170 x143 to 245 x 277 x 196 and the resolutions were 1mm x 1mm x 1mm. The dimensions were kept the same for all acquisitions.

Before proceeding with the next step, a recording checklist was used to ensure each recorded dataset has adequate information to be analyzed. A successful recording was considered when:

- the time between the scanner and PC was synchronized
- no obvious participant movement during the scanning
- continuous regular rhythm on ECG recording
- ultrasound images had the same volume rate, depth and sector size
- at least nine 3D ultrasound loops (1 beat each) were acquired
- ApSt (3 datasets), ApNSt (3 datasets) & PSLA (3 datasets) were acquired

A computer workstation (Fusion PC) with Intel Core i7-8700 processor and 64 GB RAM was used for recording and processing the data required for this study. Once the recording phase of the protocol was completed, digital DICOM data from the scanner was transferred to the Fusion PC in separate folders for each patient. Refer to Chapter 2, Figure 7 for the organization of the files and folders structure.

Chapter 2, Figure 7: The organization of the folders and files structure for the data for each patient



2. 4 Processing of datasets

Step 2: Siemens Volume Viewer Software

The DICOM digital data was converted into HDR format by using Siemens Volume Viewer software which converts the 3D data into Cartesian coordinate from polar-coordinate system. Each HDR file corresponds to a single volume frame from the ultrasound scan. HDR format allows for reading the voxel information and corresponds to the scan from the software developed in-house.

Alignment Phase

Step 3. Echo Fusion Viewer Pre-Alignment Software

The objective of the software developed in-house is to transform the ultrasound scans using the corresponding optical tracking information recorded. The R-peaks from the recorded ECG signal as well as the acquisition time obtained from the DICOM meta information were used to identify the exact time interval needed to compute the transformation. This transformation allows for an initial alignment (pre-alignment) of the ultrasound scans obtained from different locations such as apical and parasternal. In addition, the datasets were converted to nearly raw raster data (NRRD) format which allows for including the temporal frames in a single data file for further processing.

Step 4. 3D Slicer: Registration#1-TFM Module

An image registration approach was applied to improve the alignment of the transformed image datasets using the optical recording, which was performed with an image registration module developed for a well-known open-source software platform known as the 3D Slicer (www.slicer.org). In registration, one image dataset is considered fixed and the other one is considered moving which undergoes the transformation. The volume with the best quality among the apical standard scans was chosen as the fixed image and all other images are transformed using the image registration process. A rigid registration approach with six-degrees of freedom that includes translation in x, y, and z-directions as well as rotation with respect to x, y and z-axes was utilized in the process. An automated region of interest (ROI) was computed using Otsu's threshold and used as a mask in computing the similarity metric (Mattes mutual information) where all the voxels within the mask were used in the computation. Upon completion of the registration process, the output transformation was saved to a file indicating indices of the fixed and moving images (e.g., the filename *1_2_transform.tfm* indicates image 1 is considered as the fixed and image 2 is considered as moving).

Step 5. 3D Slicer: Registration#2-Transform module

The image registration module of the 3DSlicer used in this study does not allow for automatically apply the transformation and save the entire sequence of the ultrasound data to the disk. Therefore, a Slicer3D module was developed in-house that applies the transformation to the moving images and save the transformed sequence to the hard drive. A successful processing of this step was assessed by importing the fixed and transformed sequences back in 3DSlicer and checking for any anatomical misalignment. This visual assessment primarily consists of any artifacts such as double anatomical structure and/or offset of contours.

Fusion Phase

Step 6. 3D Slicer: Wavelet module

Upon the successful application of the rigid registration, the intensity value corresponds to each voxel in the overlapping region was computed using a fusion approach (30-34). Instead of relying on simple approaches such as averaging, this study utilizes wavelet-based processing. In wavelet approach, the images were decomposed into high and low frequency components. In general, the low frequency components correspond to the underlying anatomical structures whereas high frequency components are due to noise. In order to overcome the signal dropout, the maximum value of the low frequency components between the volumes was computed. To reduce the effects of noise, the average value of the high frequency components was used. At the end of this processing, an inverse wavelet-transform is applied to obtain a fused data. A module to perform the wavelet-based fusion was developed in-house and integrated into the 3D Slicer. All datasets that met the inclusion criteria, typically nine single volume data sets per patient obtained from apical standard, apical nonstandard and parasternal, are used in the wavelet processing.

2. 5 Data classification

Participants' datasets were classified into the following groups (per participant):

- S3DE: the ApSt dataset used as static image during the alignment phase of the study protocol. (one S3DE dataset)
- M3DFE: Nine S3DE (ApSt +ApNSt +PSLA) datasets fused in one M3DFE dataset.
- Standard 2DCE

2. 6 Study end points

- Feasibility evaluation of M3DFE protocol in patients with heart failure treated with CRT devices
- Assessment of LV EBD score by 2 readers using M3DFE and S3DE images, and determination of inter-observer and inter-modality variability.
- Assessment of global and regional LV systolic function by 2 readers using M3DFE and 2DCE images, and determination of inter-observer and inter-modality correlation.

2. 7 End points measures

a) Feasibility

A successfully fused dataset was considered when the M3DFE dataset integrated nine successfully aligned and fused S3DE datasets coming from multiple acoustic windows (Ap St, ApNSt and PSLA). The number of patients in whom the recording protocol could be successfully applied was recorded. Moreover, the number of datasets in which the alignment and fusion software could be successfully applied was also recorded.

b) <u>LV Endocardial Border Definition</u>

The AHA 17- segment model was used for LV EBD scoring with 7 segments per each 2D plane (Ap 4Ch, Ap2Ch), where apex was assessed in both planes. The EBD was visually graded as: good (2), intermediate (1), poor (0). Out of sector segments were labeled as such. Then, the EBD score was calculated. The segment was graded as good, when the entire border of the endocardium could be clearly visualized during the entire cardiac cycle. The segment was graded as poor when the endocardial border was not displayed at all. The segment was graded as intermediate when nether the criteria of good or poor delineation were met. The out of sector was graded when more than 50% of the segment was out of the sector. The assessment was performed independently by 2 readers.

c) <u>Global LV systolic function: LV volumetric measurements</u>

The LV volume quantification was performed by using the segmentation module of 3D Slicer. The M3DFE dataset, typically consisting of nine single volume data sets per patient obtained from apical standard, apical nonstandard and parasternal long axis views was imported to the 3D Slicer. During the segmentation process, the Ap 4Ch, Ap 2Ch and PSA 2D views of the fused dataset were reconstructed using the reformat module of the 3D Slicer. After reconstruction, the end diastolic frame was identified as defined in ASE guidelines and manual segmentation is performed by selecting control points in each view. These control points were used to define the ROI using the spline interpolation. The same process was repeated for the end systolic frame. The segmented ROIs corresponding to end systole and end diastole were saved under each participant's folder. The LV volumetric measurements were performed independently by 2 readers.

d) <u>Global LV systolic function: Ejection Fraction</u>

Volumetric measurements of M3DFE datasets were computed, and EF was calculated (EDV-ESV/ EDV x 100%).

e) <u>Regional LV systolic function</u>

The assessment of regional LV function was performed in M3DFE datasets by using the ASE guidelines recommendations. The left ventricle was divided into 16 segments. The regional myocardial function was evaluated visually by assessing the segmental wall thickening and endocardial motion. A wall motion score was assigned to each segment. The following scoring system was used: (1) normal or hyperkinetic, (2) hypokinetic (reduced thickening), (3) akinetic (absent or negligible thickening), and (4) dyskinetic (systolic thinning or stretching). The assessment of regional LV function was performed independently by 2 readers.

2. 8 Statistical Analysis

Commercially available software: SPSS version 25; SPSS, Inc, Chicago, IL and STATA/IC version 16.0; Texas, USA were used. All statistics were two tailed and P values of < 0.05 were considered significant (35). Continuous variables were expressed as mean ± SD. Paired T test was used to compare the means of EBD score in M3DFE group and S3DFE group. Spearman correlation coefficient was used to measure strength and direction of association between the 2 readers in EBD score assessment in M3DFE and S3DE groups. Spearman correlation analysis was also used to compare the strength and direction of association between both readers of M3DFE datasets, and each of the reader of M3DFE group with the reader of standard 2DCE group, in assessing global LV systolic function. Cohen Kappa and percentage of agreement analysis were used to assess the degree of consistency among the 2 readers in evaluating the regional LV systolic function.

3. Results

3. 1 Study participants

Twelve heart failure patients treated with CRT devices were enrolled in the study. Participants characteristics are shown in Chapter 3, Table 1.

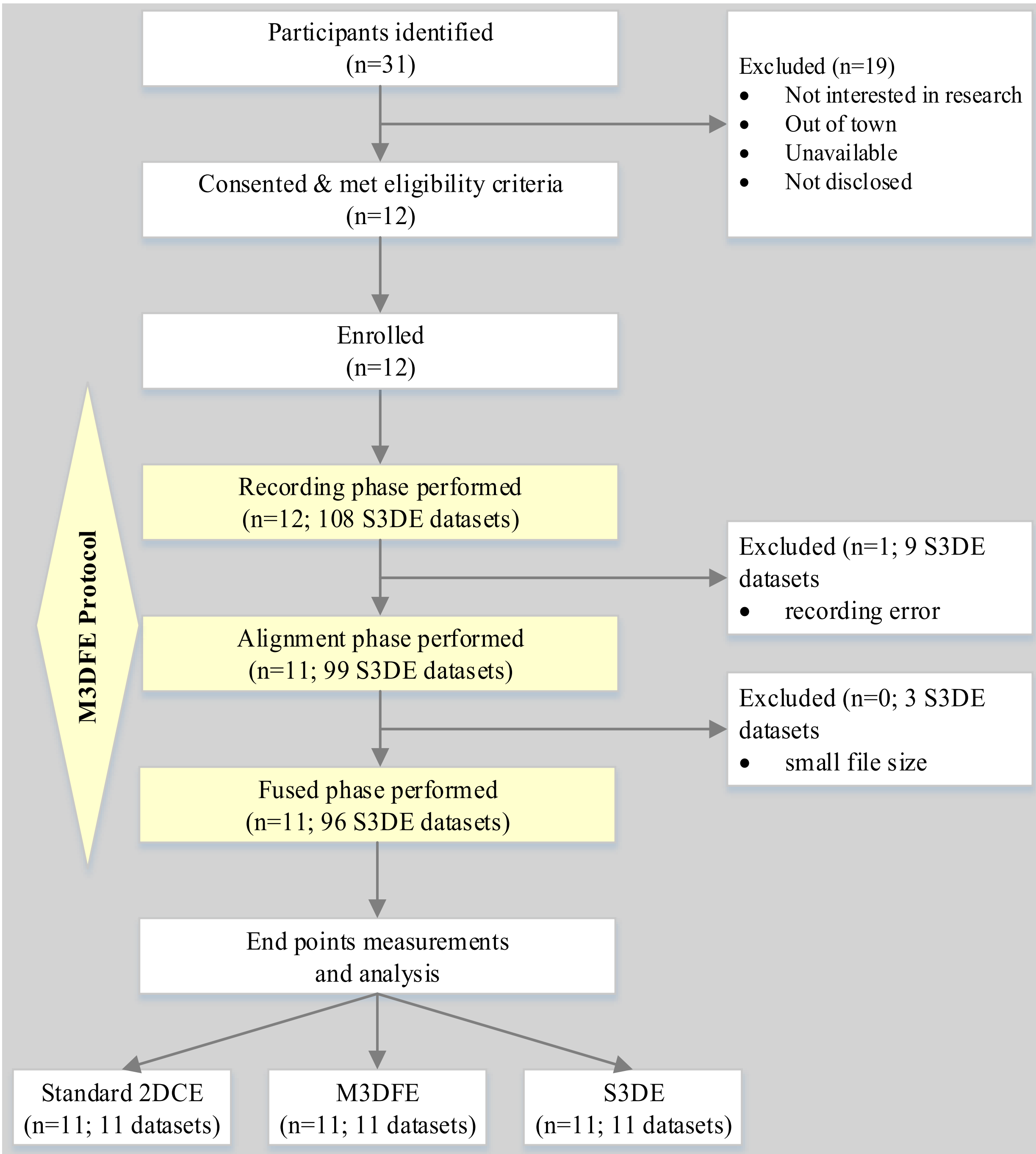
Chapter 3, Table 1: Participants Characteristics

Variables	Participants (n=12)
Age, years (mean ± SD)	70.2 ±11.4
Gender, M/F (%)	83.3
BSA, m^2 (mean ± SD)	2.0±0.2
SBP, mmHg (mean ± SD)	123.2±23.3
DBP, mmHg (mean ± SD)	70.3±8.7
HR, beats/min (mean ± SD)	64.7±9.0

3. 2 Feasibility

The recruitment and the results on the feasibility are summarized in Chapter 3, Figure 1.

Chapter 3, Figure 1: Overview of the recruitment and the feasibility of M3DFE system



11/12 (91.7%) participants successfully underwent the recording phase of the M3DFE protocol and 99/108 (91.7%) S3DE datasets could be successfully recorded (Chapter 3, Table 2).

Chapter 3, Table 2: Feasibility of the application of M3DFE protocol

Variables	Participants, N (%)	Datasets, N (%)
Recording phase of M3DFE protocol applied successfully	11/12 (91.7 %)	99/108 (91.7 %)
Alignment phase of M3DFE protocol applied successfully	11/12 (91.7 %)	96/108 (88.9 %)
Registration phase of M3DFE protocol applied successfully	11/12 (91.7 %)	96/108 (88.9 %)

1/12 patients (9/108 datasets) had to be excluded from further analysis due to a recording error which only became apparent when reviewing the recorded data. The alignment and fusion software could be successfully applied in 11/12 (91.7%) patients and 96/108 (88.9%) of S3DE datasets could be successfully processed.

3. 3 LV endocardial border definition

154 segments of 11 participants in both, M3DFE and S3DE groups were assessed for EBD. The mean improvements in EBD score by the 2 independent readers were as follows: 24.0±3.3 (95% CI, 19 and 27) and 24.3±3.8 (95% CI, 17 and 28) in M3DFE group. The corresponding values in the S3DE group were 11.7 ±6.0 (95% CI, 3 and 24) and 10.5 ±5.6 (95% CI, 2 and 24). The LV EBD score in M3DFE group was significantly better compared to S3DE group ($P<0.01$). Both readers reached comparable scores in grading EBD (Chapter 3, Tables 3 and 4).

Chapter 3, Table 3: Endocardial Border Definition (EBD) score by two readers in M3DFE and S3DE groups using AHA 17 segment model

Variables	M3DFE Group (N=11 patients; 154 segments)	S3DE Group (N=11 patients; 154 segments)
EBD Score Reader 1 (mean ±SD)	24.0±3.3	11.7±6.0
EBD Score Reader 2 (mean ±SD)	24.3±3.8	10.5±5.6

Chapter 3, Table 4: Paired t-test. Endocardial border definition score by two readers of M3DFE and S3DE datasets.

Variables	95% CI of lower	95% CI of upper	t	df	Sig. (2-tailed)
Reader 1: M3DFE vs S3DE group	8.3	16.2	6.8	10	.000
Reader 2: M3DFE vs S3DE group	10.1	17.3	8.4	10	.000

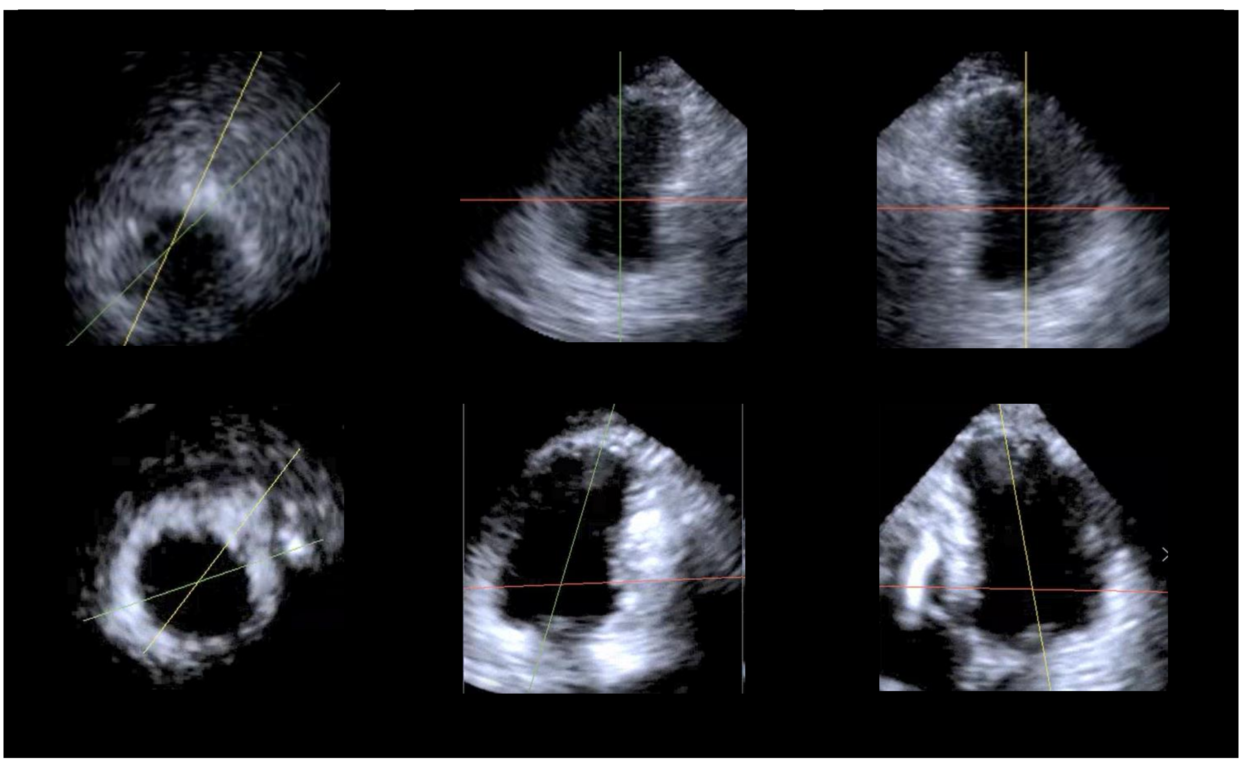
The correlation coefficient of EBD score (r) between the 2 readers was r = 0.831; p<0.001 (Chapter 3, Table 5).

Chapter 3, Table 5: Spearman correlation (r) of endocardial border definition (EBD) score measured by the two readers of M3DFE datasets

Variables		EBD Score (N=11 patients, 154 M3DFE segments)	
		Reader 1	**Reader 2**
EBD Score (N=11 patients, 154 M3DFE segments)	**Reader 1**		r = 0.831; p<0.001
	Reader 2	r = 0.831; p<0.001	

In many of the S3DE datasets, there were several segments that could not be delineated by visual assessment, whereas in the M3DFE datasets the majority of segments were well visualized and graded as clearly defined. An example showing the comparison between S3DE dataset and M3DFE dataset is shown in Chapter 3, Figure 2.

Chapter 3, Figure 2: An example showing the comparison between S3DE dataset and M3DFE dataset

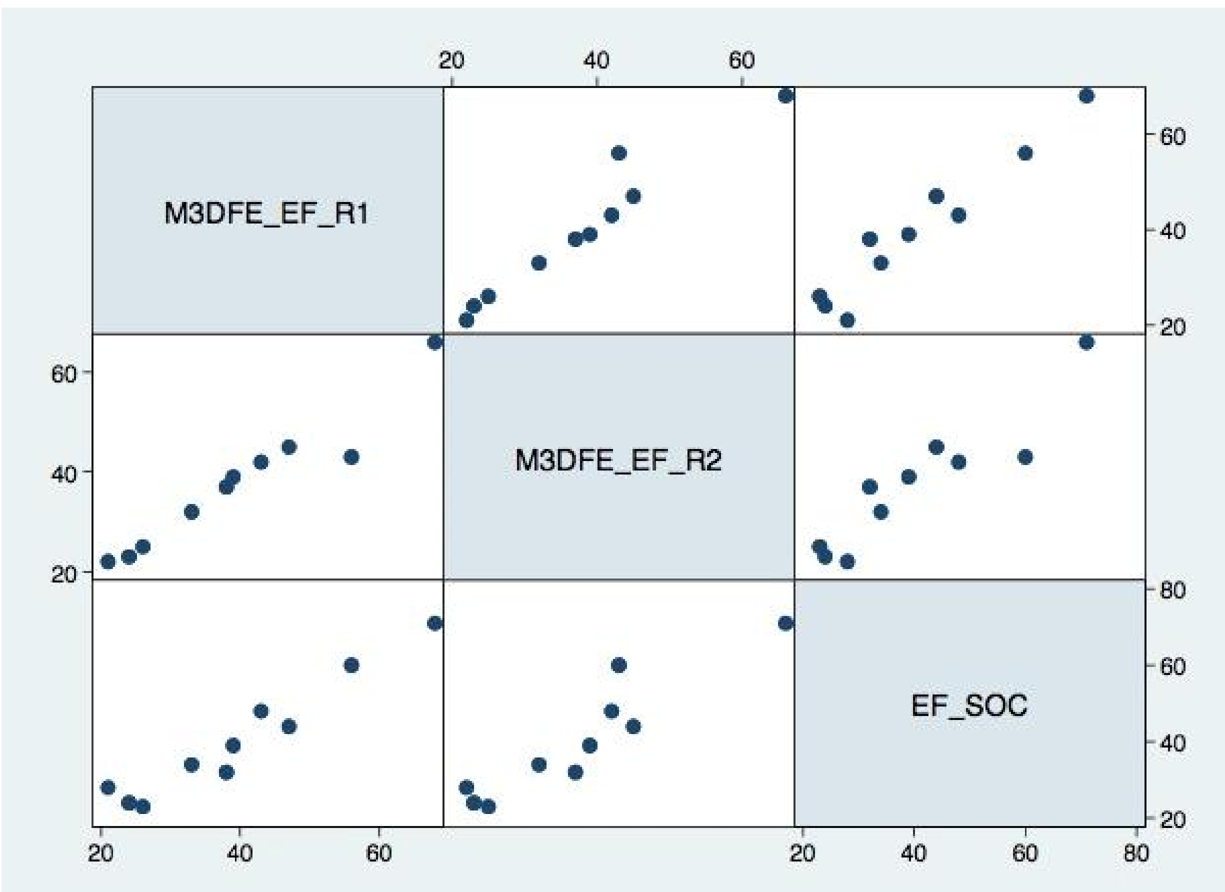


An example showing the comparison between S3DE apical standard view dataset (top row) and a M3DFE dataset (bottom row) integrating 9 S3DE datasets obtained from the apical and parasternal windows. Three orthogonal 2D planes showing a short axis plane (left), apical planes representing a two-chamber (middle) and a four-chamber (right) views.

3. 4 Global LV systolic function

The M3DFE datasets of 10 out of 11 patients deemed to be adequate for manual tracing of the endocardial borders. The EF measured on M3DFE datasets was not significantly different from that measured by standard 2DCE ($p > 0.05$). The agreement of EF between the 2 readers and between each of the readers with standard 2DCE is shown in Chapter 3, Figure 3.

Chapter 3, Figure 3: EF correlation between both readers of M3DFE datasets and Standard 2DCE reader.



The correlation coefficient of EF (r) between the 2 readers of M3DFE datasets was r = 0.927, p<0.001; r = 0.927, p<0.001 between M3DFE reader 1 and standard 2DCE reader, and r = 0.903, p<0.001 between M3DFE reader 2 and standard 2DCE reader . Correlation is significant at the 0.01 level. (Chapter 3, Table 6).

Chapter 3, Table 6: Spearman correlation (r) of EF measured by M3DFE and standard 2DCE readers

Variables		M3DFE group (N=10 patients)	
		Reader 1	Reader 2
M3DFE group (N=10 patients)	Reader 1		r = 0.988; p<0.001
	Reader 2	r = 0.988; p<0.001	
Standard 2DCE group (N=10 patients)		r = 0.927; p<0.001	r = 0.903; p<0.001

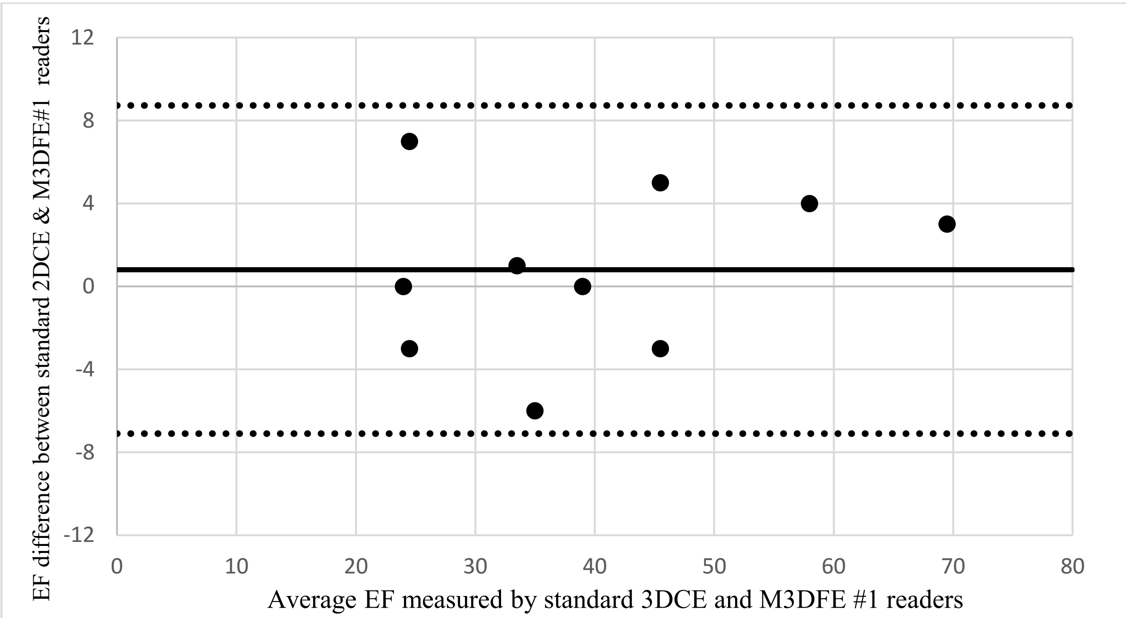
The mean and standard deviation of the LVEF was 39.5±14.8 in M3DFE group by reader 1, 37.7±13.1 in M3DFE group by reader 2, and 40.30±15.7 by reader of the standard 2DCE (Chapter 3, Table 7).

Chapter 3, Table 7: LV volumes and EF measurements in M3DFE and standard 2DCE groups

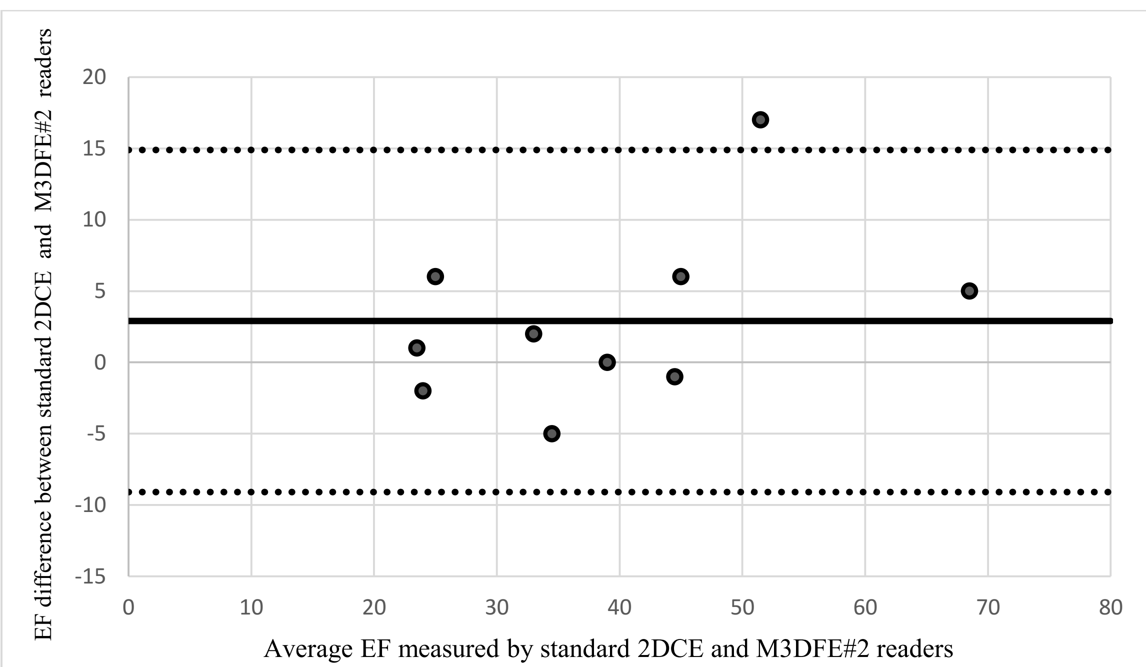
Variables	M3DFE Group (N= 10 patients)		Standard 2DCE (N=10 patients)
	Reader 1	Reader 2	
EDV, ml (mean +/- SD)	172.0±47.6	174.6±55.1	210.0±54.2
ESV, ml (mean +/- SD)	106.9±51.3	112.6±54.79	124.8±58.1
EF, % (mean +/- SD)	39.5±14.8	37.4±13.1	40.3±15.7

Bland-Altman analysis of ejection fraction (EF) between standard 2DCE reader and both readers of M3DFE datasets is shown in Chapter 3, Figures 4 and 5.

Chapter 3, Figure 4: Bland-Altman analysis of ejection fraction (EF) between standard 2DCE reader and reader 1of M3DFE datasets.



Chapter 3, Figure 5: Bland-Altman analysis of ejection fraction (EF) between standard 2DCE reader and reader 2 of M3DFE datasets.



3.5 Regional LV systolic function

A total of 132 segments of 11 patients (12 segments per dataset) were analyzed. Assessment of regional wall motion couldn't be performed in S3DE datasets due to suboptimal EBD. In the M3DFE datasets, the readers could grade the wall motion and in the majority of segments there was agreement with between the readers and between each reader of M3DFE group with standard 2DCE group. The percentage of agreement and Cohen Kappa coefficient (k) in assessing the degree of consistency among the 2 readers in evaluating the regional LV systolic function was 83.3% (k=0.7) between the 2 readers of the M3DFE group, 76.5% (k=0.6) between reader 1 of the M3DFE group and reader of the standard 2DCE group, and 74.2 % (k=0.6) between reader 2 of the M3DFE group and reader of the standard 2DCE group (Chapter 3, Table 8).

Chapter 3, Table 8: Percentage of agreement and Cohen Kappa coefficient (k) between readers of M3DFE and standard 2DCE datasets in the visual assessment of regional wall motion where 6 segments per each 2D plane (Ap4Ch, Ap2Ch) were scored

<table>
<tr><th colspan="2" rowspan="2">Variables</th><th colspan="2">M3DFE group
(N=11 patients; 132 segments)</th></tr>
<tr><th>Reader 1</th><th>Reader 2</th></tr>
<tr><td rowspan="2">M3DFE group (N=11 patients, 132 segments)</td><td>Reader 1</td><td></td><td>83.3 %
k=0.7</td></tr>
<tr><td>Reader 2</td><td>83.3 %
k=0.7</td><td></td></tr>
<tr><td colspan="2">Standard 2DCE group
(N=11 patients, 132 segments)</td><td>76.5 %
k=0.6</td><td>74.2 %
k=0.6</td></tr>
</table>

4. Discussions

4.1 Addressing the M3DFE challenges

For the first time, optical tracking of the transducer and the 3D sound field were combined with further processing of the recorded datasets using a registration technique in a patient study. To our knowledge, this is the first study that demonstrates the feasibility of the fusion procedure as the majority of the datasets were suitable for 3D fusion. Because of the improved image quality of the fused datasets non-diagnostic single view 3D recordings of the left ventricle could be upgraded to M3DFE datasets which were suitable for quantitative analysis of LV function. The measurements of the EF obtained from M3DFE datasets were in good agreement with the findings of 2DCE which is currently standard of practice in our center. These results represent a major advance towards a clinically applicable system for 3D fusion echocardiography and a wider application of 3D echocardiography using transthoracic recordings.

The improvement in image quality/endocardial border delineation by M3DFE is comparable to what has been reported for 2DCE (36). When regional LV wall motion was assessed, a good agreement was observed between the 2 readers as well as each reader of the M3DFE group with standard 2DCE group. The observed minor differences are most likely due to the known inter-observer variability in assessing regional LV wall motion (37). The end-diastolic volumes measured on the M3DFE datasets were 18% smaller than the volumes measured by 2D contrast echocardiography. This is in agreement with previous studies comparing non-contrast with contrast enhanced recordings (12, 13).

In order to process the 3D datasets with the new fusion software the image format had to be modified from Siemens DICOM to NRRD. At present, there is no software to translate the fused datasets back into the original DICOM format and then to perform quantification of the LV volumes using the original analysis software of the manufacturer or to use a third party program, like TomTec (38). The quantification using the 3D slicer software was feasible, however a correction factor may be necessary to compensate for the systematic under-estimation of the LV EDV and ESV. That would need further studies involving more patients.

Multiview fusion of 3D echocardiographic recordings require procedures which are not yet available on commercially available scanners. In order to accurately align 3D datasets from different acoustic windows, the movements of the heart, the respiration, and the patient movement have to be tracked and considered in the fusion process. So far, the most advanced system was tested in a previous volunteer study (16). Lamb et al. have shown that in addition to tracking the transducer position, a quantitative respiratory tracking technique could help to guide spatial alignment in M3DFE. Using the proposed approach, more than 89% of M3DFE datasets were found to be suitable for diagnostic assessment. However, this was only possible by recording the single 3D datasets during a breath hold. This limits the number of 3D datasets, which can be acquired and fused. Holding the breath at the same depth and the subjects staying exactly in the same position on the scanning bed was a prerequisite of optimal alignment of the 3D datasets obtained from different windows. This was already challenging for volunteers, however may be impossible for many patients. More importantly, the previous approach ignores the fact that scanning the heart from a different location is not always feasible with patients on the same breath hold.

The system developed and applied in this project represents a major advancement compared to the method described by Lamb et al. and Punithakumar et al. (16, 19-23). In addition to the initial alignment based on the optical tracking of the transducer, an alignment correction procedure was included in the analysis software. This is based on registration technology which corrected misalignment of the transformed image datasets using the optical recording. The image registration module was developed by a well-known open-source software platform known as the 3D Slicer (39). 3D fusion by registration has been used by other groups (17-18, 25, 28, 42-53). On its own registration is of limited value. The datasets need to have a major overlap. Therefore, successful fusion was only reported for datasets from the same acoustic window, when relatively small changes of the transducer position were applied. No success of the fusion of datasets from parasternal and apical windows has been reported. In order to fuse datasets with small overlap and different orientation, our group developed multiview fusion by optical tracking to pre-align these datasets. The current system therefore includes a two-step alignment procedure with pre-alignment using optical tracking of the transducer to create datasets which sufficient overlap followed by a registration process which corrects the misalignment due to different depth of breath in different views and patient movements. With this two-step alignment procedure, the tracking of the respiration becomes less relevant.

4.2 Impact

This study focused on the assessment of LV function in CRT patients, who currently all undergo 2DCE. The optimal method is 3D echocardiography because it has no geometrical assumptions. However, in this population the image quality of the S3DE datasets is often not sufficient to quantify LV function. The standard 2DCE method, involves administration of contrast agents which exposes the patient to risks of adverse events and is associated with additional costs (12). The enhanced image quality of M3DFE may be used to avoid contrast agents and to get reliable results from 3D echocardiography. There are other potential applications of M3DFE, such as echocardiographic volumetric measurement of the atria and the right ventricle. In particular, the quantification of RV volumes still suffers from suboptimal display in many patients. M3DFE also increases the field of view. Lamb et al. demonstrated an improvement of field of view in a M3DFE volunteer study (16). In principle, the M3DFE has the potential to provide a dataset which includes the entire heart. In the future, a 3D dataset displaying the entire heart “full heart” may be used for teaching, planning of procedures or as the main dataset for diagnostics.

4.3 Limitations

Even though the study includes only 12 patients, the results are promising, and further studies are warranted to study more patients and with different pathologies. In addition, the M3DFE analysis system has several limitations. The current system incorporates several different types of software with minimal automation, which makes its use cumbersome and time consuming. The analysis system is not yet integrated into a clinically used echocardiography system. We hope that the results of this pilot study will trigger interest in linking the advanced M3DFE system with the commercially available echocardiography systems.

Only DICOM files of the 3D recordings were processed. We don’t know whether processing raw data would make a major difference in image quality. As the DICOM files are smaller compared to the raw data, computing is faster. The full potential of the fusion technology with regards to image quality may only be appreciated when raw 3D datasets are processed.

Optical tracking of the transducer is not the optimum method to get the spatial data of the 3D datasets, which is the first step of the fusion procedure. Losing line-of-sight of chest or transducer markers was less frequent than in previous studies of Lamb et al, because of more markers on the ultrasound probe. However, the mount and optical markers attached to the transducer is quite bulky and limits the handling of the probe. Putting markers directly on the probe without a mount reduced the tracking in a previous phantom study. A solution to this problem is to use another tracking method. For electromagnetic tracking, small markers can be used and detected under the cover of a gown (19-23). However, there are interferences with metallic material and the safety of the electromagnetic field of the sensors has not been tested in patients with pacemakers. In the future, attachment of the ultrasound probe to a measurement or robot arm is probably the best approach (19-23). These arms always track the position of the limb which can hold the probe. Apart from being useful for 3D fusion echocardiography robot arm assisted echocardiography has also a great potential to reduced sonographer musculoskeletal strain (54).

It is still unknown how many datasets and which acoustic windows are necessary to get the optimum results in M3DFE. The study was not designed to determine the number of datasets for optimal fusion. In this pilot study, we used only the standard parasternal and apical windows.

4.4 Conclusion

The new M3DFE system is feasible in patients with heart failure treated with CRT devices and resulted in impressive improvement in image quality of standard 3D Echocardiography. M3DFE technique allowed to assess regional and global function in patients in whom standard 3D was non-diagnostic. Although the sample size is still small, the thesis showed the "proof of principle" and further studies involving more patients are warranted.

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