Optimal threshold of three-dimensional echocardiographic fully automated software for quantification of left ventricular volumes and ejection fraction: Comparison with cardiac magnetic resonance disk-area summation method and feature tracking method

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Abstract

Aims

Novel fully automated left chamber quantification software for three-dimensional echocardiography (3DE) has a potential for reliable measurement of left ventricular (LV) volumes and ejection fraction (LVEF). However, the optimal setting of global LV endocardial border threshold has not been settled.

Methods and results

We performed LV volumes and LVEF analysis using fully automated left chamber quantification software (Dynamic HeartModel¹,², Philips Medical Systems) in 65 patients who had undergone both 3DE and cardiac magnetic resonance (CMR) examinations on the same day. We recorded LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV) according to the change in LV global border threshold settings from 0-point to 100-point with each increment of 10-point. These values were compared to the corresponding values of CMR with disk-area summation method and feature tracking (FT) method. Coverage probability (CP) was calculated as an index of accuracy and reliability. Fully automated software provided LV volumes and LVEF in 57 patients (feasibility: 88%). LVEDV and LVESV increased steadily according to the increase in border threshold and reached minimal bias when border threshold setting was 80 against CMR disk-summation method and 90 against CMR FT method. Corresponding CP of LVEF was 0.74 and 0.84 against disk-area summation method and FT method.
Conclusions
With CMR values as a reference, LV endocardial border threshold value can be set around 80 to 90 with the same number of LV end-diastole and end-systole threshold to approximate LVEDV, LVESV and LVEF with clinically acceptable CP values of LVEF.

Introduction
Left ventricular (LV) ejection fraction (LVEF) using transthoracic two-dimensional echocardiography (2DE) is still one of the most important cardiac metrics to quantify LV function. Several cut-off values of LVEF has been used to select candidates for implantable cardiac defibrillator [1] and to determine discontinuation of cancer therapy [2, 3]. However, manual tracing on the endocardial border produces inter-observer measurement variabilities that may not be negligible. To overcome this problem, several ultrasound vendors have produced semiautomated LV border detection software that have still limitations due to several reasons.

Recent advances in fully automated software (HeartModel\textsuperscript{A.I.}) for left heart chamber quantification with three-dimensional echocardiography (3DE) have been shown promising to quantify LV volumes and LVEF in a routine clinical setting [4–6]. If editing was not performed, the software provides identical numerical values of the measurements on the same 3DE datasets every time. Several studies had determined its accuracy against 3DE manual quantification analysis [4–8] or cardiac magnetic resonance (CMR) as a reference [7, 9–12]. However, it still underestimates LV volumes and overestimate LVEF against CMR [7, 9–12]. The software allows regional and global LV endocardial border editing. Although regional LV endocardial border editing produces a minor change of LV volumes, resulting in the subtle change in LVEF calculation, change of LV endocardial border threshold from 0-point to 100-point makes a remarkable change in LV volumes and LVEF. There are no reports to systematically determine optimal border setting for LV volumes as well as LVEF measurements. Recently, the updated version of the software (Dynamic HeartModel\textsuperscript{A.I.}) has been released, and it now provides LV volume curve using 3DE speckle tracking technology.

Accordingly, the aim of this study was to determine optimal LV border threshold at end-diastole (ED) and end-systole (ES) using Dynamic HeartModel\textsuperscript{A.I.} and HeartModel\textsuperscript{A.I.} for the measurements of LVEDV, LVESV, and LVEF against CMR as a reference.

Methods
Study population
We retrospectively searched patients who had clinically indicated CMR examination and also agreed to undergo 3DE examination on the same day in University of Occupational and Environmental Health Hospital from January 2017 to July 2018. Among 107 patients for potentially eligible patients, a total of 65 patients who had one-beat 3DE datasets acquisition with specific ultrasound machine that were required for fully automated left chamber quantification software analysis was finally selected for the analysis. All study patients were ethnic Japanese. The ethics committee of the University of Occupational and Environmental Health Hospital approved the study protocol, and informed consent was waived due to the retrospective nature of the analysis.

3D echocardiography
Real-time 3DE full-volume datasets were acquired from the apical window with the patient in the left lateral decubitus position using EPIQ 7G scanner (Philips Medical Systems, Andover,
MA) equipped with a fully sampled matrix-array transducer (X5-1). The depth and sector angle were adjusted to include the entire left and right chambers. Specific one-beat acquisition mode (3D HMQ) was used to acquire 3DE datasets. Several one-beat acquisitions were performed. These datasets were stored digitally for offline analysis.

3D echocardiographic analysis: Automated quantification

HeartModel\textsuperscript{A.I.}. One-beat 3DE full-volume data sets were analyzed using fully automated quantification software (HeartModel\textsuperscript{A.I.}, QLAB, version 10.5, Philips Medical Systems) that detects LV endocardial surfaces using an adaptive analytical algorithm that consists of knowledge-based identification of initial global shape and LV chamber orientation, followed by patient-specific adaptation \cite{7}. After initiating the program, the software automatically determined the ED and ES frames using motion analysis, followed by construction of ED and ES LV casts. The software subsequently determined LVDEV, LVESV, and LVEF without geometric assumptions. To determine the effect of global editing on LV volumes and LVEF, we adjusted ED and ES endocardial border threshold with each increase of threshold value from 0-point to 100-point via 10-point increment, and obtained LVEDV and LVESV at each increment, although adjustments at increments of 1-point are possible. We did not perform any manual editing of endocardial border in every patient and every border setting. LVEF was calculated as LVEDV at specific border threshold—LVESV at specific border threshold divided by LVEDV at specific border threshold multiplied by 100.

This fully automated quantification software produces LV cast based on ultrasound knowledge database, and it occasionally creates erroneous LV cast. Erroneous LV cast constructions are defined if the border of the casts were constructed not on the actual myocardial-blood interface with manual editing correction impossible.

Dynamic HeartModel\textsuperscript{A.I.}. In contrast to HeartModel that provides LVEDV and LVESV, the new software (Dynamic HeartModel\textsuperscript{A.I.}, QLAB version 11.0, Philips Medical Systems) incorporates 3DE speckle tracking technology. It provides LV volume curve during one cardiac cycle. Like HeartModel analysis, we adjusted ED and ES endocardial border threshold with each increase of threshold value from 0-point to 100-point via 10-point increment and obtained LVEDV and LVESV at each increment. Again, we did not perform manual editing. LVEF was calculated as the same process.

CMR acquisition

CMR imaging was performed with a 3T scanner (Discovery 750W, GE Healthcare) with a phased-array cardiovascular coil. In each patient, retrospective electrocardiographically-gated localizing spin-echo sequences were used to identify the long axis of the heart. Steady state fully precession (SSFP) dynamic gradient-echo cine loops were acquired using retrospective electrocardiographic gating and parallel imaging techniques during 10-sec to 15-sec breath-holds, with a following general parameters: slice thickness of the imaging planes 8 mm, field of view $40\times40$ cm, scan matrix $200\times160$, flip angle 50˚, repetition/echo times 3.8/1.7 ms, views per segment 20, number of reconstructed cardiac phases 20.

CMR analysis

CMR LV volumes were measured from multiple short-axis SSFP images using an analytical software (Segment v2.2, Medviso, Lund, Sweden), and the disk-area summation method was used for the calculation of the LVEDV and LVESV. LVEF was measured by standard formula.
Feature tracking (FT) CMR analysis

CMR images were analyzed using commercial FT software (2D CPA MR; TomTec Imaging Systems, Unterschleissheim, Germany), which is a vector-based analysis tool based on a hierarchical algorithm [13–15]. Using three apical long-axis cine SSFP images, the LV endocardial border at end-systole was semi-automatically drawn after 3-point clicking. Manual adjustment of endocardial border was performed when required. Subsequently, the software automatically propagates the contour and follows its features throughout the cardiac cycle to generate LV volume curve, from which the software provided LVEDV, LVESV and LVEF.

Statistical analysis

Continuous variables are expressed as mean ± SD or median and 25th to 75th percentile according to data distribution. All statistical analyses were performed using commercially available software (JMP version 13.1.0, SAS Institute, Cary, NC; R version 3.4.3, The R foundation for Statistical Computing, Vienna, Australia; and Prism 8, GraphPad Software, Inc., La Jolla, CA). Freedman analysis with post-hoc comparison was performed to compare LVEDV, LVESV, and LVEF among different border settings and CMR. Linear correlations and Bland-Altman analysis were performed between the two methods. Since Dynamic HeartModel and CMR FT provide LV volume curves, we determined the reliability of the curves from Dynamic

Table 1. Clinical characteristics in study population (n = 65).

| Age            | 71 (64 to 79) |
|----------------|--------------|
| Male/female    | 39/26        |
| Height (cm)    | 158 ± 14     |
| Weight (kg)    | 57 ± 13      |
| BSA (m²)       | 1.57 ± 0.22  |
| HR at the time of 3DE (bpm) | 68 ± 15 |
| HR at the time of CMR (bpm) | 66 ± 14 |
| SBP (mmHg)     | 130 ± 27     |
| DBP (mmHg)     | 69 ± 12      |
| Clinical diagnosis |
| DCMP           | 5            |
| ICM            | 11           |
| Secondary cardiomyopathy | 22 |
| VHD            | 9            |
| HCM            | 2            |
| PH             | 4            |
| IHD            | 4            |
| Others         | 8            |
| Image quality  |
| Good           | 12 (18%)     |
| Fair           | 29 (45%)     |
| Poor           | 24 (37%)     |

Continuous data are expressed as mean ± SD or median and interquartile interval.

3DE, three-dimensional echocardiography; BSA, body surface area; CMR, cardiac magnetic resonance; DCMP, dilated cardiomyopathy; DBP, diastolic blood pressure; HCM, hypertrophic cardiomyopathy; HR, heart rate; ICM, ischemic cardiomyopathy; IHD, ischemic heart disease; PH, pulmonary hypertension; SBP, systolic blood pressure; VHD, valvular heart disease

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HeartModel against that obtained from CMR FT. Data were extracted using plots digitalization (WebPlotDigitizer), and each curve was digitized and interpolated 100 points during one cardiac cycle. A linear correlation was performed using 100 plots between the two methods, and r-values from linear correlation analysis were calculated in each patient. We calculated coverage probability (CP) as the percentage of the number of measurements whose difference fulfilled pre-defined criteria. Regarding LVEDV and LVESV, the cut-off value was 30 mL between 3DE and CMR measurements [16–18]. Regarding LVEF, the cut-off value was set as 10% between 3DE and CMR determined LVEFs [16–18].

**Results**

Table 1 describes clinical characteristics in study population. 3DE datasets had good image quality in 18%, fair image quality in 45% and poor image quality in 37%, respectively. Among 65 patients, 8 patients were excluded because of no 3DE datasets acquisition due to extremely poor echocardiographic image quality (n = 6) or erroneous LV cast construction (n = 2) by 3DE fully automated software (Feasibility: 88%). Thus, final analysis was conducted in 57 patients. Standard CMR measurements (disk-area summation method) provided LV volumes and LVEF in all patients. CMR FT method provided LV volumes and LVEF in 55 patients.

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**Fig 1. Flow chart of the study population.** 3DE, three-dimensional echocardiography; CMR, cardiac magnetic resonance; DHM, Dynamic HeartModel; LV, left ventricular.

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The mean values of LVEF measured on standard CMR method and CMR FT method were 35 ±17% and 35 ±14%.

**Comparison of Dynamic HeartModelA.I. to CMR standard method**

Fig 2 shows LVEDV, LVESV and LVEF among different border threshold using Dynamic HeartModel and corresponding value of CMR disk-area summation method. There were gradual increases in LVEDV and LVESV according to increase of border threshold from 0-point to 100-point. Endocardial border setting from 0-point up to 60-point significantly underestimated LVEDV and border setting of 100-point significantly overestimated LVEDV compared to LVEDV measured by CMR disk-area summation method. Similar tendency was observed in LVESV. LVEF decreased gradually from 0-point to 100-point, if we used the same border threshold of ED and ES.

Fig 2. Box and whiskers (minimum to maximum) of left ventricular end-diastolic volume (A), left ventricular end-systolic volume (B), and left ventricular ejection fraction (C) between cardiac magnetic resonance disk-summation method and 3D echocardiography with automated quantification software (Dynamic HeartModel) according to change in border setting. LVEDV, end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume. #: p<0.05 compared with CMR.

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Fig 3A to 3C depict Bland-Altman analysis of LVEDV, LVESV and LVEF between the two methods. Table 2 presents statistical analysis of correlation, bias, 95% limit of agreement (LOA) and CP between Dynamic HeartModel with each border setting and CMR disk-area summation method. Smallest bias of LVEDV, LVESV, and LVEF between CMR and Dynamic HeartModel with high CP value (0.74) of LVEF was observed at border threshold value of 80-point at both ED and ES.

Comparison of Dynamic HeartModel to CMR FT method

Fig 4 shows LVEDV, LVESV and LVEF among different border threshold using Dynamic HeartModel and corresponding value of CMR FT method. Endocardial border setting from 0-point up to 70-point significantly underestimated both LVEDV and LVESV compared with corresponding values measured by CMR FT method. There were no significant differences in LVEDV and LVESV between Dynamic HeartModel with border setting from 80-point to 100-point and CMR FT method.

Fig 5A to 5C depict Bland-Altman analysis of LVEDV, LVESV and LVEF between the two methods. Table 3 represents statistical analysis of correlation, bias, 95% LOA and CP between Dynamic HeartModel with each border setting and CMR FT method. Smallest bias of LVEDV, LVESV, and LVEF between CMR and Dynamic HeartModel with high CP value (0.84) of LVEF was observed at border threshold value of 90-point at both ED and ES.

Fig 6 shows ED LV border tracing line used by different LV endocardial border threshold in a representative case.

Fig 7 represents 2 cases with LV volume curves from Dynamic HeartModel and CMR FT and their correlations. Upper case shows good correlation (r = 0.95) and lower case shows poor correlation (r = 0.26) of LV volume curves between the two modalities. Overall
Comparison showed that a median value of r was 0.87 (25th to 75th percentile: 0.80 to 0.93) in 55 patients.

Comparison of HeartModel A.I. to CMR

Comparison of HeartModel A.I. to CMR S1 and S2 Tables show analysis of correlation, bias, 95% LOA and CP between HeartModel with serial border setting and CMR disk-area summation method (S1 Table) and between HeartModel and CMR FT method (S2 Table). Smallest bias of LVEDV, LVESV, and LVEF between CMR disk-area summation method and HeartModel with high CP value (0.67) of LVEF was observed at border threshold value of 80 at both ED and ES. Smallest bias of LVEDV, LVESV, and LVEF between CMR FT method and HeartModel with high CP value (0.82) of LVEF was observed at border threshold value of 90 at both ED and ES. However, observed CP values of LVEDV, LVESV and LVEF were lower than that observed using Dynamic HeartModel.

Comparison of Dynamic HeartModel A.I. to HeartModel A.I.

Fig 8 showed linear correlation and Bland-Altman analysis of LVEDV, LVESV, and LVEF between Dynamic HeartModel and HeartModel with use of a border threshold value of 80 at

Table 2. Comparison of LV volumes and EF between Dynamic HeartModel and CMR disk-area summation method (n = 57).

|         | CMRstd | DHM 0 | DHM 10 | DHM 20 | DHM 30 | DHM 40 | DHM 50 | DHM 60 | DHM 70 | DHM 80 | DHM 90 | DHM 100 |
|---------|--------|-------|--------|--------|--------|--------|--------|--------|--------|--------|--------|---------|
| **LVEDV** | median | 182   | 114    | 121    | 133    | 141    | 147    | 155    | 165    | 175    | 184    | 197     | 208     |
| 25th-75th | 124–230 | 80–156 | 86–164 | 92–176 | 98–186 | 105–194 | 113–203 | 123–212 | 131–221 | 140–233 | 148–249 | 155–261 |
| difference | <0.001  | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | 0.006  | 1.000  | 1.000  | 1.000  | 1.000  | 0.0082  |
| r         | 0.91    | 0.89   | 0.91   | 0.92   | 0.92   | 0.92   | 0.92   | 0.92   | 0.92   | 0.92   | 0.91   | 0.91    |
| bias      | -68     | -62    | -54    | -46    | -38    | -29    | -20    | -11    | -9     | 0      | 9       | 20      |
| 95% LOA   | -150 to 14 | -147 to 22 | -132 to 24 | -122 to 30 | -112 to 36 | -102 to 43 | -91 to 51 | -81 to 59 | -71 to 68 | -60 to 78 | -50 to 90 | -      |
| CP        | 0.16    | 0.18   | 0.23   | 0.32   | 0.44   | 0.51   | 0.60   | 0.65   | 0.65   | 0.65   | 0.53    |         |

| **LVESV** | median | 112   | 72     | 78     | 85     | 92     | 98     | 104    | 109    | 116    | 123    | 132     | 142     |
| 25th-75th | 68–167 | 44–106 | 48–111 | 51–117 | 55–124 | 60–131 | 64–139 | 68–148 | 73–160 | 78–168 | 84–177 | 90–185  |
| difference | <0.001  | <0.001 | <0.001 | <0.001 | <0.001 | 0.001  | 0.082  | 1.000  | 1.000  | 1.000  | 1.000  | 1.000   | 0.1492  |
| r         | 0.91    | 0.92   | 0.92   | 0.92   | 0.92   | 0.92   | 0.92   | 0.92   | 0.91   | 0.91   | 0.91   | 0.91    |
| bias      | -55     | -50    | -44    | -38    | -32    | -25    | -18    | -11    | -3     | 5      | 14      |         |
| 95% LOA   | -144 to 35 | -137 to 37 | -129 to 41 | -120 to 44 | -112 to 48 | -103 to 52 | -94 to 57 | -85 to 64 | -76 to 70 | -67 to 77 | -58 to 85 | -      |
| CP        | 0.33    | 0.35   | 0.46   | 0.56   | 0.61   | 0.58   | 0.63   | 0.61   | 0.67   | 0.65   | 0.65   | 0.60    |

| **LVEF**  | median | 35     | 38     | 37     | 37     | 37     | 37     | 37     | 37     | 37     | 37     | 37      | 37      |
| 25th-75th | 22–49  | 29–54  | 29–53  | 29–51  | 28–50  | 28–48  | 27–47  | 27–47  | 26–45  | 26–44  | 26–43  | 25–42   |         |
| difference | <0.001  | 0.003  | 0.019  | 0.104  | 0.349  | 1.000  | 1.000  | 1.000  | 1.000  | 1.000  | 1.000  | 1.000   |         |
| r         | 0.80    | 0.81   | 0.81   | 0.82   | 0.82   | 0.83   | 0.83   | 0.83   | 0.83   | 0.83   | 0.83   | 0.83    |
| bias      | 6.3     | 5.3    | 4.5    | 3.7    | 2.9    | 2.1    | 1.2    | 0.4    | -0.3   | -1.1   | -1.9   |         |
| 95% LOA   | -13.8 to 26.3 | -14.4 to 25.0 | -14.6 to 23.6 | -15.3 to 22.7 | -15.7 to 21.5 | -16.3 to 20.5 | -17.0 to 19.5 | -17.9 to 18.7 | -18.7 to 18.2 | -19.5 to 17.3 | -20.5 to 16.7 | -      |
| CP        | 0.58    | 0.65   | 0.70   | 0.72   | 0.72   | 0.70   | 0.72   | 0.77   | 0.74   | 0.74   | 0.72   |         |

25th-75th, 25th to 75th percentile; CMRstd, cardiac magnetic resonance standard method (disk-area summation method); CP, coverage probability; DHM, Dynamic HeartModel; LOA, limit of agreement; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume.

DHM “x” means DHM using threshold of “x”.

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both ED and ES. Although two methods showed tight linear correlations, measurement values were different in majority of cases.

**Discussion**

This is the first systematic study to investigate optimal endocardial border threshold values for determination of LV volumes and LVEF using 3DE fully automated left chamber quantification software (Dynamic HeartModel) and its earlier version (HeartModel) against CMR as a reference. Our results showed that the bias between both Dynamic HeartModel and HeartModel determined LVEDV and LVEDV were smallest when the border threshold value was set to 80-point against CMR disk-area summation method, or 90-point when compared to CMR FT method. Dynamic HeartModel could improve measurement accuracy over previous version of the software because the former was yielded with higher values of CP with equivalent border setting.
Previous studies

The importance of cardiac chamber size and function in cardiac imaging cannot be over-emphasized. The limitations of 2DE have been inexorably mentioned in previous studies, including foreshortening and geometric assumptions [19–21]. The Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults from American Society of Echocardiography and European Association of Cardiovascular Imaging suggested although LV size should be routinely assessed by 2DE, 3DE measurement and reporting of LV volumes is recommended when feasible [22]. Despite the good correlation with CMR, several previous studies using manual or semi-automated contour method showed underestimation of 3DE derived-LV volumes against CMR [19, 20]. With the 3DE gaining popularity and momentum, efforts have been made to integrate its practice into daily routine of ultrasound laboratories. However, previous software were at best semi-automatic and often manual adjustment were required, true border delineation often necessitates additional extra times with observer variabilities that cannot be negligible. Therefore, even though 3DE offers significant improvements, there are impediments to its adoption into clinical practice due to tedious manual editing.

Fully automated left chamber quantification software with knowledge-based technology utilizes 3DE datasets with less technical demanding steps, and the time required to analyze 3DE LV volumes and LVEF is only less than 30 seconds without any manual editing [4, 7]. Time required for the analysis is quite short compared with that using standard CMR disk-summation method (5–10 minutes) or CMR FT method (2–3 minutes). The software allows global and regional editing to correct endocardial border. The global editing permits adjustment of the border threshold value from 0-point to 100-point on ED and ES borders to obtain

**Fig 5. Bland-Altman analysis of left ventricular end-diastolic volume (Fig 5A), left ventricular end-systolic volume (Fig 5B), and left ventricular ejection fraction (Fig 5C) between cardiac magnetic resonance feature tracking method and 3D echocardiography with automated quantification software (Dynamic HeartModel) according to change in border setting from 10 to 100.**

A, border threshold of 10; B, border threshold of 20; C, border threshold of 30; D, border threshold of 40; E, border threshold of 50; F, border threshold of 60; G, border threshold of 70; H, border threshold of 80; I, border threshold of 90; J, border threshold of 100.

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Optimal threshold of fully automated software
Previous validation studies consistently reported that 3DE with fully automated quantification software underestimate LVEDV (~13 mL to ~30 mL) and LVESV (~7 mL to ~29 mL) against CMR as a reference, albeit each author used different LV endocardial border settings [7, 9–12]. It is well known that the accurate endocardial border setting is essential for the accurate measurement of LV volumes and LVEF. However, there are still no recommendations regarding the optimal endocardial border threshold values that can be routinely employed for clinical practice.

**Current study**

In this study, feasibility of LV volumes and LVEF measurements was 88%, and the values were in agreement with the previous studies [4, 6]. Fully automated quantification software is designed and trained to recognize two myocardial borders—the inner and outer extents of the myocardial tissue—that being at the blood-tissue interface and at the interface of the non-compacted and compacted myocardium. Border line can be changed according to global border threshold setting. We investigated how the ED and ES border threshold value setting in fully automated left chamber quantification software affected our quantification of LV volumes.

**Table 3. Comparison of LV volumes and EF between Dynamic HeartModel and CMR FT method (n = 55).**

|        | CMR FT | DHM 0 | DHM 10 | DHM 20 | DHM 30 | DHM 40 | DHM 50 | DHM 60 | DHM 70 | DHM 80 | DHM 90 | DHM 100 |
|--------|--------|-------|--------|--------|--------|--------|--------|--------|--------|--------|--------|---------|
| **LVEDV** |        |       |        |        |        |        |        |        |        |        |        |         |
| median | 210    | 114   | 121    | 133    | 141    | 147    | 155    | 165    | 175    | 184    | 197    | 208     |
| 25<sup>th</sup>–75<sup>th</sup> | 80–156 | 86–164 | 93–177 | 100–186 | 108–196 | 116–203 | 125–212 | 131–223 | 140–234 | 148–252 | 155–263 |
| difference | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | 0.005 | 0.950 | 1.000 | 1.000   |
| r      | 0.93   | 0.91  | 0.94   | 0.94   | 0.94   | 0.94   | 0.94   | 0.94   | 0.93   | 0.93   | 0.93   | 0.93    |
| bias   | -79    | -74   | -65    | -57    | -49    | -40    | -31    | -22    | -12    | -2     | 9      |         |
| 95% LOA | -161 to 2 | -158 to 10 | -142 to 11 | -131 to 17 | -121 to 23 | -110 to 30 | -99 to 37 | -89 to 45 | -78 to 54 | -67 to 64 | -57 to 76 |
| **LVESV** |        |       |        |        |        |        |        |        |        |        |        |         |
| median | 119    | 72    | 78     | 85     | 92     | 98     | 104    | 109    | 116    | 123    | 132    | 142     |
| 25<sup>th</sup>–75<sup>th</sup> | 78–176 | 44–107 | 51–121 | 55–128 | 60–135 | 64–142 | 68–150 | 73–161 | 79–170 | 85–178 | 91–185 |
| difference | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | 0.021 | 1.000 | 1.000 | 1.000   |
| r      | 0.94   | 0.94  | 0.94   | 0.94   | 0.95   | 0.95   | 0.95   | 0.94   | 0.94   | 0.94   | 0.93   |         |
| bias   | -63    | -57   | -52    | -46    | -39    | -33    | -26    | -18    | -10    | -2     | 7      |         |
| 95% LOA | -145 to 20 | -137 to 22 | -129 to 25 | -120 to 28 | -111 to 32 | -101 to 36 | -92 to 41 | -83 to 47 | -73 to 53 | -64 to 60 | -55 to 69 |
| **LVEF** |        |       |        |        |        |        |        |        |        |        |        |         |
| median | 33.5   | 38    | 37     | 37     | 37     | 36     | 36     | 34     | 35     | 34     | 32     |         |
| 25<sup>th</sup>–75<sup>th</sup> | 22–46 | 29–53 | 29–52 | 29–50 | 28–49 | 27–48 | 27–47 | 26–46 | 26–45 | 25–44 | 24–41 |         |
| difference | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | 0.003 | 0.036 | 0.326 | 1.000 | 1.000 | 1.000 | 1.000   |
| r      | 0.86   | 0.87  | 0.87   | 0.87   | 0.87   | 0.88   | 0.88   | 0.87   | 0.87   | 0.87   | 0.86   |         |
| bias   | 6.6    | 5.7   | 4.8    | 4.0    | 3.2    | 2.5    | 1.6    | 0.8    | 0.1    | -0.7   | -1.5   |         |
| 95% LOA | -8.9 to 22 | -9.2 to 20.6 | -9.5 to 19.2 | -10.0 to 18.1 | -10.5 to 17.0 | -11.0 to 15.9 | -11.7 to 15.0 | -12.7 to 14.2 | -13.5 to 13.7 | -14.4 to 13.0 | -15.7 to 12.7 |
| CP     | 0.71   | 0.76  | 0.78   | 0.82   | 0.82   | 0.82   | 0.87   | 0.89   | 0.84   | 0.84   | 0.84   |         |

Data are expressed as median and 25<sup>th</sup>–75<sup>th</sup> percentile. CMR, cardiac magnetic resonance; CP, coverage probability; DHM, dynamic HeartModel; FT, feature tracking; LOA, limit of agreement; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume.

DHM “x” means DHM using threshold of “x”.

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...an LV casts that fit the visual assessment. Previous validation studies consistently reported that 3DE with fully automated quantification software underestimate LVEDV (~13 mL to ~30 mL) and LVESV (~7 mL to ~29 mL) against CMR as a reference, albeit each author used different LV endocardial border settings [7, 9–12]. It is well known that the accurate endocardial border setting is essential for the accurate measurement of LV volumes and LVEF. However, there are still no recommendations regarding the optimal endocardial border threshold values that can be routinely employed for clinical practice.
and LVEF, in comparison to the measurement by CMR as references. In addition to standard disk-area summation method with serial SSFP short axis images, we also applied CMR FT analysis in this study. CMR FT analysis is another method of choice to quantify LV function. Since FT analysis uses 3 apical views to generate LV volumes and LVEF like echocardiography, the comparison between the two methods are more appropriate. It also provides LV volume curves from 3 apical SSFP images. Thus, it had an opportunity to compare LV volume curves derived from Dynamic HeartModel and CMR FT. As seen in Figs 2 and 4, we found there was parallel increase in LVEDV and LVESV and corresponding parallel decrease in LVEF when ED and ES endocardial border threshold were adjusted simultaneously from value of 0-point to 100-point at increment of 10-point. We observed that larger border threshold values allowed LV volumes to closely approximate volumes obtained by CMR. These findings reaffirm the fact that previous routine echocardiographic endocardial border delineations usually result in smaller sizes of LV volumes compared to CMR quantifications, if echocardiographers do not specifically adjust outwardly their manual LV border tracing. Our results showed that the bias of LVEDV and LVESV between both Dynamic HeartModel/HeartModel and CMR disk-area summation method were smallest when the border threshold value was set to 80, or 90 when compared to CMR FT method. Using border threshold value 80 or 90 at

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Fig 6. Left ventricular end-diastolic endocardial border tracing line used by different LV endocardial border threshold in a representative case. Upper, middle, and lower panels show apical 4-chamber, 2-chamber, and long-axis views extracted from 3D dataset. A, no border line; B, border threshold of 0; C, border threshold of 50; D, border threshold of 80; E, border threshold of 90; F, border threshold of 100.
both ED and ES for determination of LVEF, the bias between fully automated quantification software and CMR was also smallest with acceptable CP values. Higher CP value of Dynamic HeartModel over HeartModel supports improved measurement accuracy, and this could be relating to updated algorithm of the software.

The Dynamic HeartModel performs 3DE speckle tracking on the LV endocardial border in each frame over the entire cardiac cycle, resulting in the generation of LV volume curves. We determined its reliability against corresponding LV volume curves derived from CMR FT method. Median r-values by linear regression analysis from the whole subjects (r = 0.87) supported its accuracy and reliability.

In summary, this is the first study to perform systematically the determination of optimal border threshold by fully automated left chamber quantification software for the quantification of LV volumes and LVEF compared to the standard CMR disk-area summation method and
the novel CMR FT method. The fully automated quantification software with appropriate border threshold value setting has a potential for the evaluation of LV function with confidence.

Study limitations
There were several limitations that should be acknowledged in this study. First, the software was not associated with 100% feasibility. In this study, there were 2 cases of incorrect LV casts that could not be edited, and other 6 patients were excluded due to very poor image quality rejected 3DE datasets acquisition, resulting in overall feasibility of 88%. The number however, was similar to previously performed feasibility studies [6]. Second, we only investigated ED and ES border threshold settings at every 10-point basis. Third, to determine the reliability of LV volume curves by Dynamic HeartModel, we used corresponding LV volume curve using CMR FT that has not been validated as a reference standard. Fourth, temporal resolution of CMR (76ms) used in this study was above the Society for Cardiovascular Magnetic Resonance recommendations for LV function assessment [23]. It may overestimate LVESV, resulting in some underestimation of LVEF. Last, further study should be required to validate our results in the larger number of study patients with multicenter setting.

Conclusion
We concluded that LV endocardial border threshold value can be set around 80 to 90 with the same number of LV ED and ES threshold to approximate LVEDV, LVESV and LVEF with clinically acceptable CP values of LVEF as CMR values as a reference.
Supporting information

S1 Table. Analysis of correlation, bias, 95% LOA and CP between HeartModel with serial border setting and CMR disk-area summation method.

(DOCX)

S2 Table. Analysis of correlation, bias, 95% LOA and CP between HeartModel with serial border setting and CMR FT method.

(DOCX)

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References

1. Abraham WT, Young JB, Leon AR, Adler S, Bank AJ, Hall SA, et al. Effects of Cardiac Resynchronization on Disease Progression in Patients With Left Ventricular Systolic Dysfunction, an Indication for an Implantable Cardioverter-Defibrillator, and Mildly Symptomatic Chronic Heart Failure. Circulation. 2004; 110:2864–8. https://doi.org/10.1161/01.CIR.0000146336.92331.D1 PMID: 15505095

2. Curigliano G, Cardinale D, Suter T, Plataniotis G, de Azambuja E, Sandri MT, et al. Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines. Annals of Oncology. 2012; 23:vii155–vii66. https://doi.org/10.1093/annonc/mds293 PMID: 22997448

3. Plana JC, Galdersii M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2014; 15:1063–93. https://doi.org/10.1093/ehjci/jeu192 PMID: 25239940

4. Otani K, Nakazono A, Salgo IS, Lang RM, Takeuchi M. Three-Dimensional Echocardiographic Assessment of Left Heart Chamber Size and Function with Fully Automated Quantification Software in Patients with Atrial Fibrillation. J Am Soc Echocardiogr. 2016; 29:955–65. https://doi.org/10.1016/j.echo.2016.06.010 PMID: 27477865

5. Medvedofsky D, Mor-Avi V, Amzulescu M, Fernandez-Golfin C, Hinojar R, Monaghan MJ, et al. Three-dimensional echocardiographic quantification of the left-heart chambers using an automated adaptive analytics algorithm: multicentre validation study. Eur J Heart Cardiovas Imaging. 2017:1–12.

6. Medvedofsky D, Mor-Avi V, Byku I, Singh A, Weinert L, Yamat M, et al. Three-Dimensional Echocardiographic Automated Quantification of Left Heart Chamber Volumes Using an Adaptive Analytics Algorithm: Feasibility and Impact of Image Quality in Nonselected Patients. J Am Soc Echocardiogr. 2017; 30:879–85. https://doi.org/10.1016/j.echo.2017.05.018 PMID: 28688857

7. Tsang W, Salgo IS, Medvedofsky D, Takeuchi M, Prater D, Weinert L, et al. Transthoracic 3D Echocardiographic Left Heart Chamber Quantification Using an Automated Adaptive Analytics Algorithm. J Am Coll Cardiol Img. 2016; 9:769–82.

8. Sun L, Feng H, Ni L, Wang H, Gao D. Realization of fully automated quantification of left ventricular volumes and systolic function using transthoracic 3D echocardiography. Cardiovascular Ultrasound. 2018; 16:1–9.
9. Yang L-T, Nagata Y, Otani K, Kado Y, Otsuji Y, Takeuchi M. Feasibility of One-Beat Real-Time Full-Volume Three-Dimensional Echocardiography for Assessing Left Ventricular Volumes and Deformation Parameters. J Am Soc Echocardiogr. 2016; 29:853–60.e2. https://doi.org/10.1016/j.echo.2016.05.001 PMID: 27302414

10. Levy F, Schouver E-D, Iacuzio L, Civaia F, Russek S, Dommecq C, et al. Performance of new automated transthoracic three-dimensional echocardiographic software for left ventricular volumes and function assessment in routine clinical practice: Comparison with 3 Tesla cardiac magnetic resonance. Arch Cardiovasc Dis. 2017; 110:580–9. https://doi.org/10.1016/j.acvd.2016.12.015 PMID: 28566200

11. Tamborini G, Piazzese C, Lang RM, Muratori M, Chiorino E, Mapelli M, et al. Feasibility and Accuracy of Automated Software for Transthoracic Three-Dimensional Left Ventricular Volume and Function Analysis: Comparisons with Two-Dimensional Echocardiography, Three-Dimensional Transthoracic Manual Method, and Cardiac Magnetic Resonance Imaging. J Am Soc Echocardiogr. 2017; 30:1049–58. https://doi.org/10.1016/j.echo.2017.06.026 PMID: 28916243

12. Barletta V, Hinojar R, Carbonella A, Gonzalez-Gomez A, Fabiani I, Di Bello V, et al. Three-dimensional full automated software in the evaluation of the left ventricle function: from theory to clinical practice. Int J Cardiovasc Imaging. 2018; 34:1205–13. https://doi.org/10.1007/s10554-018-1336-y PMID: 29605902

13. Hor KN, Gottliebson WM, Carson C, Wash E, Cnota J, Flick R, et al. Comparison of magnetic resonance feature tracking for strain calculation with harmonic phase imaging analysis. J Am Coll Cardiol Img. 2010; 3:144–51.

14. Buss SJ, Breuninger K, Lehrke S, Voss A, Galuschky C, Lossnitzer D, et al. Assessment of myocardial deformation with cardiac magnetic resonance strain imaging improves risk stratification in patients with dilated cardiomyopathy. Eur Heart J Cardiovasc Imaging. 2015; 16:307–15. https://doi.org/10.1093/ehjci/jeu181 PMID: 25246506

15. Schuster A, Hor KN, Kowallick JT, Beerbaum P, Kutty S. Cardiovascular Magnetic Resonance Myocardial Feature Tracking: Concepts and Clinical Applications. Circ Cardiovasc Img. 2016; 9:e004077.

16. Daubert MA, Yow E, Barnhart HK, Rabineau D, Crowley AL, Douglas PS. Quality Improvement Implementation: Improving Reproducibility in the Echocardiography Laboratory. J Am Soc Echocardiogr. 2015; 28:959–68. https://doi.org/10.1016/j.echo.2015.03.004 PMID: 25868600

17. Crowley AL, Yow E, Barnhart HK, Daubert MA, Bigelow R, Sullivan DC, et al. Critical Review of Current Approaches for Echocardiographic Reproducibility and Reliability Assessment in Clinical Research. J Am Soc Echocardiogr. 2016; 29:1144–54.e7. https://doi.org/10.1016/j.echo.2016.08.006 PMID: 27720558

18. Khouri MG, Ky B, Dunn G, Plappert T, Englefeld V, Rabineau D, et al. Echocardiography Core Laboratory Reproducibility of Cardiac Safety Assessments in Cardio-Oncology. J Am Soc Echocardiogr. 2018; 31:361–71.e3. https://doi.org/10.1016/j.echo.2017.11.018 PMID: 29395626

19. Dorosz JL, Lezotte DC, Weitzenkamp DA, Allen LA, Salcedo EE. Performance of 3-dimensional echocardiography in measuring left ventricular volumes and ejection fraction: a systematic review and meta-analysis. J Am Coll Cardiol. 2012; 59:1799–808. https://doi.org/10.1016/j.jacc.2012.01.037 PMID: 22575319

20. Lang RM, Badano LP, Tsang W, Adams D, Agricola E, Buck T, et al. EAE/ASE Recommendations for Image Acquisition and Display Using Three-Dimensional Echocardiography. J Am Soc Echocardiogr. 2012; 25:3–46. https://doi.org/10.1016/j.echo.2011.11.010 PMID: 22183020

21. Tsang W, Lang RM. Reporting of three-dimensional echocardiography-derived left ventricular volumes comes of age. Arch Cardiovasc Dis. 2017; 110:577–9. https://doi.org/10.1016/j.acvd.2017.05.004 PMID: 28882433

22. Lang RM, Badano LP, Mor-Avi V, Alfaiata J, Armstrong A, Emandi L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015; 28:1–39.e14. https://doi.org/10.1016/j.echo.2014.10.003 PMID: 25559473

23. Kramer CM, Barkhausen J, Flamm SD, Kim RJ, Nagel E, Protocols Society of Cardiac Magnetic Resonance. Standardized cardiovascular magnetic resonance (CMR) protocols 2013 update. J Cardiovasc Magn Reson. 2013; 15:91. https://doi.org/10.1186/1532-429X-15-91 PMID: 24103764