RESEARCH ARTICLE

Evaluation of Left Ventricular Mathematical Model for Estimation the Cardiac Mechanics in Heart Failure Patients

Mais O. Al–Saffar,[1]* Ziad Al-Dahhan,[1] Rafid B. Al-taweel[2]

[1]*Department of Biomedical Engineering, Al-Nahrain University, Baghdad, Iraq*
[2]*Internal Medicine Branch, Al-Nahrain University, Baghdad, Iraq*

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ABSTRACT

Objectives: The specific aim was to develop the tools and methods to construct patient-specific mathematical models incorporating clinical, anatomical, biomechanical, and hemodynamic data. The models' ability to make accurate quantitative predictions to clinical data was validated.

Methods: In the developed world, many cardiac imaging modalities are now commonly available and are utilized as a part of routine steps prescribed by appropriate medical societies. These imaging modalities would typically be collected to create personalized models as models expand into clinical application. A successful collaboration with computer modeling includes recognizing the strengths and drawbacks of the various methods. This study investigates the feasibility of using echocardiography as a basis for the development of patient-specific cardiac models and its implementation on the analysis of the mechanics of heart in a ventricular dysfunction patient. Imaging has become an important aspect of the assessment of heart health and disease. For six patients with heart disease who are supposed to undergo a cardiac resynchronization therapy (CRT) implant, research has been performed at the Ibn Al-Bitar center for cardiac surgery. Extreme HF (heart failure) with (NYHA class III or IV) left ventricular ejection fraction >35% and QRS interval >120 ms were selected for CRT. Latest MI (myocardial infarction) or DHF (decompensated heart failure) patients (less than 3 months) were omitted. The clinical valuation was measured before CRT implantation, and 2-D echocardiography was performed to measure left ventricular volume and ejection fraction.

Combining both M-mode echocardiography and TDI color-coded tissue, left ventricular desynchrony has been tested. Clinical condition and increased left ventricular ejection fraction and volume were re-assessed after 3 months of follow-up.

Results: Simulation results of the left ventricle mathematical model for pre-and post-CRT implantation were agreed with clinical and echocardiographic data as obtained for the heart failure patients included in this study.

Conclusion: The left ventricle mathematical model allows realistic cardiac mechanism estimation in heart failure patients.

Keywords: 2D Echocardiography, Cardiac mechanics, CRT, Ejection Fraction, Heart failure, Mathematical models.

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INTRODUCTION

Heart failure (HF) has been a significant cause of death worldwide for over two decades. During the past two decades, advancements in HF care have decreased mortality and morbidity. The diagnosis and therapy of certain types of HF, however, remains difficult.[1]

This is largely because HF is a complex, heterogeneous and multifactorial syndrome. Despite developments in heart failure diagnosis and treatment, the essential mechanisms and interrelationships between the various forms of this condition are not yet well known. Because most existing HF therapies typically focus on symptoms, it has been assumed that mechanism-targeted therapy will be more successful.[2] We have vastly enhanced our understanding of the HF mechanism, largely due to recent technological advances for cardiac imaging and computer simulation. Structural remodeling of left ventricle (LV) (i.e. improvements in the microstructure or tissue form, or both) has been reported as one of the key markers of HF.[3]

Medical imaging modalities can be divided into two main categories according to their energy sources: the former uses ionizing electromagnetic radiation, such as standard X-ray and computed tomography (CT) using X-ray and positron emission tomography (PET); the latter uses single-photon emission computed tomography (SPECT) gamma-ray; the latter uses non-ionizing electromagnetic radiation, such

**Author for Correspondence: mais.o.abdulrassul@ced.nahrainuniv.edu.iq*

as acoustic radiation. The most commonly used imaging modalities in medical practice are currently echocardiography, CT, and MRI.[4] In diagnosing HF patients treated with CRT, and echocardiography plays an evolving and significant role. Researchers ' studies have demonstrated that a major predictor of CRT response is critical left ventricular dyssynchrony. Different echocardiographic methods may be superior in selecting possible CRT responders. Echocardiographic techniques have been used in several recent published studies to potentially help patient selection for CRT before implantation and enhance system settings afterward.[5] With the continuous advances in computational processing speed and modeling and simulation methods, computer models of human physiology are starting to become viable clinical tools to be utilized to improve diagnoses, aid in the planning of treatment, and predict therapeutic outcomes.[6] In particular, for cardiac modeling, one of the main fields of interest regards heart failure (HF) due to LV systolic dysfunction with additional ventricular dyssynchrony. Cardiac resynchronization therapy, which resynchronizes the irregular contraction sequences in a way that improves the efficacy of pumping without raising the intake of heart rate or myocardial oxygen, treats these patients.[4]

MATERIALS AND METHODS

Study Populations and Patient Selections

The study involved six consecutive patients with heart failure (age 51.17 ± 4.12) planned to implant a CRT system at the Ibn Al Bitar cardiac center. Serious HF with New York Heart Association classification (NYHA) of class III or IV, left ventricular ejection fraction (LVEF) less than 35% and the interval of QRS is greater than 120 (ms), represent the selection criteria for CRT. The clinical condition was assessed prior to CRT implantation, and 2-D Echo was performed to evaluate LV volume and ejection fraction. Left ventricular desynchrony was tested using both M-mode echocardiography and TDI color-coded tissue. Clinical status and improvements in left ventricular ejection fraction and volume were reassessed after 3 months of follow-up.

M-mode echocardiography for the left ventricle is as shown in Figure 1.

Bull's eye is a plot displaying color-coded and numerical values for any LV section of the GLS longitudinal peak systolic axis. This bull's eye map offers an intuitive explanation of the state of LV systolic function in a single diagram. Curves of the systolic strain peak, as seen in Figure 2.

Patient's Clinical Evaluation

Medical condition assessment including NYHA class assessment, quality of life score (use the Minnesota HF questionnaire), and exercise ability assessment with the 6-minute Hall-walk test.

Cardiac Function Evaluation

Ultrasound is widely used to measure heart function in routine clinical settings, and multiple echocardiographic tests have been used over the years to test cardiac function. Initially, the Ultrasonic cardiac function measurement centered mainly on the visual perception of myocardial motion in various imaging planes in 2D gray-scale images. Patients were seen in the left side decubitus position using the widely available device (Vingmed System Seven, General Electric-Vingmed) with a transducer of 1,713 MHz at a depth of 16 cm in parasternal and apical view (standard long-axis, 2- and 4-chamber images). Conventional 2-D data and color doppler data in the Cine-loop format, caused by the QRS complex.[7] All echocardiographic information was examined offline using the commercial tool (Echopac 4.0.3, General Electric GE).

Some of the ultrasonic scan planes that are standardized and most widely used are described in Figure 3, That is, (4CH) the four-chamber apical view, (2CH) the two-chamber apical view, (APLAX or 3CH), the apical long-axis view, and the transverse plane of the center, also known as the parasternal short-axis view. Between each projection, the probe is apically

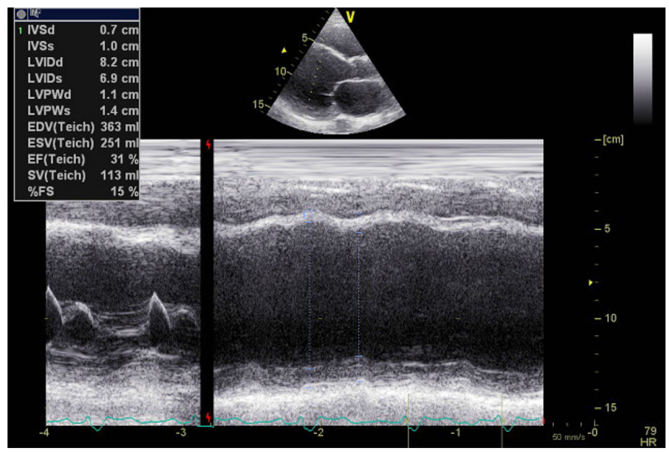

Figure 1: M-mode left ventricle echocardiography, displaying the measurements and function of the LV, (IVSD): Interventricular Septum Thickness in cm at End Diastole, (IVSS): Interventricular Septum Thickness in cm at End systole, (LVIDd): Left Ventricular Internal Diameter in cm at End Diastole, (LVIDs): Left Ventricular Internal Diameter in cm at End systole, (LVPWd): Left Ventricular Posterior Wall Thickness in cm at End Diastole, (LVPWs): Left Ventricular Posterior Wall Thickness in cm at End systole, (EDV): End Diastolic Volume in ml, (ESV): End Systolic Volume in ml, (LVEF): Left Ventricular Ejection Fraction (%), (SV): Stroke Volume (%), (FS): Fractional Shortening (%).

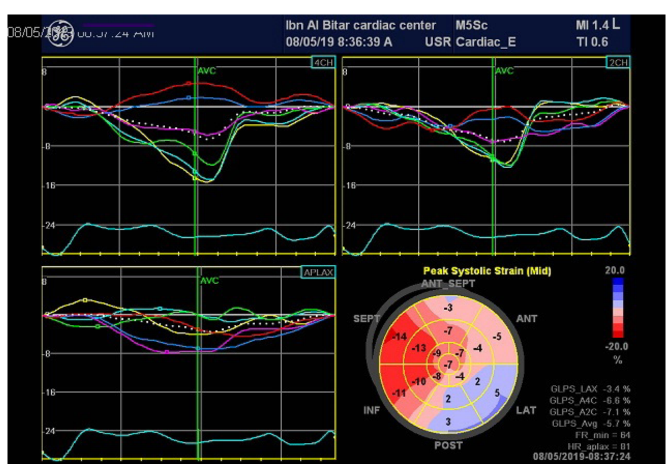

Figure 2: Peak strain curves and Bull's eye plot for LV.

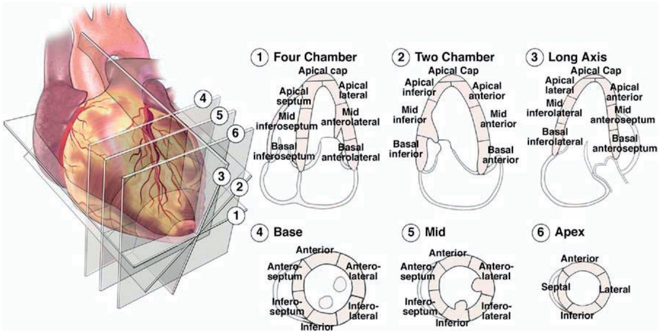

Figure 3: Description of the heart's imaging planes. Based on schematic views, a segmental study of left ventricular walls. The long-axis apical views are seen in the top figures: (4CH), (2CH), and (3CH). The lower figures represent the short-axis view of the heart at the basal, middle, and apical stages.[9]

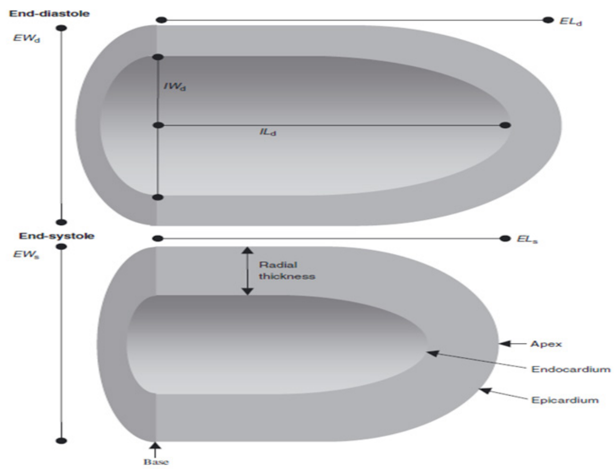

Figure 4: Schematic diagram of the left ventricle used in the model to calculate internal (I) and external (E) volumes during diastole from the short-axis diameter/width (&)and long-axis length (&).[10]

located between two ribs and rotated 60° to obtain 4CH, 3CH, and 2CH.[8]

LV Size Measurement

Linear internal volumes and dimensions are among the most frequently used parameters for left ventricular cavity size characterization. End-diastole and end-systole measurements that are eventually utilized for extract worldwide LV function parameters are widely stated. End-diastole is usually defined for this reason as the first frame after the mitral valve closure or the frame during the cardiac cycle in which the respective LV dimension or volume calculation is the greatest. End-systole can be defined as the frame after the aortic valve is closed or the frame in which the smallest cardiac dimension or volume is found.

The method employs one or other of two well-established three-dimensional internal (*I*) left ventricular geometric shapes using a combination of the area perpendicular to the long-axis at the level of the mitral valve and length (L) of long-axis to determine internal left ventricular volume (see Figure 4).

If one assumes that the external (E) left ventricular volume is similar to the internal volume, then total or external left ventricular volume can be calculated using the same formula.

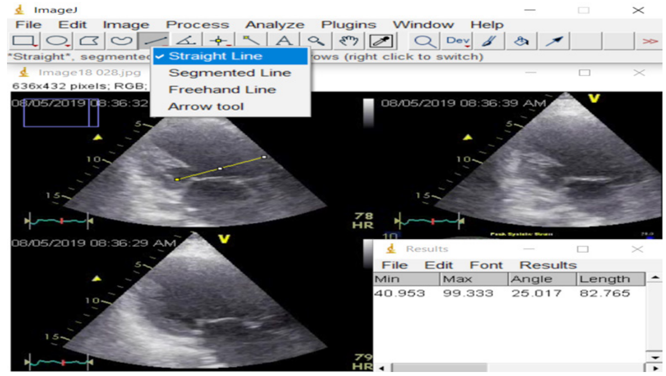

Figure 5: (LVIDd) as measured by using the function Straight-line in Image J program.

The apex, base, endocardium, and epicardium are labeled. The diastolic external and internal volumes are calculated and the myocardial volume is obtained from the difference. The external short-axis width and length are reduced to simulate systole (EW_s and EL_s, respectively) and the new external volume calculated. The internal end-systolic volume is calculated by subtracting the muscle volume from the external end-systolic volume.[10] The total myocardial volume is derived from the difference in total (external) left ventricular volume and the internal volume (Figure 4). The formula that is used in this modeling assumes the geometry of the left ventricle as Area-length method of Dodge

$$V = \frac{\pi}{6} W^2 . L \qquad ...(1)$$

where

V = volume, W =width (i.e., short-axis diameter), L =long-axis length.

For each of the six patients analyzed, LV dimensions were measured manually from two 2D echocardiographic images at the end-diastolic and end-systolic state: long-axis two-chambers (2CH), four-chambers (4CH), and apical long-axis (3CH) views. This operation was carried out in image J workspace, which supports different imaging tools. The dimensions of the left ventricle can be determined in several views. A four-chamber view is the optimal and most commonly used one. Using a four-chamber view with a simple description of the lateral wall and septum endocardial margin and measurement at the level between the papillary muscle and the mitral valve margins. At end-diastolic state, LV diameter was measured papillary muscle to the posterior wall using the function straight-line in image J program as shown in Figure 5.

The contour is closed by connecting the two opposite parts of the mitral ring to a straight line at the mitral valve point. The length of the LV is defined as distance between the bisector of this line and the top of the LV outline that is most distant. Just like the one seen in Figure 6. For use between the two and four apical chambers, the longer LV length is recommended.[11]

For measuring GLS, a line is drawn around the left ventricular endocardium, and is obtained by using the "segmented-line" feature of image J software from apical 2-, 3- and 4-chamber views in end-diastole and end-systolic

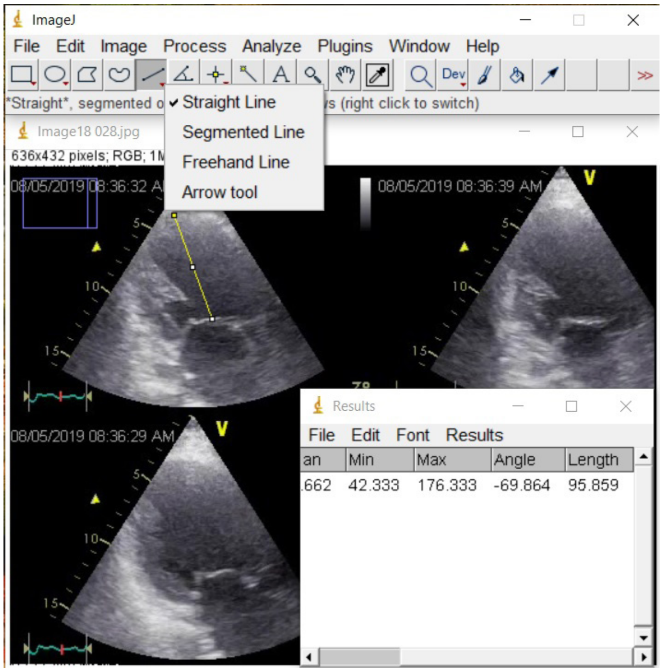

Figure 6: (LVLd) measured by "Straight-line" function in Image J program.

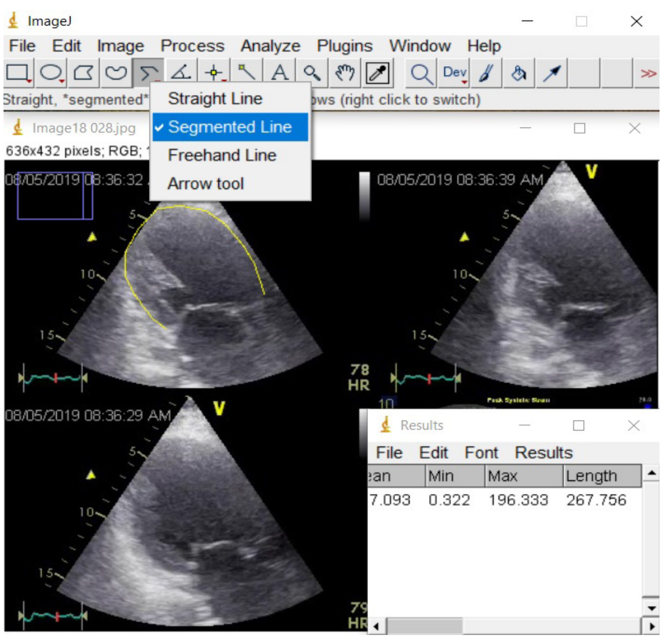

Figure 7: Left ventricular wall length in cm denoted by L measured by "Segmented-line" function in image J program and then interpolated.

states, then this line was interpolated to make a U- shaped line as shown in Figure 7.

From these lines, GLS (%) was measured as:

$$GLS\ (\%) = \frac{L\ (end-diastole) - L\ (end-Systole)}{L\ (end-diastole)} \times 100\% \qquad ...(2)$$

Where the length of the region of interest is L.[12]

Characterization of the Mechanical Properties Through Mathematical

Volume estimates, derived from linear measurements assuming that the volume of LV was derived from the ellipsoid ventricle using Dodge and associate's formulae. The length of the long axis (L) from a mid-aortic to the apex was calculated.[13]

The LV function has been defined by:

Left Ventricular Volume

LV volumes can be measured from 4- and 2-chamber apical views. End-diastole and end-systole measurements, which are then used to derive parameters of the global LV function. LV volumes are measured using the following equation:

$$\mathrm{LVEDV} = \frac{\pi}{6} * (LVIDd)^2 * LVLd \qquad ...(3)$$

Where LVEDV is the volume of the left ventricle in ml at end-diastole, LVIDd is the inner ventricular diametric left in cm at end-diastole, and LVLd at end-diastole in the long-axis ventricular left in cm.

$$\mathrm{LVESV} = \frac{\pi}{6} * (LVIDs)^2 * LVLs \qquad ...(4)$$

Where LVESV is the left ventricular volume in ml at end-systole, LVIDs is the left ventricular internal diameter in cm at end-systole and LVLs is the left ventricular long-axis length in cm at end-systole.

LV Ejection Fraction

EF is calculated from EDV and ESV estimates, using the following formula:

$$LVEF(\%) = \frac{LVEDV - LVESV}{LVEDV} * 100 \qquad ...(5)$$

Where LVEF (%) is the left ventricular ejection fraction (%), LVEDV is the left ventricular volume in ml at end-diastole and LVESV is the left ventricular volume in ml at end-systole.[13]

Stroke Volume

Stroke volume (SV) defined as the difference between the volume of LV at end-diastole (LVEDV) and end-systole (LVESV) as shown in the formula:

$$\mathrm{SV} = \mathrm{LVEDV} - \mathrm{LVESV} \qquad ...(6)$$

Where (SV) is the stroke volume in ml, LVEDV is the end-diastole volume of left ventricular in ml, LVESV is the end-systole volume of left ventricular in mL.[14]

Cardiac Output

CO is known as blood volume per minute that a heart pumps. CO can be measured from the following formulas:

$$\mathrm{CO} = \mathrm{SV} * \mathrm{HR} \qquad ...(7)$$

Where CO is the cardiac output in litter per minute, (SV) is the stroke volume in ml, and (HR) is the heart rate in beat per minute.[14]

LV Fractional Shortening

Fractional shortening of LV was measured from echocardiography as seen in equation (8), from Linear measurements taken from 2D echocardiography images.

$$\mathrm{FS}(\%) = \frac{\mathrm{LVIDd} - \mathrm{LVIDs}}{\mathrm{LVIDd}} * 100 \qquad ...(8)$$

Where FS (%) is the fractional shortening (%), LVIDd is the left ventricular internal diameter in cm at end-diastole, and (LVIDs) is the left ventricular internal diameter in cm at end-systole.[15]

LV Global Systolic Function

The strain of Lagrange in a certain direction is characteristic of changing the length of an object concerning its base length. GLS is usually assessed by measuring the global LV function as shown in equation (9).

$$\text{GLS}\ (\%) = \frac{\text{LVLs} - \text{LVLd}}{\text{LVLd}} * 100 \qquad ...(9)$$

Where GLS (%) is the global longitudinal strain (%), LVLd is the left ventricular long-axis length in cm at end-diastole, LVLs is the left ventricular long-axis length in cm at end-systole.[12]

RESULTS

For the six patients included in this study, mathematical model validation to measured dimensions is made. Comparison between the mathematical model and 2D echocardiography data in Pre-and Post-CRT state were shown in Table 1. Statistical analyses were performed using SPSS software version 22. Results are expressed as mean ± standard deviation or median. Data were compared with paired or unpaired Student's t test when appropriate. Model validation was examined by comparing model vs. measured parameters using Student's paired t-test for comparisons of quantitative variables as shown in Table 2. For all tests, a p-value < 0.05 was considered statistically significant. A bar chart is made for each model parameter to compare them graphically with measured values as shown in Figure 8.

DISCUSSION

In the present study, we investigated the relationship between the mathematical modeling of LV and echocardiographic data in heart failure patients who underwent CRT implantation. From the simulation results of the left ventricle in pre-and post-CRT states, we demonstrated a strong positive correlation between mathematical model and echocardiographic data in all patients included in this study.

CONCLUSION

Combinations between experimental methods (i.e., functional maps and image data) and theory (computational models) are crucial to generating new insights into cardiovascular science.[16] Computer modeling of the LV and cardiac imaging can work synergistically to uncover important mechanisms in a range of LV pathophysiology and their treatment. This growth is motivated by the availability of modern images and the innovativeness and expansion of current ones. Dramatic advances in imaging technology and accelerated technology growth have been seen in recent years.[17] Models also changed to the provision of dynamic function measurements from the characterization of static structures,[18] Various facets of metabolic function, including electrophysiology, mechanics, and blood flow, and new methods, are still being investigated.[19] Imaging and modeling are increasingly related for these purposes. Computational model creation relies on image-acquired information. Image data in three general fields have been drivers of advancement in cardiac computational modeling:

Table 1: Mathematical model validation to measured data for pre- and post-CRT operation patients.

Pre-CRT	*Measured data*											*Model*										
Patient	*LVIDd (cm)*	*LVLd (cm)*	*LVIDs (cm)*	*LVLs (cm)*	*EDV (ml)*	*ESV (ml)*	*EF %*	*SV (ml)*	*FS %*	*CO L/min*	*%*	*LVIDd (cm)*	*LVLd (cm)*	*LVIDs (cm)*	*LVLs (cm)*	*EDV (ml)*	*ESV (ml)*	*EF %*	*SV (ml)*	*FS %*	*CO L/min*	*GLS_{avg} %*
P1	8.2	10.3	6.9	9.5	363	251	31	113	15	9.1	-5.7	8.3	10.1	7.1	9.5	364	251	31	113	15	9.1	-5.6
P2	7.9	10.2	7.3	10.03	333	280	16	53	7	4.2	-5.4	7.8	10.1	7.2	10.03	322	272	16	50	7.7	4	-5.4
P3	6.5	9.7	5.2	9.04	215	128	41	87	20	7	-12	6.5	9.6	5.3	9.1	212	134	37	78	19	6.2	-11.8
P4	9.2	10.5	8	10.2	466	341	27	124	13	8.1	-2.8	9.2	10.4	8.1	10.2	461	350	24	111	12	7.2	-4.6
P5	7.1	10.04	5.7	9.5	265	162	39	103	20	6.7	-7	7.1	10	5.6	9.5	264	156	41	108	21	7	-7.1
P6	6.9	10.1	5.6	9.4	251	155	38	96	19	6.7	-8.8	6.9	10	5.5	9.4	249	149	40	100	20	7	-7.1
Post-CRT	*Measured data*											*Model*										
Patient	*LVIDd (cm)*	*LVLd (cm)*	*LVIDs (cm)*	*LVLs (cm)*	*EDV (ml)*	*ESV (ml)*	*EF %*	*SV (ml)*	*FS %*	*CO L/min*	*%*	*LVIDd (cm)*	*LVLd (cm)*	*LVIDs (cm)*	*LVLs (cm)*	*EDV (ml)*	*ESV (ml)*	*EF %*	*SV (ml)*	*FS %*	*CO L/min*	*GLS_{avg} %*
P1	7.9	10.4	6.8	9.6	340	239	29	100	14	7	-6.7	8	10.6	6.9	9.3	355	232	35	123	14	8.6	-6.7
P2	8.4	9.1	7.6	10.05	338	304	22	83	10	6.6	-5	8.6	9.1	7.7	10.1	352	313	11	39	10	3	-5.1
P3	6.5	9.6	4.9	8.8	213	111	48	102	25	8.2	-9.9	6.5	9.6	5	8.6	212	113	47	99	23	7.9	-9.7
P4	8.1	10.3	6.9	9.8	354	244	31	110	15	9	-3.9	8.1	10.4	6.9	9.8	357	244	32	113	15	9.4	-3.9
P5	6.7	9.8	5.7	9.4	231	160	31	72	15	5.6	-8.4	6.7	9.7	5.8	9.4	228	166	27	62	13	4.8	-8.3
P6	4.9	8.8	3.8	8.1	111	61	45	46	22	3.2	-9.1	4.8	8.9	3.75	8.1	107	60	44	47	22	3.2	-8.7

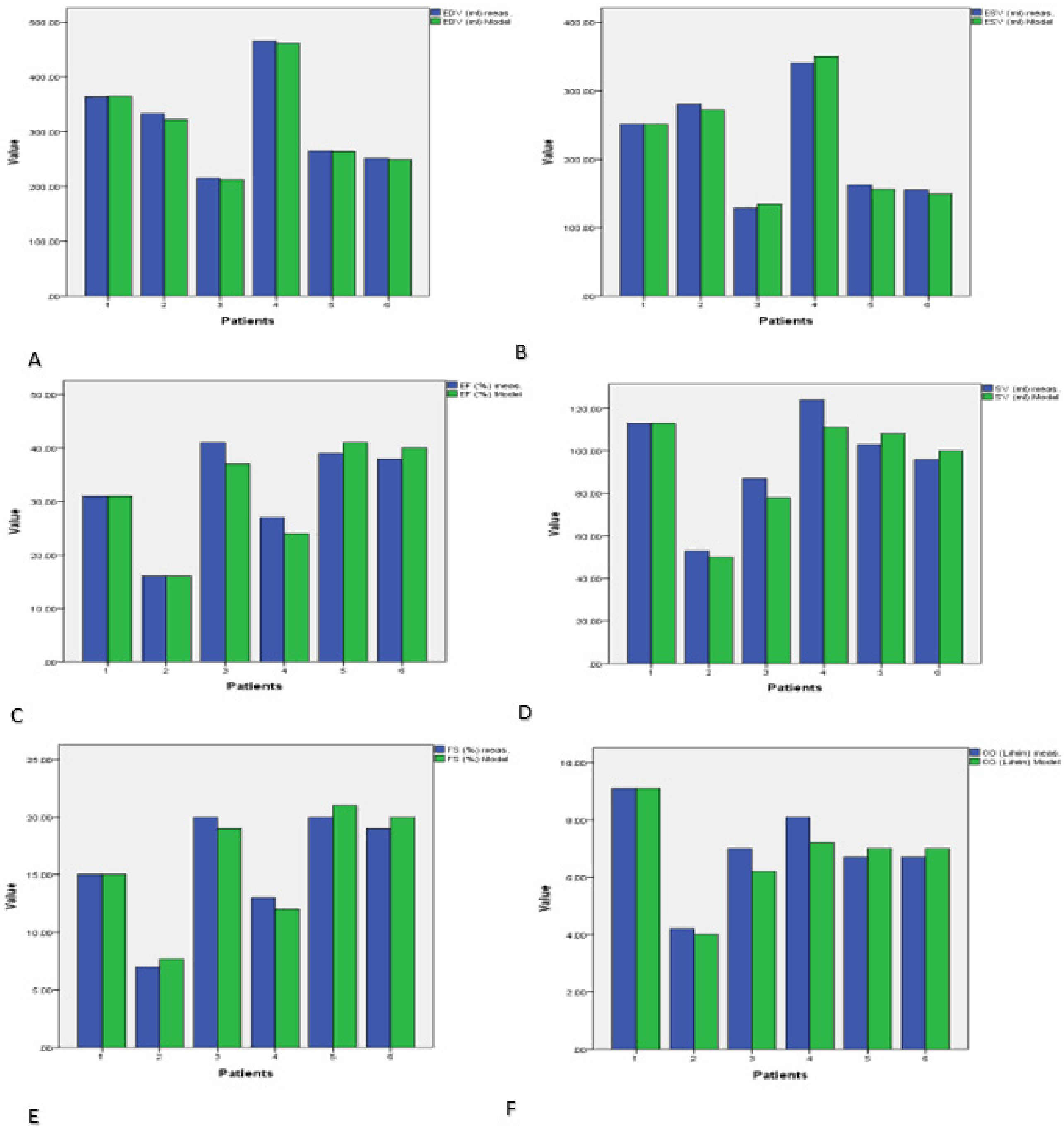

Figure 8: Model parameter bar map validation for (A) end-diastolic volume (B) end-systolic volume (C) ejection fraction (D) stroke volume (E) fractional shortening (F) cardiac output.

First, anatomy is captured and the structural knowledge required to run simulations is given.[20] Secondly, cardiac images will provide functional knowledge utilized to construct models to alter and validate.[21] Thirdly, cardiac images will be used via data assimilation to estimate model parameters,[2] finding the model parameters that better describe the observed data. It is then possible to return these parameters to laboratory investigations or to use them as biomarkers. Models often provide input on imaging methodologies to incorporate images across multiple scales, interpret measurements that implement the system's biophysics, and link data across various imaging platforms.[17] Computer modelling is a powerful tool for understanding cardiac function that has been under-utilized for studying the LV so the left ventricle mathematical model allows realistic cardiac mechanism estimation in heart failure patients.

Table 2: Paired samples T-test for pre- and post-CRT patients showing the comparison between model and measured parameters.

Parameters	*Pre CRT*	*P(significance)*	*Correlation*	*Post CRT*	*P(significance)*	*Correlation*
LVEF (%)						
Measured	32 ± 9.5	Sig.	.967	34 ± 10	Sig.	.911
Model	32 ± 9.9			33 ± 13		
LVIDd (cm)		Sig.				
Measured	7.6 ± .995		.998	7.08 ± 1.3	Sig.	.999
Model	7.6 ± 1.0			7.12 ± 1.4		
LVIDs (cm)						
Measured	6.45 ± 1.1	Sig.	.994	5.95 ± 1.4	Sig.	.999
Model	6.47 ± 1.15			6.01 ± 1.46		
LVEDV (mL)						
Measured	316 ± 91.7	Sig.	.999	265 ± 96	Sig.	.999
Model	312 ± 90.9			269 ± 103		
LVESV (mL)						
Measured	220 ± 84	Sig.	.997	187 ± 92	Sig.	.998
Model	219 ± 86			188 ± 93		
CO						
Measured	7 ± 1.7	Sig.	.949	6.6 ± 2.1	0.061	.791
Model	6.8 ± 1.7			6.2 ± 2.8		
SV (ml)						
Measured	96 ± 24.7	Sig.	.958	86 ± 24	.057	.798
Model	93 ± 24.8			86 ± 36		
FS (%)						
Measured	15.7 ± 5.1	Sig.	.984	17 ± 5.6	Sig.	.984
Model	15.8 ± 5.2			16 ± 5.2		
GLS (Avg) (%)						
Measured	-6.95 ± 3.2	Sig.	.945	-7.2 ± 2.4	Sig.	.999
Model	-6.9 ± 2.6			-7.3 ± 2.3		

Compliance with Ethics Requirements for Human Studies

The study protocol was approved by the Ibn Al-Bitar Specialized Center for Cardiac Surgery research committee. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

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