Am J Cardiovasc Dis 2022;12(4):192-204
www.AJCD.us /ISSN:2160-200X/AJCD0143172

Original Article

4 Dimensional XStrain speckle tracking echocardiography: comprehensive evaluation of left ventricular strain and twist parameters in healthy Indian adults during COVID-19 pandemic

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Received March 28, 2022; Accepted June 10, 2022; Epub August 15, 2022; Published August 30, 2022

Abstract: Introduction: 4D XStrain speckle tracking echocardiography (STE) is a feasible newer technology to evaluate the strain and rotational deformation of left ventricle (LV). We aimed to exhaustively present the normal value ranges of LV strain and twist parameter in healthy Indian adults during COVID-19 pandemic and furthermore to analyse their relationship with age and gender. Method: Study population consisted of 80 adults of 18-60 years (58 men, 22 women), which was arbitrarily divided into two groups: Group A <30 years and Group B >31 years. Results: GLS was higher in females (P<0.01) and in Group A (P<0.01). On the contrary GCS and GRS were higher in men (P=NS) and in Group B (P<0.01), at the mitral valve level. At the papillary muscle level GCS and GRS values are more in men (P<0.01) and in <30 years of age (P<0.01 and P<0.05 respectively). Furthermore, the values of numerous other strain parameters-GLSR, GCSR, GRSR, LGV, TV, TS, TSR, Shear, Shear rate, ROV and RV, reflected heterogeneous variation across gender and various age groups. Twist was greater in men and increased with increasing age (P<0.01). Conclusion: We have demonstrated a comprehensive data obtained in the current study utilizing 4D XStrain STE in healthy subjects. The LV speckle tracking software simultaneously provided 4D volumetric, strain, rotation and twist data in great detail. However, this distinctive technology has not been widely adopted and its evaluation is still limited to research applications. Therefore, further clinical studies are needed to validate our findings.

Keywords: XStrain 4D, speckle tracking echocardiography, LV rotational mechanics, LV twist, LV rotational, shear, transverse strain

Introduction

Global longitudinal strain (GLS) is the most-studied two dimensional speckle tracking echocardiography (2D-STE) parameter worldwide [1]. American Society of echocardiography suggested a GLS value of ≥ -20 + 2% to be normal, after reviewing the enormous data on the subject [2]. STE by three dimensional techniques is advantageous and can expeditiously measure LV volumetric data, strain components, rotation, twist and torsion, in all the left ventricular (LV) segments by a single acquisition [3]. Even though temporal and spatial resolution of 3D imaging is inferior to 2D echocardiography, but 3D-STE remarkably overcomes the other constraints of 2D-STE [4, 5]. The innovative technology of XStrain 4D merges Tomtec GMBH's 3D/4D rendering and Beutel™ computation capabilities [6] for LV border tracking, by fusing speckle tracking information obtained from standard apical 2CH, 3CH and 4CH views, thereby delivering a more complete picture of cardiac function. This tool, relying or high spatial and temporal resolution of 2D imaging, addresses the major limitations currently related to use of full volume 3D-STE [7-11].

LV rotational deformation mimics wringing of a towel and was first described by Lower [12]. It is well known that LV twist (LVT) and LV untwist (LVUT) occurs in systole and diastole, respectively [13]. The net difference between basal and apical rotation is designated as LV twist.

An integrated approach for determination of indices of LV rotational and strain deformation would be ideal (6-8). Furthermore to compliment these two mechanisms with the traditional parameters of systolic function, such as LVEF, would be more advantageous [9]. To be clinically useful, there is a necessity of normal reference values, to compare with data obtained from patients with suspected myocardial diseases. To date, values of strain and rotational parameters in healthy subjects are limited, heterogeneous and inconsistent [13-15]. Hence, we aimed to comprehensively report, the normal value ranges of left ventricular STE, obtained by the advanced technique of 4 Dimensional XStrain echocardiography, in healthy Indian adults.

Material and methods

Study design and patient population

The present study was carried out at Prakash Heart Station and Diagnostic, Lucknow India. This was prospective, observational study in which 107 healthy Indian adults were recruited and later on 27 cases were omitted due to inferior image quality. Finally 80 participants were enrolled, during a period of 9 months, from June 2021-Feb 2022. Study group was of the age group 18-60 years of either sex; and was arbitrarily divided into two groups: Group A comprising of subjects from 18-30 years and Group B from 31-60 years. Those participants were included, if they were asymptomatic with a normal physical examination, BMI-23 or less, waist size 85 cm^2 or less in men and 80 cm^2 or less in women, free from overt cardiovascular disease, not receiving any drugs, non-smoker, non-tobacco chewer, non-diabetic, non-hypertensive according to JNC-8 guidelines, having normal thyroid and lipid profile, normal resting ECG in sinus Rhythm with a normal 2DE and Treadmill Stress ECG. Those individuals were excluded if there was presence of diabetes mellitus, neurological or psychiatric illness, malignany, CAD, Aortic root abnormalities, aortic dilatation, thyroid disease, valvular heart disease, history of cardiac rhythm abnormalities, heart failure, systemic hypertension and significant pulmonary hypertension.

The study procedure was approved by research ethics committee of our institution (approval no IEC/PDC/PHSD/2021: 01, 02). All subjects gave their written informed consent for the current study.

Data collection and study procedure

All patients underwent full history taking, clinical examination and a standard resting 12 lead ECG. A negative COVID-19 RT-PCR report conducted within 72 hours prior to the data of enrollment and echocardiography, was the essential requirement.

Echocardiography

All echocardiographic evaluations were performed by the author himself, using-My Lab X7 4D XStrain echocardiography machine, Esaote, Italy. The images were acquired using a harmonic variable frequency (1-5 Mhz) electronic single crystal array transducer while the subject was lying in left lateral decubitus position, as recommended by American Society of Echocardiography [16].

Conventional echocardiography

Conventional M-mode, two dimensional and pulse wave doppler (PWD) echocardiography was performed from parasternal long axis, short axis and apical four chamber views according to the recommended guidelines [16], and following parameters were derived: interventricular septum and LV posterior wall thickness in end-diastole and end-systole (IVS d and LVPW d, respectively), LV internal dimension at end-diastole and end-systole (LVID d and LVID s, respectively), LV end-diastolic and end-systolic volumes (LVEDV and LVESV respectively), ejection fraction (EF%), LV Mass in diastole (LV Mass d), Cardiac Output (CO) and Cardiac Index (CI). Devereux formula [17] was employed for calculating the LV Mass. By using PWD early diastolic velocity (E), late diastolic velocity (A) and E/A ratio was measured.

Tissue doppler echocardiography

Tissue Doppler Echocardiography (TDI) was conducted by placing the PWD sample volume at the lateral mitral annulus in apical 4 chamber view and early diastolic velocity (E') and E/E' ratio were determined in the TDI mode.

4D XStrain speckle tracking echocardiography

From the apical position 2 Dimensional cine loops were acquired from two chamber, three chamber and four chamber views. High quality

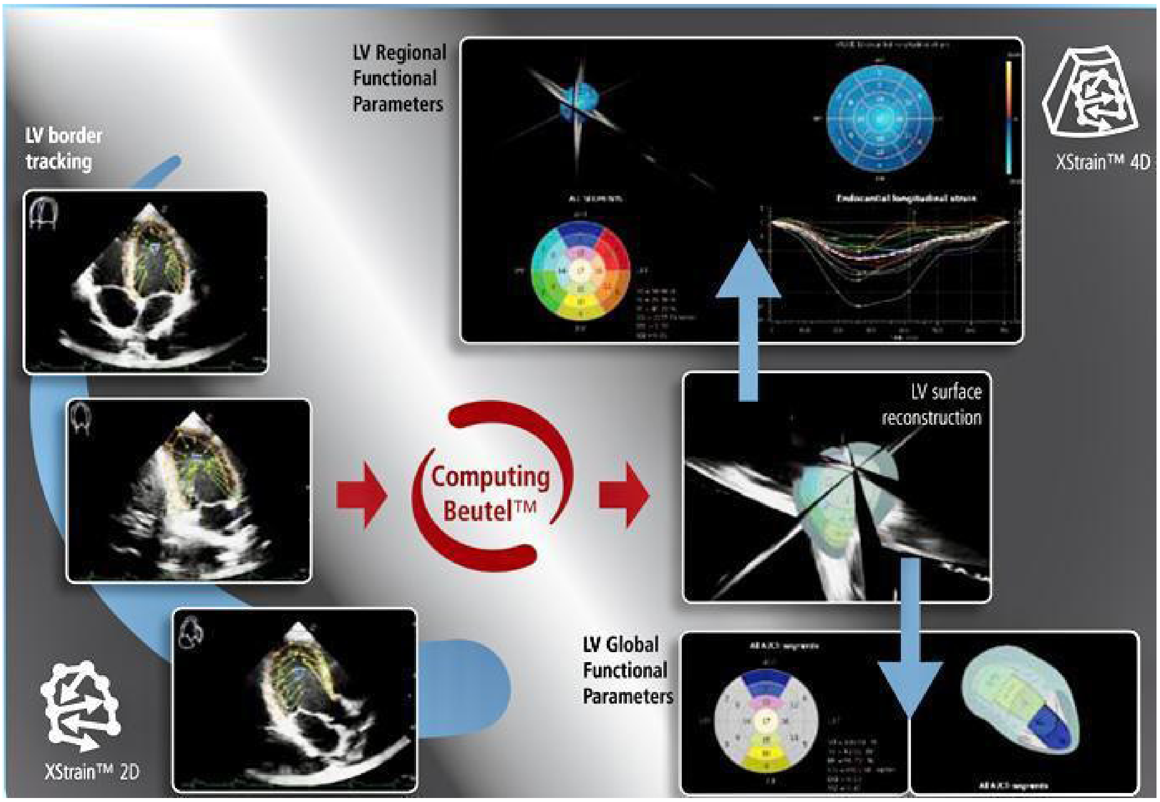

Figure 1. XStrain 4D global LV strain analysis.

ECG signal was must for proper gating and a minimum of three cardiac cycles were acquired of each cine loop. The study was performed with a frame rate between 40-75 fps and then stored digitally on a hard disk for offline analysis by software package XStrain™ advanced technology TOMTEC GMGH 3D/4D rendering Beutel™ computation capabilities [6] (**Figure 1**). The LV endocardial and epicardial borders were identified tracked and highlighted by a semi-automatic tool-AHS Aided Heart Segmentation Esaote, for border segmentation. 13 equidistant tracking points were automatically incorporated along the LV endocardial border and where necessary manual adjustment of endocardial tracing was done. The software automatically divided the LV wall into 6 segments and then the acquired cine loop of each apical view was tracked frame by frame throughout the entire cardiac cycle. The cine loops with inadequate tracing quality and with any signs of arrhythmia, were excluded.

The LV bull's eye depiction according to 17 segment model was generated by XStrain 4D software, by integrating the results of each set of cine loops [18, 19]. The unique software provided segmental, regional and global peak systolic values of various LV strains and strain rates. Moreover, XStrain-4D software created a 3D reconstruction for calculating LV volumes and EF [20], and XStrain 4D-EF by the "Beutel Mode" method (TOMTEC, Germany) [21].

LV twist (**Figure 2**) and rotation measurements were obtained from short axis views, at the level of mitral valve, papillary muscle and apex (**Figure 3**). The following 4D XStrain estimated values of volumetric, strain, rotation and twist parameters were statistically analyzed.

Volumetric data

Sphericity index in diastole and systole, LVEDV, LVESV, 4D-EF%, CO and CI.

Strain parameters

Global longitudinal strain (GLS), Global longitudinal strain rate (GLSR), Global circumferential strain (GCS), Global Circumferential strain rate (GCSR), Global radial strain (GRS), Global radial strain rate (GRSR), Transverse strain (TS),

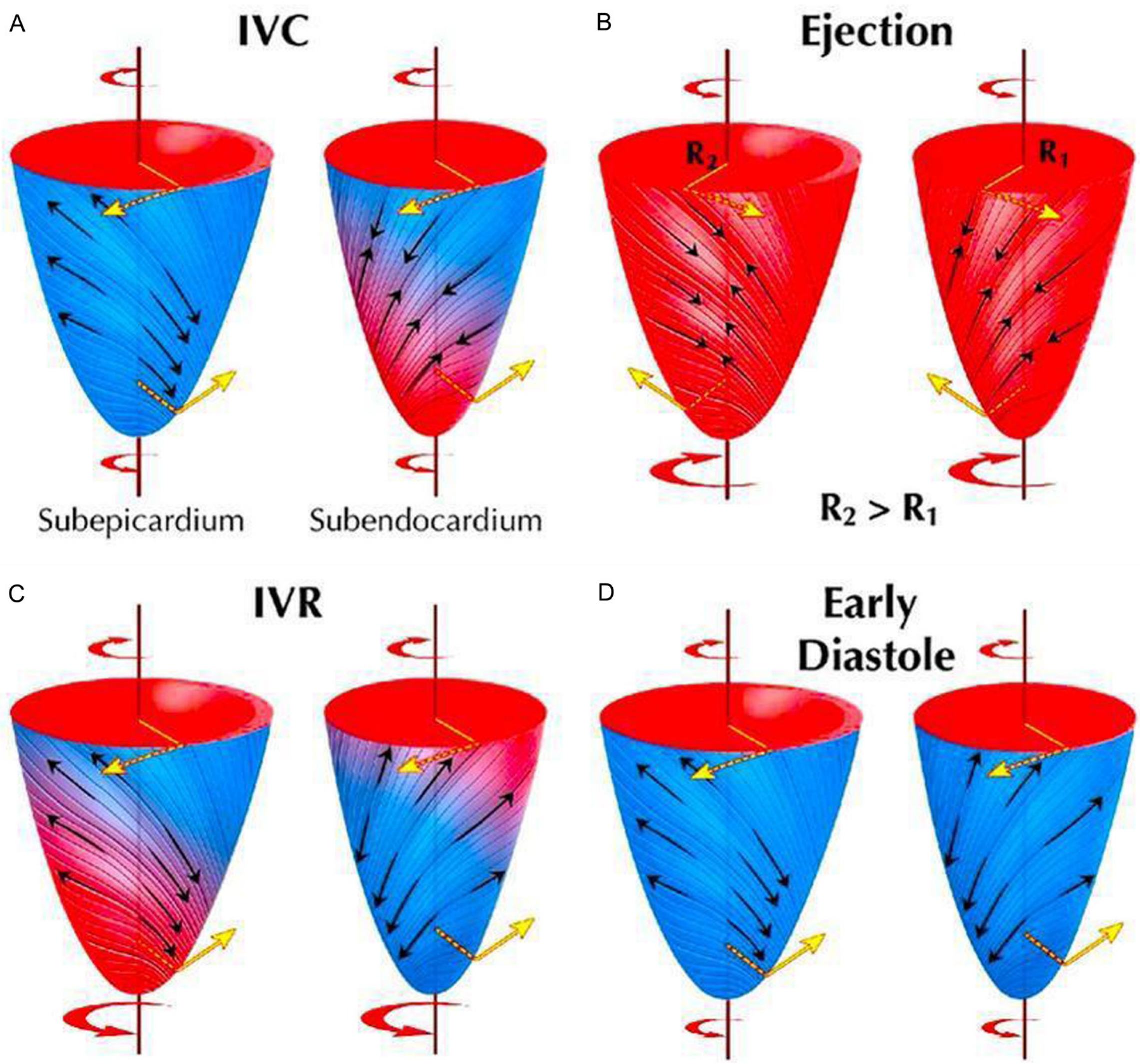

Figure 2. Sequence of Twist Mechanics Explained in an Experimental Animal Model Electric and mechanical activation are initiated in the apical subendocardial region. During isovolumic contraction (IVC) (A), the subendocardial myofibers (right-handed helix) shorten with stretching of the subepicardial myofibers (left-handed helix), producing a brief clockwise rotation of the apex and a counterclockwise rotation of the left ventricular base. During ejection (B), the subendocardial and subepicardial layers shorten simultaneously, with shortening strains near the apex exceeding those of the base. The larger arm of moment of the subepicardial fibers dominates the direction of twist, causing rotation of the apex and base in counterclockwise and clockwise directions, respectively. During isovolumic relaxation (IVR) (C), subepicardium lengthens from the base toward the apex and the subendocardium from the apex toward the base. The subsequent period of diastole is characterized by relaxation in both layers with minimum untwisting (D).

Transverse strain rate (TSR), Transverse velocity (TV), Longitudinal velocity (LGV), Radial velocity (RV), Rotational velocity (ROV), Shear (S) and Shear rate (SR). Longitudinal and circumferential strains have negative values in systole and the radial one is characterized by positive values. Strain, Strain rate and velocity were d*elineated in %, 1/s, cm/sec and o/s wh*ere suitable.

Rotation and twist parameters

Peak apical rotation (PAR), Time to peak apical rotation (t PAR), peak twist (PT), time to peak twist (t PT), twist rate (TR), time to peak twist rate (t TR), untwist rate (UR) and time to peak untwist rate (t UR). The rotation, twist and untwist parameter indices are expressed in *0, ms and o/s* where appropriate.

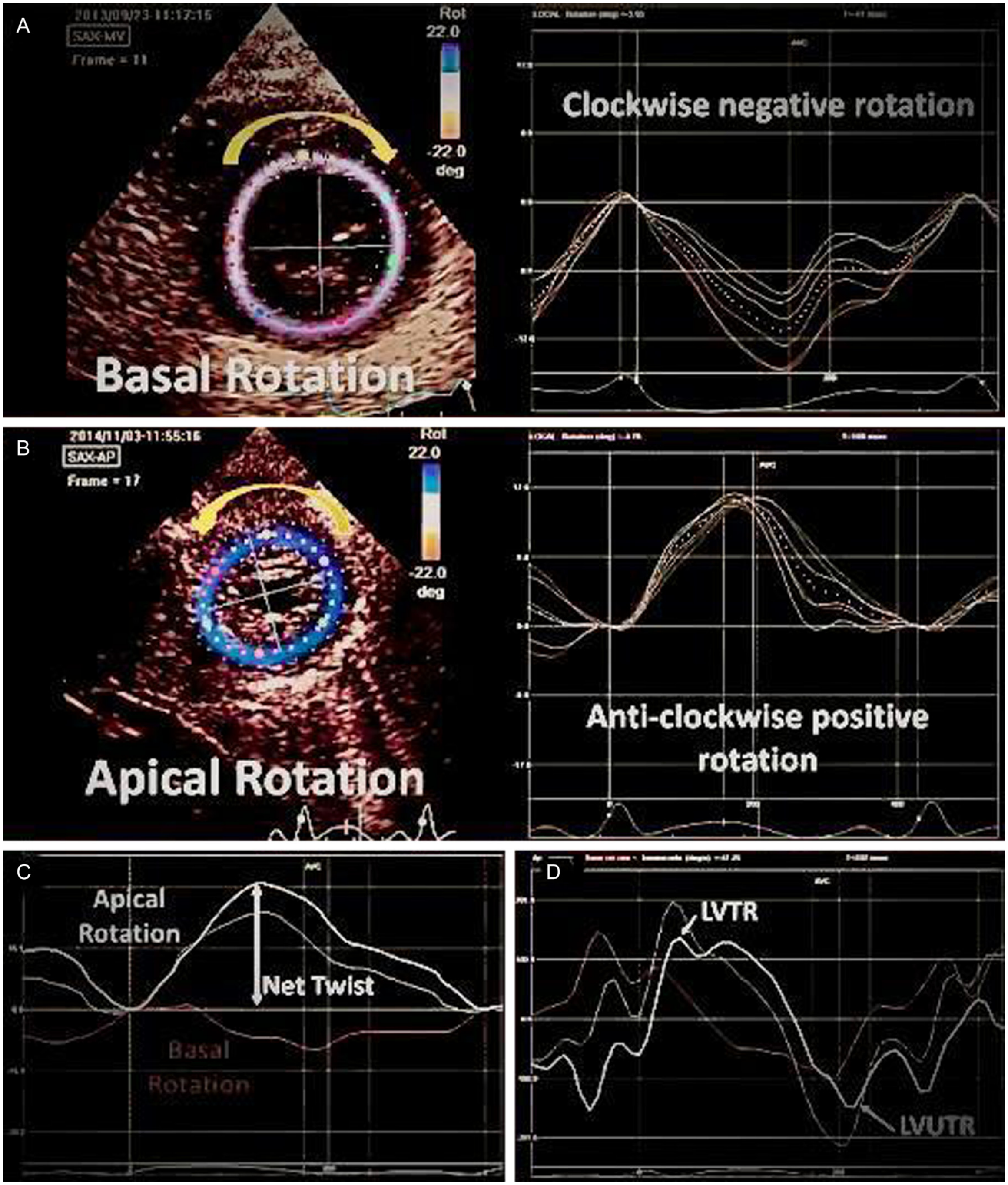

Figure 3. LV apical, basal rotation, LV twist rate (LVTR) and LV untwist rate (LVUTR).

Statistical analysis

Statistical analysis was performed with the Microsoft excel® (Excel 2019, Microsoft corp, Seattle Washington, USA). Normal distribution of data was checked by Kolmogorov-Smirnov test. The continuous variables are expressed as mean ± SD. The 95% confidence interval of mean was also calculated. Enrolled participants were stratified according to age (Group A and Group B) and sex. Comparison of various datasets between men and women and between Group A and Group B were performed by Students t-test for independent groups.

The level of significance used was <0.05. A higher t value having a probability <0.05 was marked significant. A *p* value <0.01 was marked highly significant.

Table 1. Demographic data (n=80)

VARIABLES	Study Population (n:80)	MALE (N-58) MEAN ± SD	FEMALE (N-22) MEAN ± SD	P		Age wise Group (Years)		P	
				P-Val	Sign	Group A (n=45)	Group B (n=35)	*P*-Val	Sign
AGE (YRS)	30.6 ± 11.49	29.07 ± 11.60	34.64 ± 10.42	<0.01	**	22.47 ± 4.14	41.06 ± 9.21	<0.01	**
WEIGHT (kg)	62.23 ± 11.02	64.40 ± 10.56	56.55 ± 10.65	<0.01	**	59.67 ± 10.22	65.54 ± 11.44	0.07	NS
HT (cm)	165.4 ± 7.87	167.76 ± 6.15	159.18 ± 8.84	<0.01	**	165.04 ± 6.35	165.86 ± 9.67	<0.01	**
BSA (M^2)	1.68 ± 0.17	1.73 ± 0.15	1.57 ± 0.18	<0.01	**	1.65 ± 0.15	1.73 ± 0.19	<0.01	**
BMI	22.62 ± 2.90	22.80 ± 2.94	22.17 ± 2.87	<0.01	**	21.81 ± 2.94	23.66 ± 2.58	0.04	*
SBP (mmhg)	118.4 ± 10.75	118.38 ± 10.70	118.45 ± 11.38	<0.01	**	114.93 ± 10.59	122.86 ± 9.52	0.02	*
DBP (mmhg)	76.7 ± 6.65	76.66 ± 6.84	76.82 ± 6.46	<0.01	**	74.58 ± 6.56	79.43 ± 5.91	0.02	*
HEART RATE (bpm)	79.25 ± 13.39	77.16 ± 12.04	84.77 ± 15.68	<0.01	**	78.69 ± 12.41	79.97 ± 14.89	<0.01	**

NS = Not Significant (P>0.05), **Highly Significant = (P<0.01), *Significant = (P<0.05). Group A: 18 to 30 years of age, Group B: 31 to 60 years of age. HT-Height, BSA-Body Surface Area, BMI-Body Mass Index, SBP-Systolic blood pressure, DBP-Diastolic blood pressure.

Table 2. Conventional echocardiogrpahy data (n=80)

VARIABLES	MALE (N-58) MEAN ± SD	FEMALE (N-22) MEAN ± SD	P		Age wise Group (Years)		P	
			P-Val.	Sign.	Group A* (n=45)	Group B* (n=35)	*P*-Val.	Sign.
EPSS (mm)	0.57 ± 0.25	0.66 ± 0.40	<0.01	**	0.58 ± 0.32	0.61 ± 0.26	0.12	NS
Left Atrium (cm)	2.81 ± 0.56	2.72 ± 0.49	<0.01	**	2.63 ± 0.44	2.97 ± 0.61	0.14	NS
IVS d (cm)	0.76 ± 0.17	0.73 ± 0.13	<0.01	**	0.72 ± 0.17	0.79 ± 0.15	0.07	NS
LVID d (cm)	4.80 ± 0.41	4.45 ± 0.47	<0.01	**	4.65 ± 0.46	4.77 ± 0.45	<0.01	**
LVPW d (cm)	0.80 ± 0.14	0.73 ± 0.13	<0.01	**	0.73 ± 0.13	0.83 ± 0.13	0.13	NS
LVEDV (ml)	76.02 ± 51.94	32.64 ± 44.94	<0.01	**	80.17 ± 46.94	43.43 ± 54.96	<0.01	**
LV MASS d (gm)	124.09 ± 32.38	101.14 ± 30.91	<0.01	**	108.87 ± 27.84	129.23 ± 36.76	0.42	NS
C.O. (L/min)	5.20 ± 1.42	5.31 ± 2.02	<0.01	**	4.98 ± 1.39	5.56 ± 1.79	0.17	NS
E/A RATIO	1.58 ± 0.58	1.34 ± 0.54	<0.01	**	1.79 ± 0.54	1.16 ± 0.39	<0.01	**
Lateral TDI E’	10.68 ± 7.15	5.09 ± 6.62	<0.01	**	12.34 ± 6.94	5.03 ± 5.85	<0.01	**
Lateral TDI E/E’ RATIO	0.23 ± 0.30	0.50 ± 0.48	0.55	NS	0.19 ± 0.33	0.46 ± 0.38	<0.05	*
2D-EF (%)	0.63 ± 0.07	0.69 ± 0.07	<0.01	**	0.64 ± 0.08	0.64 ± 0.08	<0.01	**

NS = Significant (P>0.05). **Highly Significant = (P<0.01). *Significant = (P<0.05). Group A: 18 to 30 years of age. Group B: 31 to 60 years of age.

Results

Demographic data

A total of 80 healthy Indian adults were enrolled in this study (**Table 1**). There were 58 males (72.5%) and 22 females (27.5%) and their mean age was 29.07 ± 11.60 years and 35.64 ± 10.42 years respectively. Men had larger body surface area and body mass index than women (P<0.01), however women were having higher BP and HR values than men (P<0.01).

Conventional echocardiography data

LA size, IVS d, LVPW d, LVID d, LVEDV, LV Mass d, E/A ratio and E’ are having higher values in men (P<0.01) (**Table 2**). However E/E’ ratio, CO and 2D-EF% were higher in women (P<0.01). Moreover, LVEDV, E/A ratio, E’ and 2D-EF% values were more in Group A (P<0.01), even though LVID d and E/E’ ratio were greater in Group B (P<0.01 and P<0.05 respectively).

4 Dimensional volumetric data

The 4 Dimensional volumetric data illustrates (**Table 3**), that LVEDV, 4D-EF%, CO and CI are greater in females (P<0.01), furthermore sphericity index was greater in Group A and LVEDV, LVESV, 4D-EF% and CI were higher in Group B (P<0.01, P<0.01 and P<0.05, respectively).

4 Dimensional XStrain STE-LV strain data

GLS was higher in females (P<0.01) and in Group (P<0.01) (**Table 4**). On the contrary GCS and GRS were having higher values in men, at the mitral valve and papillary muscle level (P=NS and P<0.01, respectively) (**Table 5**). These values were more negative in Group B (P<0.01), at the mitral valve level and conversely more negative in Group A, at papillary muscle

Table 3. 4 Dimensional volumetric data (n=80)

VARIABLES	MALE (N-58) MEAN ± SD	FEMALE (N-22) MEAN ± SD	P		Age wise Group (Years)		P	
			P-Val.	Sign.	Group A* (n=45)	Group B* (n=35)	*P*-Val.	Sign.
Sphericity Index d	0.46 ± 0.11	0.43 ± 0.10	<0.01	**	0.46 ± 0.12	0.44 ± 0.10	<0.01	**
Sphericity Index s	0.38 ± 0.11	0.36 ± 0.12	<0.01	**	0.39 ± 0.12	0.36 ± 0.10	<0.01	**
LVEDV (ml)	74.47 ± 17.88	72.10 ± 16.96	<0.01	**	72.08 ± 19.09	76.06 ± 15.34	0.03	*
LVESV (ml)	32.93 ± 9.39	31.95 ± 10.06	<0.01	**	32.61 ± 9.93	32.73 ± 9.11	<0.01	**
EF (%)	56.33 ± 5.56	56.45 ± 6.44	<0.01	**	55.47 ± 5.58	57.51 ± 5.89	<0.01	**
CO (L/min)	3.17 ± 0.82	3.23 ± 0.95	<0.01	**	3.07 ± 0.82	3.33 ± 0.89	0.08	NS
Cardiac Index (L/mm/m^2)	1.84 ± 0.47	2.05 ± 0.52	<0.01	**	1.86 ± 0.47	1.94 ± 0.51	0.03	*

NS = Not Significant (P>0.05). **Highly Significant = (P<0.01). *Significant = (P<0.05). Group A: 18 to 30 years of age. Group B: 31 to 60 years of age.

level (P<0.01 and P<0.05, respectively) (**Table 5**).

On deeper analysis of other strain parameters, our study revealed that GLSR, LGV, TV and shear rate were having greater values in males than in females (P<0.01) (**Table 4**). Otherwise, shear was higher in females (P <0.01), in 2CH and 3CH views, although it was greater in males (P<0.01), in 4CH view. Interestingly, TV and TSR were having higher values in women (P<0.01), in 2CH and 3CH views and 3CH and 4CH views, respectively. However, there heterogenous distribution of the values of these parameters in Group A and Group B.

Additionally strain parameters - ROV, Radial Velocity (RV), GCSR, and GRSR values showed a non-congruous pattern, at the mitral and papillary muscle level, when analysed for gender and age (**Table 5**).

4 Dimensional XStrain STE-LV rotation and twist data

Despite 80 healthy adults being enrolled in the current study, LV rotation and twist parameters could be satisfactorily delineated in 65 subjects (**Table 6**). Peak apical rotation, peak twist and untwist rate and their time to peak were significantly increased (P<0.01) in men, however peak basal rotation, on the contrary, was higher in women (P<0.01). In Group B values of basal rotation, twist and untwist rate were higher than in Group A (P<0.01). Thus, twist, untwist and apical rotation were greater is men and the values increased with increasing age (P<0.01), even though apical rotation being more in Group A (P<0.01).

Discussion

We are presenting the comprehensive data of LV strain and rotational deformation, obtained by 4 Dimensional XStrain STE. Impact of age and sex on these parameters, were also assessed. The current study was implemented during COVID-19 pandemic, and to encounter healthy adults during these difficult times was an extremely arduous task.

STE has been widely studied and been found to be a highly effective tool for analysis of LV functions [22]. LV myocardial fibers are oriented in a right handed helix in the subendocardium and left handed helix in the subepicardium, with circumferential fibers lying between the two. Various patterns of myocardial deformation is because of this complex anatomical structure. During systole the LV shortens (longitudinal and circumferential dimension) and twists along its long axis, while its wall thickens (radial dimension). Strain is a measure of myocardial deformation of a segment in relation to its original dimension [6]. Moreover, the LV is also characterised by rotational mechanics. Several studies have highlighted that LV torsion is due to movement of spiral double helix like structure of muscle fibers in the subendocardium, which on contraction move in the opposite direction to the subepicardium [23-27]. LV torsion is induced by the synchronous movement of LV base towards the apex [28]. Therefore, simultaneous and combined action of ventricular rotation and longitudinal shortening gives rise to LV contraction [28]. LV dysfunction may not affect these two mechanisms in the same way [29], and their assessment may be important in clinical practice because they may be detected very early in pathological states where the classic haemodynamic parameters are unable to identify them [30-32].

GCS the chief predictor of LV twist is maintained according to many trials of heart failure with preserved ejection fraction (HFpEF) [33-

Table 4. LV strain parameters-part-1 (n=80)

Apical long axis views	VARIABLES	MALE (N-58) MEAN ± SD	FEMALE (N-22) MEAN ± SD	P		Age wise Group (Years)		P	
				P-Val.	Sign.	Group A*	Group B*	*P*-Val.	Sign.
Global longitudinal strain (%) (-19.10 ± 3.12)		-18.99 ± 3.08	-19.41 ± 3.27	<0.01	**	-19.1 ± 2.56	-18.96 ± 3.76	<0.01	**
2 CH View	(a) Global longitudinal strain (%)	-20.83 ± 4.16	-20.72 ± 3.51	<0.01	**	-21.13 ± 3.39	-20.37 ± 4.62	<0.01	**
	(b) Global longitudinal strain Rate (1/s)	-1.79 ± 0.49	-1.75 ± 0.42	<0.01	**	-1.84 ± 0.49	-1.70 ± 0.44	<0.01	**
	(c) Longitudinal velocity (cm/s)	0.43 ± 0.11	0.42 ± 0.13	<0.01	**	0.45 ± 0.10	0.40 ± 0.13	<0.01	**
	(d) Transverse velocity (cm/s)	0.38 ± 0.08	0.36 ± 0.07	<0.01	**	0.38 ± 0.07	0.38 ± 0.09	<0.01	**
	(e) Transverse strain (%)	24.29 ± 8.83	29.62 ± 10.79	<0.01	**	25.05 ± 8.84	26.67 ± 10.65	0.09	NS
	(f) Transverse strain rate (1/s)	2.82 ± 0.94	2.69 ± 0.72	<0.01	**	2.72 ± 0.86	2.86 ± 0.91	<0.05	*
	(g) Shear (%)	0.12 ± 0.06	0.13 ± 0.06	<0.01	**	0.13 ± 0.06	0.11 ± 0.05	<0.01	**
	(h) Shear rate (1/s)	2.26 ± 0.99	1.99 ± 0.68	<0.01	**	2.20 ± 0.76	2.17 ± 1.10	<0.05	*
3 CH View	(a) Global longitudinal strain (%)	-17.38 ± 3.17	-18.92 ± 3.42	<0.01	**	-17.52 ± 2.92	-18.16 ± 3.73	<0.05	*
	(b) Global longitudinal strain Rate (1/s)	-1.67 ± 0.39	-1.60 ± 0.38	<0.01	**	-1.68 ± 0.38	-1.61 ± 0.39	<0.01	**
	(c) Longitudinal velocity (cm/s)	0.43 ± 0.13	1.42 ± 5.04	0.79	NS	0.95 ± 3.52	0.37 ± 0.08	0.21	NS
	(d) Transverse velocity (cm/s)	0.35 ± 0.07	0.34 ± 0.08	<0.01	**	0.33 ± 0.07	0.35 ± 0.07	<0.05	*
	(e) Transverse strain (%)	25.15 ± 7.54	27.42 ± 9.65	<0.01	**	23.35 ± 8.67	28.89 ± 6.33	0.71	NS
	(f) Transverse strain rate (1/s)	2.48 ± 0.58	2.50 ± 0.64	<0.01	**	2.39 ± 0.63	2.62 ± 0.52	0.09	NS
	(g) Shear (%)	0.10 ± 0.04	0.12 ± 0.07	<0.01	**	0.11 ± 0.06	0.10 ± 0.04	<0.01	**
	(h) Shear rate (1/s)	2.24 ± 0.76	2.14 ± 0.71	<0.01	**	2.29 ± 0.82	2.12 ± 0.63	<0.01	**
4 CH View	(a) Global longitudinal strain (%)	-19.12 ± 3.91	-18.59 ± 4.97	<0.01	**	-19.00 ± 3.56	-18.94 ± 4.96	<0.01	**
	(b) Global longitudinal strain Rate (1/s)	-1.64 ± 0.32	-1.49 ± 0.41	<0.01	**	-1.62 ± 0.36	-1.58 ± 0.33	<0.01	**
	(c) Longitudinal velocity (cm/s)	0.42 ± 0.10	0.39 ± 0.13	<0.01	**	0.44 ± 0.11	0.37 ± 0.09	<0.01	**
	(d) Transverse velocity (cm/s)	0.36 ± 0.07	0.33 ± 0.08	<0.01	**	0.34 ± 0.08	0.35 ± 0.07	<0.01	**
	(e) Transverse strain (%)	24.04 ± 8.83	26.94 ± 11.15	<0.01	**	23.95 ± 8.79	25.98 ± 10.46	0.14	NS
	(f) Transverse strain rate (1/s)	2.50 ± 0.78	2.71 ± 1.59	<0.01	**	2.41 ± 0.76	2.74 ± 1.34	0.31	NS
	(g) Shear (%)	0.15 ± 0.06	0.14 ± 0.06	<0.01	**	0.15 ± 0.06	0.15 ± 0.06	0.07	NS
	(h) Shear rate (1/s)	2.07 ± 0.51	1.92 ± 0.72	<0.01	**	2.08 ± 0.57	1.95 ± 0.59	<0.01	**

NS = Not Significant (P>0.05). **Highly Significant = (P<0.01). *Significant = (P<0.05). Group A: 18 to 30 years of age. Group B: 31 to 60 years of age.

Table 5. LV strain parameters-part-2 (n=80)

Short axis views	VARIABLES	MALE (N-58) MEAN ± SD	FEMALE (N-22) MEAN ± SD	P		Age wise Group (Years)		P	
				P-Val.	Sign.	Group A* (n=45)	Group B* (n=35)	*P*-Val.	Sign.
At LV apex	(a) Apical Rotation-Peak (o)	Values Presented in **Table 6**							
	(b) Apical Rotation-Time to peak (ms)								
At mv level	(a) Rotational velocity (o/s)	-111.61 ± 57.23	-93.96 ± 60.67	<0.01	**	-106.52 ± 68.37	-107.06 ± 43.14	0.09	NS
	(b) Radial Velocity (cm/s)	0.41 ± 0.12	0.38 ± 0.12	<0.01	**	0.39 ± 0.13	0.42 ± 0.10	<0.05	*
	(c) Global Circumferential strain (GCS) (%)	-16.71 ± 6.55	-15.88 ± 6.01	<0.01	**	-15.46 ± 6.44	-17.79 ± 6.16	0.34	NS
	(d) Global Circumferential strain Rate (GCSR) (1/s)	-2.21 ± 0.79	-2.12 ± 0.82	<0.01	**	-2.16 ± 0.84	-2.23 ± 0.73	<0.05	*
	(e) Global Radial Strain (GRS) (%)	23.11 ± 11.75	18.33 ± 6.70	<0.01	**	20.99 ± 11.51	22.83 ± 9.82	0.21	NS
	(f) Global Radial Strain Rate (GRSR) (1/s)	3.12 ± 0.87	3.01 ± 1.04	<0.01	**	2.97 ± 0.95	3.25 ± 0.84	0.10	NS
At pap. muscle level	(a) Rotational velocity (o/s)	96.47 ± 39.37	99.30 ± 29.79	<0.01	**	97.88 ± 38.54	96.44 ± 35.02	<0.05	*
	(b) Radial Velocity (cm/s)	0.38 ± 0.09	0.40 ± 0.13	<0.01	**	0.39 ± 0.09	0.39 ± 0.11	<0.01	**
	(c) Global Circumferential strain (GCS) (%)	-23.13 ± 6.52	-22.76 ± 7.06	<0.01	**	-23.66 ± 6.74	-22.22 ± 6.49	<0.01	**
	(d) Global Circumferential strain Rate (GCSR) (1/s)	-1.95 ± 0.46	-2.03 ± 0.47	<0.01	**	-1.99 ± 0.47	-1.95 ± 0.46	<0.01	**
	(e) Global Radial Strain (GRS) (%)	25.10 ± 9.93	23.54 ± 11.07	<0.01	**	24.80 ± 9.72	24.50 ± 10.95	<0.05	*
	(f) Global Radial Strain Rate (GRSR) (1/s)	2.63 ± 0.96	2.78 ± 1.06	<0.01	**	2.71 ± 1.03	2.63 ± 0.92	<0.01	**

NS = Not Significant (P>0.05). **Highly Significant = (P<0.01). *Significant = (P<0.05). Group A: 18 to 30 years of age. Group B: 31 to 60 years of age.

Table 6. Rotation and twist data (n=65)

VARIABLES	MALE (N-51) MEAN ± SD	FEMALE (N-14) MEAN ± SD	P		Age wise Group (Years)		P	
			P-Val.	Sign.	Group A* (n=39)	Group B* (n=26)	*P*-Val.	Sign.
Apical rotation peak (o)	6.32 ± 3.95	5.64 ± 2.28	<0.01	**	6.45 ± 4.03	5.74 ± 3.01	<0.01	**
Time to Peak (ms)	267.09 ± 166.26	266.86 ± 85.37	<0.01	**	252.83 ± 158.40	288.35 ± 141.96	0.12	NS
Basal rotation peak (o)	-6.51 ± 3.63	-6.76 ± 2.81	<0.01	**	-6.44 ± 4.02	-6.75 ± 2.44	<0.05	*
Time to Peak (ms)	345.33 ± 172.25	345.07 ± 101.66	<0.01	**	362.25 ± 179.69	319.81 ± 120.46	<0.01	**
Twist peak (o)	10.89 ± 5.50	10.67 ± 3.94	<0.01	**	10.77 ± 5.86	10.94 ± 4.04	<0.01	**
Time to Peak (ms)	309.75 ± 169.76	307.43 ± 82.24	<0.01	**	305.21 ± 178.07	315.31 ± 113.57	<0.05	*
Twist Rate peak (o/s)	124.38 ± 61.87	99.96 ± 23.37	<0.01	**	127.70 ± 67.17	106.26 ± 32.53	<0.01	**
Time to Peak (ms)	197.09 ± 185.30	138.00 ± 90.50	<0.01	**	206.53 ± 189.89	151.12 ± 133.18	<0.01	**
Untwist Rate peak (o/s)	-116.35 ± 51.71	-107.57 ± 38.35	<0.01	**	-113.67 ± 49.06	-115.65 ± 49.86	<0.01	**
Time to Peak (ms)	364.29 ± 168.25	347.21 ± 170.35	<0.01	**	314.36 ± 156.92	430.00 ± 161.44	0.55	NS

NS = Not Significant (P>0.05). **Highly Significant = (P<0.01). *Significant = (P<0.05). Group A: 18 to 30 years of age. Group B: 31 to 60 years of age.

35]. Moreover, longitudinal strain (LS) is the most important prognosticator of CV death and/or heart failure [36, 37]. GLS, GCS and GRS values are highly inconsistent across previous studies of normal healthy population [18-20]. In our study GLS and GCS values are similar to those reported in the literature, even though GRS values are lower, which maybe because of different ethnicity of the study population, and different echocardiography system being utilized, with non identical software algorithm for STE analysis.

The effects of age on LV strain remains controversial, while some studies showing reduced strain values with increasing age [22, 24], others have reported no change [1, 18, 38]. In our study GLS values decreased with increasing age, which is similar to earlier studies. However, GRS and GCS values increased with advancing age, which maybe because of low number of participants in the age group of 31-60 years (n=35), in our study. Moreover, it is extremely difficult to find healthy participants >40 years of age in the Indian population.

The effect of gender on LV strain remains debatable. Several earlier studies reported no difference in values between men and women [1, 14, 38]. However, GLS, GCS and GRS were higher in women, according to various other publications [11, 15, 40]. Furthermore, the HUNT study showed that LV strain values were consistently higher in women below 60 years of age [40]. Our data for GLS is congruous with previous studies [11, 15, 40], even though there is divergence regarding GCS and GRS, showing increased values in men. The more negative GLS may be responsible for the higher LV ejection function found in normal women compared to normal men [41]. We are unable to provide any reason for increased values of GCS and GRS in men, in the current study.

LV apical rotation is a predictor of global LV function [42]. Generally, apical rotation value is higher than basal rotation and has parallel relation with LV global functions [41, 42]. The normal values reported by Takahashi et al. [10], is non congruous with our data, which showed higher values of apical rotation and lower values of basal rotation. The reasons may be manifold and are expressed later, under the study limitation section. Van Dalen et al. [43], have emphasized the importance of acquisition of LV short axis view. We have taken great care to obtain the most apical and circular view. Maharaj et al. [44], reported that twist changed substantially after 40 years of age. In our study the LV twist values were 10.89 ± 5.50° in males and 10.67 ± 3.94° in females ($P<0.01$), similar to findings of Maharaj et al. Moreover, the twist values increased with age, and is likely related to imbalance between subendocardial and subepicardial layers while aging [45].

The main results of our study can be outlined as follows: (i) we provided extensive data on numerous strain components and LV rotational mechanics. (ii) global GLS values were more negative in women than in men ($P<0.01$), leading to higher LVEF by 2D imaging as well as by 4 Dimensional XStrain volumetric analysis ($P<0.01$). (iii) age had a non homogenous effect on various myocardial deformation parameters. (iv) amongst the LV rotational mechanics twist, untwist and apical rotation were greater in men the in women, and increased in later decades of life.

Recommendation and future research direction

From the above discussion it is noteworthy that both LV strain and rotational mechanism are harmoniously involved in the dynamic function of LV and therefore amalgamation of complementary mechanism of LV pump function (EF), LV strain and twist must be attempted to bring forward the normal values ranges of these parameters, in a comprehensive manner. The authors recommend, in future large scale clinical studies to be conceptualized, to validate this integrated approach, in which trivial aberrations in LV ejection fraction, strain, twist and torsion can be picked up at a very early stage of disease. The variations may be used to assess incremental prognostic value for predicting mortality and adverse events. However 4D XStrain STE has not been widely adopted and its evaluation is still limited to research applications. Therefore, further research may optimize its use in various clinical settings and identity its benefits in comparison with the established methods.

Study limitations

The current study has few limitations. All the participants are of Indian ethnicity, and therefore the normal values ranges of the present study cannot be anticipated to be identical with other ethnic groups. The echocardiography machine used has an important bearing for the evaluation of deformation values, and these values may change according to the echocardiography system and the offline software being employed for tracking the endocardial border [46]. Other concerning limitation is the non standardisation of the speckle tracking deformation values across different vendors, because of which the strain and rotational values acquired will vary [47]. Moreover we did not validate the accuracy of strain measurements against the reference standards, such as MRI.

Conclusion

The authors report a comprehensive analysis of LV geometry and function using 4D XStrain echocardiography in a modest cohort of healthy subjects. The values obtained may serve to establish age specific and gender specific reference value ranges, which are fundamental for detection of early LV remodeling and dysfunction in clinical practice.

The innovative method of 4D XStrain speckle tracking echocardiography is extremely valuable in bringing new insights into the complex ventricular motion and is feasible to assess LV myocardial deformation and rotational mechanics.

Acknowledgements

Our special gratitude to Ms. Shubham Kacker and Mrs. Laxmi Kannoujia, for their persistent, relentless and tireless endeavor to finalise the manuscript.

Disclosure of conflict of interest

None.

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