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VENTRICULAR FUNCTION

Normalized Left Ventricular Systolic and Diastolic Function by Steady State Free Precession Cardiovascular Magnetic Resonance

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ABSTRACT

We used state of the art CMR to define ranges for normal left ventricular volumes and systolic/diastolic function normalized to the influence of gender, body surface area and age. New CMR normalized ranges were modeled and displayed in graphical form for clinical use, with normalization for body surface area, gender, and age. The determination of normality, or the severity of abnormality, depends on the use of the appropriate reference ranges normalized to all 3 variables. These novel data have particular importance for clinical practice and clinical trials using CMR.

INTRODUCTION

Cardiovascular magnetic resonance (CMR) has been applied for the measurement of left ventricular (LV) volumes, systolic function and mass for several years in the clinical arena, with standardized methods of short axis multi-slice acquisition (1). The excellent accuracy and reproducibility of CMR is well established (2), making it a gold standard technique which can be very cost effective (3). Normal clinical ranges were initially established from the Fast Low Angle Shot (FLASH) technique (4). However, in recent years, the Steady State Free Precession (SSFP) technique has been introduced which yields significantly improved blood-myocardium contrast, acquisition speed, and the ability to greatly improve the temporal resolution of the cines without loss of image quality (5). SSFP acquisitions yield slightly different results to FLASH for cardiac volumes because of superior discrimination between blood and endocardium and between epicardium and epicardial fat (6). This requires the determination of new normal ranges. However, the high fidelity of this newer technique also allows the novel assessment of normal ventricular diastolic function and the systematic study of the influences of age, gender and body surface area (BSA) on normal values. The aim of this study was to establish SSFP based reference values in normal subjects for LV systolic and diastolic function which were normalized for independent influences such as gender, body surface area and age. It was also our aim to make these data useful in the clinical environment by graphical display as an alternative to tabulation of values, which are considerably less easy to handle.

Keywords: Magnetic Resonance, Heart, Volumes, Function, Reference Values.
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METHODS

Patients

We studied 120 subjects, with 10 men and 10 women in each of 6 age deciles from 20 to 80 years. All subjects were completely asymptomatic, with no known risk factors or history of cardiac disease, and normal physical examination and electrocardiogram (ECG). Also measured were the height, weight,

Table 1. Baseline characteristics of normal subjects studied (mean ± SD)

	20–29 years	30–39 years	40–49 years	50–59 years	60–69 years	70–79 years
			Males			
Height [m]	178 ± 9	181 ± 9	175 ± 6	177 ± 6	175 ± 8	179 ± 3
Weight [kg]	71 ± 9	81 ± 8	83 ± 10	78 ± 12	79 ± 9	83 ± 9
Body surface area [m^2]	1.88 ± 0.13	2.01 ± 0.13	1.99 ± 0.15	1.94 ± 0.11	1.94 ± 0.13	2.01 ± 0.10
Body mass index [kg/m^2]	22 ± 3	24 ± 3	27 ± 2	25 ± 5	26 ± 3	26 ± 3
Systolic blood pressure [mmHg]	125 ± 7	130 ± 4	123 ± 3	123 ± 9	126 ± 7	134 ± 9
Diastolic blood pressure [mmHg]	73 ± 5	77 ± 5	73 ± 4	77 ± 6	75 ± 7	77 ± 7
10 year CAD risk [%]	0.2 ± 0.2	1.3 ± 0.9	3.6 ± 1.2	9.8 ± 4.4	14.0 ± 3.4	16.6 ± 6.5
B natriuretic peptide [pmol/L]	1.2 ± 1.6	1.4 ± 1.6	1.5 ± 1.6	1.7 ± 2.5	2.1 ± 2.2	3.4 ± 2.3
			Females			
Height [m]	166 ± 11	167 ± 8	168 ± 6	165 ± 5	163 ± 5	162 ± 3
Weight [kg]	64 ± 15	59 ± 6	64 ± 9	66 ± 12	68 ± 11	70 ± 16
Body surface area [m^2]	1.71 ± 0.23	1.66 ± 0.11	1.72 ± 0.11	1.71 ± 0.11	1.73 ± 0.13	1.74 ± 0.16
Body mass index [kg/m^2]	23 ± 3	21 ± 2	23 ± 3	24 ± 5	25 ± 5	26 ± 6
Systolic blood pressure [mmHg]	121 ± 12	123 ± 6	115 ± 13	116 ± 18	119 ± 14	135 ± 12
Diastolic blood pressure [mmHg]	70 ± 9	68 ± 4	71 ± 9	71 ± 11	73 ± 6	79 ± 6
10 year CAD risk [%]	0.0 ± 0.0	0.3 ± 0.2	1.6 ± 0.6	3.2 ± 2.0	6.2 ± 2.9	8.3 ± 4.7
B natriuretic peptide [pmol/L]	1.3 ± 2.5	1.6 ± 2.7	1.9 ± 1.8	1.8 ± 2.5	2.2 ± 1.4	2.4 ± 1.4

blood pressure, total cholesterol, HDL and B-natriuretic peptide (BNP) (Table 1). BSA was calculated according to the Mosteller formula (7). With the information, the coronary artery disease risk over 10 years was calculated (8). The BNP levels were 2.5 ± 2.1 pg/mL (range 0.5–12.0), and all were in the normal range (<100 pg/mL) (9). Therefore, as far as it was possible to ascertain with conventional noninvasive techniques, all the apparently healthy subjects had a normal cardiovascular system with no evidence of heart failure. The study was approved by the institutional ethics committee, and all subjects gave written informed consent.

CMR

CMR was performed with a 1.5T scanner (Siemens Sonata) using front and back surface coils and retrospective ECG triggering for capture of the entire cardiac cycle including diastole. All CMR scans were performed by the same operator. SSFP end-expiratory breath-hold cines were acquired in the vertical and horizontal long axis planes, with subsequent contiguous short-axis cines from the atrioventricular (AV) ring to the apex. Slice thickness was 7 mm. The temporal resolution was 21.6 ± 1 ms. Sequence parameters included repetition time/echo time

Table 2. Males: Left ventricular volumes, systolic function and mass (absolute and indexed to body surface area) by age decile (mean, 95% confidence interval)

Males	20–29 years	30–39 years	40–49 years	50–59 years	60–69 years	70–79 years
			Absolute values			
EDV [mL] SD 21	167 (126, 208)	163 (121, 204)	159 (117, 200)	154 (113, 196)	150 (109, 191)	146 (105, 187)
ESV [mL] SD 11	58 (35, 80)	56 (33, 78)	54 (31, 76)	51 (29, 74)	49 (27, 72)	47 (25, 70)
SV [mL] SD 14	109 (81, 137)	107 (79, 135)	105 (77, 133)	103 (75, 131)	101 (73, 129)	99 (71, 127)
EF [%] SD 4.5	65 (57, 74)	66 (57, 75)	66 (58, 75)	67 (58, 76)	67 (58, 76)	68 (59, 77)
Mass [g] SD 20	148 (109, 186)	147 (109, 185)	146 (108, 185)	146 (107, 184)	145 (107, 183)	144 (106, 183)
			Indexed to body surface area (BSA)			
EDV /BSA [mL/m^2] SD 9.0	86 (68, 103)	83 (66, 101)	81 (64, 99)	79 (62, 97)	77 (60, 95)	75 (58, 93)
ESV /BSA [mL/m^2] SD 5.5	30 (19, 41)	29 (18, 39)	27 (17, 38)	26 (15, 37)	25 (14, 36)	24 (13, 35)
SV /BSA[mL/m^2] SD 6.1	56 (44, 68)	55 (43, 67)	54 (42, 66)	53 (41, 65)	52 (40, 64)	51 (39, 63)
Mass /BSA [g/m^2] SD 8.5	76 (59, 93)	75 (59, 92)	75 (58, 91)	74 (57, 91)	73 (57, 90)	73 (56, 89)

EDV, End-Diastolic Volume; ESV, End-Systolic Volume; SV, Stroke Volume; EF, Ejection Fraction; BSA, Body Surface Area; SD, Standard Deviation.

Table 3. Females: Left ventricular volumes, systolic function and mass (absolute and indexed to body surface area) by age decile (mean, 95% confidence interval)

Females	20–29 years	30–39 years	40–49 years	50–59 years	60–69 years	70–79 years
			Absolute values			
EDV [mL] SD 21	139	135	130	126	122	118
	(99, 179)	(94, 175)	(90, 171)	(86, 166)	(82, 162)	(77, 158)
ESV [mL] SD 9.5	48	45	43	41	39	36
	(29, 66)	(27, 64)	(25, 62)	(22, 59)	(20, 57)	(18, 55)
SV [mL] SD 14	91	89	87	85	83	81
	(63, 119)	(61, 117)	(59, 115)	(57, 113)	(56, 111)	(54, 109)
EF [%] SD 4.6	66	66	67	68	69	69
	(56, 75)	(57, 75)	(58, 76)	(59, 77)	(60, 78)	(60, 78)
Mass [g] SD 18	105	106	107	108	109	110
	(69, 141)	(70, 142)	(71, 143)	(72, 144)	(73, 145)	(74, 146)
			Indexed to body surface area			
EDV /BSA [mL/m^2] SD 8.7	82	79	76	73	70	67
	(65, 99)	(62, 96)	(59, 93)	(56, 90)	(53, 87)	(50, 84)
ESV/BSA [mL/m^2] SD 4.7	28	27	25	24	22	21
	(19, 37)	(17, 36)	(16, 34)	(14, 33)	(13, 31)	(12, 30)
SV/BSA [mL/m^2] SD 6.2	54	53	51	50	48	47
	(42, 66)	(40, 65)	(39, 63)	(37, 62)	(36, 60)	(34, 59)
Mass/BSA [g/m^2] SD 7.5	62	62	63	63	63	63
	(47, 77)	(47, 77)	(48, 77)	(48, 78)	(48, 78)	(49, 78)

EDV, End-Diastolic Volume; ESV, End-Systolic Volume; SV, Stroke Volume; EF, Ejection Fraction; BSA, Body Surface Area; SD, Standard Deviation.

of 3.2/1.6 ms, in-plane pixel size of 2.1 × 1.3 mm, flip angle 60°, and acquisition time of 18 heartbeats.

CMR analysis

Analysis was performed with a personal computer and semi-automated software (CMRtools, Cardiovascular Imaging Solutions, London, UK). Analysis included 3 principal steps: first, LV endocardial and epicardial borders were delineated in all planes in all cardiac phases; second, the systolic descent and twist of the mitral valve was calculated from tracking of the valve motion on the long axis cines and used to correct for loss of systolic LV volume due to AV ring descent; and third, blood pool thresholding was used to delineate the papillary muscles. LV mass was

Table 4. All subjects: Left ventricular volumes, systolic function and mass (absolute and indexed to body surface area) by age decile (mean, 95% confidence interval)

All subjects	20–29 years	30–39 years	40–49 years	50–59 years	60–69 years	70–79 years
			Absolute values			
EDV [mL] SD 21	153	149	144	140	136	132
	(112, 193)	(108, 189)	(104, 185)	(100, 181)	(96, 177)	(91, 172)
ESV [mL] SD 10	53	50	48	46	44	42
	(32, 73)	(30, 71)	(28, 69)	(26, 67)	(24, 65)	(21, 62)
SV [mL] SD 14	100	98	96	94	92	90
	(72, 128)	(70, 126)	(68, 124)	(66, 122)	(64, 120)	(62, 118)
EF [%] SD 4.6	66	66	67	67	68	69
	(57, 74)	(57, 75)	(58, 76)	(58, 76)	(59, 77)	(60, 77)
Mass [g] SD 19	127	127	127	127	127	127
	(90, 164)	(90, 164)	(90, 164)	(90, 164)	(90, 164)	(90, 164)
			Indexed to body surface area			
EDV /BSA [mL/m^2] SD 8.8	84	81	79	76	74	71
	(67, 101)	(64, 98)	(62, 96)	(59, 93)	(57, 91)	(54, 88)
ESV /BSA [mL/m^2] SD 5.1	29	28	26	25	24	22
	(19, 39)	(18, 38)	(16, 36)	(15, 35)	(14, 34)	(12, 32)
SV /BSA[mL/m^2] SD 6.2	55	54	52	51	50	49
	(43, 67)	(42, 66)	(40, 65)	(39, 63)	(38, 62)	(37, 61)
Mass /BSA [g/m^2] SD 8.1	69	69	69	68	68	68
	(53, 85)	(53, 85)	(53, 84)	(53, 84)	(52, 84)	(52, 84)

EDV, End-Diastolic Volume; ESV, End-Systolic Volume; SV, Stroke Volume; EF, Ejection Fraction; BSA, Body Surface Area; SD, Standard Deviation.

Table 5. Males: Left ventricular diastolic function, atrioventricular plane descent and sphericity index by age decile (mean, 95% confidence interval)

Males	20–29 years	30–39 years	40–49 years	50–59 years	60–69 years	70–79 years
			Absolute values			
PFR_E [mL/s] SD140	759 (484, 1034)	666 (392, 941)	574 (299, 848)	481 (206, 756)	388 (114, 663)	296 (21, 571)
PFR_A [mL/s] SD 82	260 (99, 421)	305 (144, 467)	350 (189, 512)	396 (234, 557)	441 (279, 602)	486 (324, 647)
PFR_E/PFR_A SD* 0.34	3.0 (1.5, 5.9)	2.2 (1.1, 4.4)	1.7 (0.8, 3.3)	1.2 (0.6, 2.4)	0.8 (0.4, 1.6)	0.5 (0.3, 1.0)
Septal AVPD [mm] SD 3.6	18 (11, 25)	17 (10, 24)	16 (9, 23)	15 (8, 22)	14 (7, 21)	13 (6, 20)
Lateral AVPD [mm] SD 4.1	19 (11, 27)	19 (11, 27)	18 (10, 26)	17 (9, 25)	16 (8, 25)	1.6 (8, 24)
Sphericity index, diastole SD 0.06	0.34 (0.21, 0.46)	0.34 (0.22, 0.47)	0.35 (0.22, 0.47)	0.35 (0.22, 0.48)	0.36 (0.23, 0.48)	0.36 (0.23, 0.49)
Sphericity index, systole SD 0.05	0.22 (0.12, 0.32)	0.21 (0.11, 0.31)	0.20 (0.10, 0.30)	0.19 (0.09, 0.29)	0.18 (0.08, 0.28)	0.17 (0.07, 0.27)
			Indexed values			
PFR_E/BSA [mL/s/m^2] SD 70	390 (254, 526)	342 (206, 478)	294 (158, 430)	246 (110, 383)	199 (62, 335)	151 (15, 287)
PFR_E/EDV [/s] SD 0.71	4.7 (3.3, 6.1)	4.2 (2.8, 5.6)	3.7 (2.3, 5.1)	3.2 (1.8, 4.6)	2.7 (1.3, 4.1)	2.2 (0.8, 3.6)
PFR_A/BSA [mL/s/m^2] SD 44	132 (46, 218)	156 (70, 243)	181 (94, 267)	205 (119, 291)	229 (143, 316)	254 (167, 340)
PFR_A/EDV [/s] SD 0.57	1.6 (0.5, 2.7)	2.0 (0.9, 3.1)	2.4 (1.3, 3.5)	2.8 (1.7, 3.9)	3.2 (2.1, 4.3)	3.6 (2.5, 4.7)
Septal AVPD/long length [%] SD 2.9	17 (11, 22)	16 (10, 22)	15 (10, 21)	15 (9, 20)	14 (8, 20)	13 (8, 19)
Lateral AVPD/long length [%] SD 3.2	18 (12, 24)	18 (11, 24)	17 (11, 23)	17 (10, 23)	16 (10, 23)	16 (10, 22)

PFR, Peak Filling Rate; E, Early; A, Active; AVPD, Atrioventricular Plane Descent; BSA, Body Surface Area; SD, Standard Deviation. *SD of log transformed data.

calculated from the end-diastolic frames. End-systolic (ESV) and end-diastolic (EDV) volumes were calculated from the LV volume/time curve generated from all frames of all cines, and there was no requirement to choose the largest and smallest ventricular frames. Stroke volume (SV) was calculated as the difference between EDV and ESV, and ejection fraction (EF) was calculated as SV/EDV. Papillary muscles were included when measuring mass (equivalent to weighing the LV) and excluded when measuring volumes (equivalent to blood pool techniques). Longitudinal AV plane descent (AVPD) was measured in the septum and lateral wall and expressed as a ratio of the ventricular length. Finally, end-diastolic and end-systolic sphericity index was measured (10, 11). Diastolic function was calculated from the derivative of the time/volume curve and expressed as peak filling rate (PFR). The early and active peak filling rates (PFR_E and PFR_A) and their ratio were calculated.

Statistical analysis

All clinical variables and LV parameters, except BNP and the PFR_E/PFR_A ratio, were found to satisfy a normal distribution using the Kolmogorov-Smirnov test and summary data for these variables are presented as mean ± SD. BNP was normally distributed after log-transformation; its means and confidence intervals were back-transformed for presentation. Simple linear regression was used to model the data and construct reference ranges as mean and 95% confidence intervals. Polynomial regression was used for the parameters for which higher power terms of age were found to be statistically significant (septal AV plane descent and % septal AV plane descent). The PFR_E/PFR_A data was normally distributed after log-transformation, and after modeling, the means and confidence intervals were back-transformed for presentation. Two-way ANOVA was used to analyze variations in parameters due to age and gender. P values <0.05 were considered significant.

RESULTS

Baseline characteristics and summary results

Table 1 summarizes the baseline patient characteristics. The results across age deciles, with differentiation into males, females and all subjects, and sub-division into absolute and body surface area normalized values are shown for systole (Tables 2–4) and diastole, longitudinal function and sphericity index (Tables 5–7). Table 8 shows the data summarized for the entire study group, and male and female groups, without age breakdown, which has valuable application in studies of unsorted individuals. Figures 1 (males) and 2 (females) show the LV systolic and diastolic parameters plotted against age,

Table 6. Females: Left ventricular diastolic function, atrioventricular plane descent and sphericity index by age decile (mean, 95% confidence interval)

Females	20–29 years	30–39 years	40–49 years	50–59 years	60–69 years	70–79 years
			Absolute values			
PFR_E [mL/s] SD 146	680 (393, 967)	599 (312, 886)	518 (231, 805)	437 (150, 724)	355 (69, 642)	274 (−13, 561)
PFR_A [mL/s] SD 69	193 (58, 327)	229 (95, 364)	265 (131, 400)	301 (167, 436)	338 (203, 472)	374 (239, 508)
PFR_E/PFR_A SD* 0.29	3.7 (2.0, 6.6)	2.7 (1.5, 4.9)	2.0 (1.1, 3.6)	1.4 (0.8, 2.6)	1.0 (0.5, 1.7)	0.6 (0.3, 1.0)
Septal AVPD [mm] SD 3.2	16 (10, 23)	16 (9, 22)	15 (9, 21)	14 (8, 20)	13 (7, 19)	12 (6, 19)
Lateral AVPD [mm] SD 3.2	19 (13, 25)	18 (12, 25)	18 (11, 24)	17 (11, 23)	16 (10, 23)	16 (9, 22)
Sphericity index, diastole SD 0.07	0.40 (0.27, 0.53)	0.40 (0.27, 0.53)	0.40 (0.27, 0.53)	0.40 (0.27, 0.53)	0.40 (0.27, 0.53)	0.40 (0.27, 0.53)
Sphericity index, systole SD 0.068	0.28 (0.14, 0.41)	0.26 (0.12, 0.39)	0.24 (0.10, 0.37)	0.22 (0.08, 0.35)	0.20 (0.06, 0.33)	0.18 (0.04, 0.31)
			Indexed values			
PFR_E/BSA [mL/s/m^2] SD 81	401 (243, 559)	352 (194, 511)	304 (145, 462)	255 (97, 413)	206 (48, 364)	157 (−1, 316)
PFR_E/EDV [/s] SD 0.83	5.0 (3.3, 6.6)	4.5 (2.9, 6.1)	4.0 (2.4, 5.6)	3.5 (1.9, 5.1)	3.0 (1.4, 4.7)	2.5 (0.9, 4.2)
PFR_A/BSA [mL/s/m^2] SD 44	110 (24, 196)	133 (47, 219)	156 (70, 242)	180 (94, 266)	203 (117, 289)	226 (140, 312)
PFR_A/EDV [/s] SD 0.49	1.3 (0.4, 2.3)	1.7 (0.8, 2.7)	2.1 (1.2, 3.1)	2.5 (1.6, 3.5)	3.0 (2.0, 3.9)	3.4 (2.4, 4.3)
Septal AVPD/long length [%] SD 3.5	17 (10, 24)	17 (10, 24)	16 (9, 23)	16 (9, 23)	15 (8, 22)	15 (8, 21)
Lateral AVPD/long length [%] SD 3.1	20 (14, 26)	19 (13, 25)	19 (13, 25)	18 (12, 24)	18 (12, 24)	17 (11, 23)

PFR, Peak Filling Rate; E, Early; A, Active; AVPD, Atrioventricular Plane Descent; BSA, Body Surface Area; SD, Standard Deviation; *SD of log transformed data.

with the use of absolute values or body surface area normalized values as most appropriate.

Influence of body surface area on LV parameters

BSA was significantly higher in males than in females ($p < 0.001$). On multivariate analysis, BSA was found to have significant independent influence on LV mass, EDV, ESV, SV, septal long axis function, PFR_E and PFR_A.

Influence of gender on LV parameters

All LV volumes, mass and mass index were significantly larger in males (all $p < 0.001$). For systolic function, only septal long axis function was significantly higher in females ($p = 0.005$). For LV diastolic function, PFR_A ($p = 0.02$) and PFR_A/BSA ($p = 0.033$) were significantly higher in males, and PFR_E/EDV was higher in females ($p = 0.009$). PFR_A was lower in females both in absolute ($p < 0.001$) and relative (PFR_A/BSA $p = 0.001$) values, and, accordingly, PFR_E/PFR_A was higher in females ($p = 0.002$). Sphericity index was higher in females ($p = 0.001$).

On multivariate analysis, gender had significant independent influence on LV mass, LV mass index, normalized LV volumes (EDV/BSA, ESV/BSA, SV/BSA) and sphericity index. It was also independent predictor of PFR_A, PFR_A/BSA, and PFR_E/PFR_A.

Influence of age on LV parameters

There was a significant decrease in absolute and normalized ESV with increasing age in females (ESV $p = 0.013$; ESV/BSA $p = 0.001$). Normalized EDV and septal AV descent also decreased with age in males and females (EDV/BSA $p = 0.019$ and 0.001; septal AV descent $p = 0.002$ and 0.048). LV mass, LV mass index and ejection fraction did not show significant changes with age in either males or females. There was a significant decrease in absolute and normalized PFR_E in males and females (both $p < 0.001$), with an increase in PFR_A (both $p < 0.001$). Accordingly, PFR_E/ PFR_A decreased with age (both $p < 0.001$).

On multivariate analysis, age was independent predictor of all absolute and normalized ventricular volumes (EDV, ESV, SV, EDV/BSA, ESV/BSA, SV/BSA), systolic variables (EF, septal and lateral AV descent) and absolute and normalized diastolic variables (PFR_E, PFR_A, PFR_E/PFR_A, PFR_E/EDV, PFR_A/EDV, PFR_E/BSA, PFR_A/BSA).

Table 7. All subjects: Left ventricular diastolic function, atrioventricular plane descent and sphericity index (absolute and indexed values) by age decile (mean ± SD, 95% confidence interval)

All subjects	20–29 years	30–39 years	40–49 years	50–59 years	60–69 years	70–79 years
			Absolute values			
PFR_E [mL/s] SD 143	720 (440, 1000)	633 (353, 913)	546 (265, 826)	459 (178, 739)	371 (91, 651)	276 (−5, 556)
PFR_A [mL/s] SD 76	226 (77, 375)	267 (118, 416)	308 (159, 456)	349 (200, 497)	390 (241, 538)	435 (286, 583)
PFR_E/PFR_A SD* 0.32	3.3 (1.8, 6.3)	2.5 (1.3, 4.7)	1.8 (1.0, 3.5)	1.3 (0.7, 2.5)	0.9 (0.5, 1.7)	0.5 (0.3, 1.0)
Septal AVPD [mm] SD 3.4	17 (10, 24)	16 (10, 23)	15 (9, 22)	14 (8, 21)	13 (7, 20)	12 (6, 19)
Lateral AVPD [mm] SD 3.7	19 (12, 26)	18 (11, 26)	18 (11, 25)	17 (10, 24)	16 (9, 24)	16 (8, 23)
Sphericity index, diastole SD 0.065	0.37 (0.24, 0.50)	0.37 (0.24, 0.50)	0.37 (0.25, 0.50)	0.38 (0.25, 0.50)	0.38 (0.25, 0.51)	0.38 (0.25, 0.51)
Sphericity index, systole SD 0.059	0.26 (0.14, 0.38)	0.25 (0.13, 0.37)	0.24 (0.12, 0.36)	0.23 (0.11, 0.35)	0.22 (0.10, 0.34)	0.21 (0.09, 0.32)
			Indexed values			
PFR_E/BSA [mL/s/m^2] SD 75	395 (248, 542)	347 (200, 494)	299 (152, 446)	251 (104, 398)	202 (55, 349)	149 (2, 296)
PFR_E/EDV [/s] SD 0.77	4.8 (3.3, 6.3)	4.3 (2.8, 5.8)	3.8 (2.3, 5.4)	3.4 (1.8, 4.9)	2.9 (1.3, 4.4)	2.3 (0.8, 3.8)
PFR_A/BSA [mL/s/m^2] SD 44	121 (35, 207)	145 (59, 230)	169 (83, 254)	192 (107, 278)	216 (130, 302)	242 (157, 328)
PFR_A/EDV [/s] SD 0.53	1.5 (0.4, 2.5)	1.9 (0.8, 2.9)	2.3 (1.2, 3.3)	2.7 (1.6, 3.7)	3.1 (2.0, 4.1)	3.5 (2.5, 4.5)
Septal AVPD /long length [%] SD 3.2	17 (11, 23)	16 (10, 23)	16 (9, 22)	15 (9, 21)	15 (8, 21)	14 (8, 20)
Lateral AVPD /long length [%] SD 3.1	19 (13, 25)	18 (12, 25)	18 (12, 24)	18 (11, 24)	17 (11, 23)	17 (10, 23)

PFR, Peak Filling Rate; E, Early; A, Active; AVPD, Atrioventricular Plane Descent; BSA, Body Surface Area. *SD of log transformed data

All absolute and normalized ventricular volumes decreased significantly with age (EDV both $p < 0.001$; ESV both $p = 0.001$; SV both $p < 0.01$). For systolic function, AV descent decreased with age (septal $p < 0.001$; lateral $p = 0.026$). Sphericity index decreased with age ($p = 0.025$). For diastolic function, absolute and normalized PFR_E decreased significantly with age (all $p < 0.001$), while absolute and normalized PFR_A increased (all $p < 0.001$). Accordingly PFR_E/PFR_A decreased significantly ($p < 0.001$).

DISCUSSION

These data show that most clinical parameters of LV volume and systolic/diastolic function are significantly and independently influenced by gender, age and BSA. This current study brings previous data up to date using state-of-the-art CMR acquisition techniques and analysis, in a healthy moderately large population which has been very well characterized for the absence of significant coronary disease and heart failure. As CMR is now considered a gold standard clinical technique to measure LV volumes and function, these data have significant current and future clinical and research utility. In particular, we are unaware of any previously published reference values over the age range from 20–80 with full normalization for gender, age and BSA, and in addition these are the first reference data for diastolic function by CMR. The findings suggest that the interpretation of LV parameters in borderline clinical cases, such as early cardiomyopathy, should be referred to age, gender and BSA normalized values in order to determine normality, or severity of abnormality. The graphical display of the normalized results in this study is also novel and is included for clinical utility. Only the graphs of the most common parameters are published in this report (Figs. 1 and 2), but the full range of graphs for all parameters is available online for this article. Go to the publisher's online edition of the *Journal of Cardiovascular Magnetic Resonance* for a downloadable file of all 46 graphs (also accessible from the JCMR website). The tables of results also have substantial additional research utility and are divided into males/females or all subjects, and in age deciles or all ages, in order to have applicability for comparison with any other future research data set.

Previous studies with other techniques accord with some of the results presented in the current study, but none have encompassed their overall scope. The decrease in LV volumes with age with no effect on LV mass is in agreement with a previous CMR study of 36 subjects using FLASH cines (12). This finding of no significant effect of age on LV mass is in contrast to previous echocardiographic studies (13–17). This may be because echocardiography requires geometric assumptions when calculating LV mass. Also, we controlled carefully for cardiovascular abnormality in all age groups whereas previously studies may have identified an effect of increased

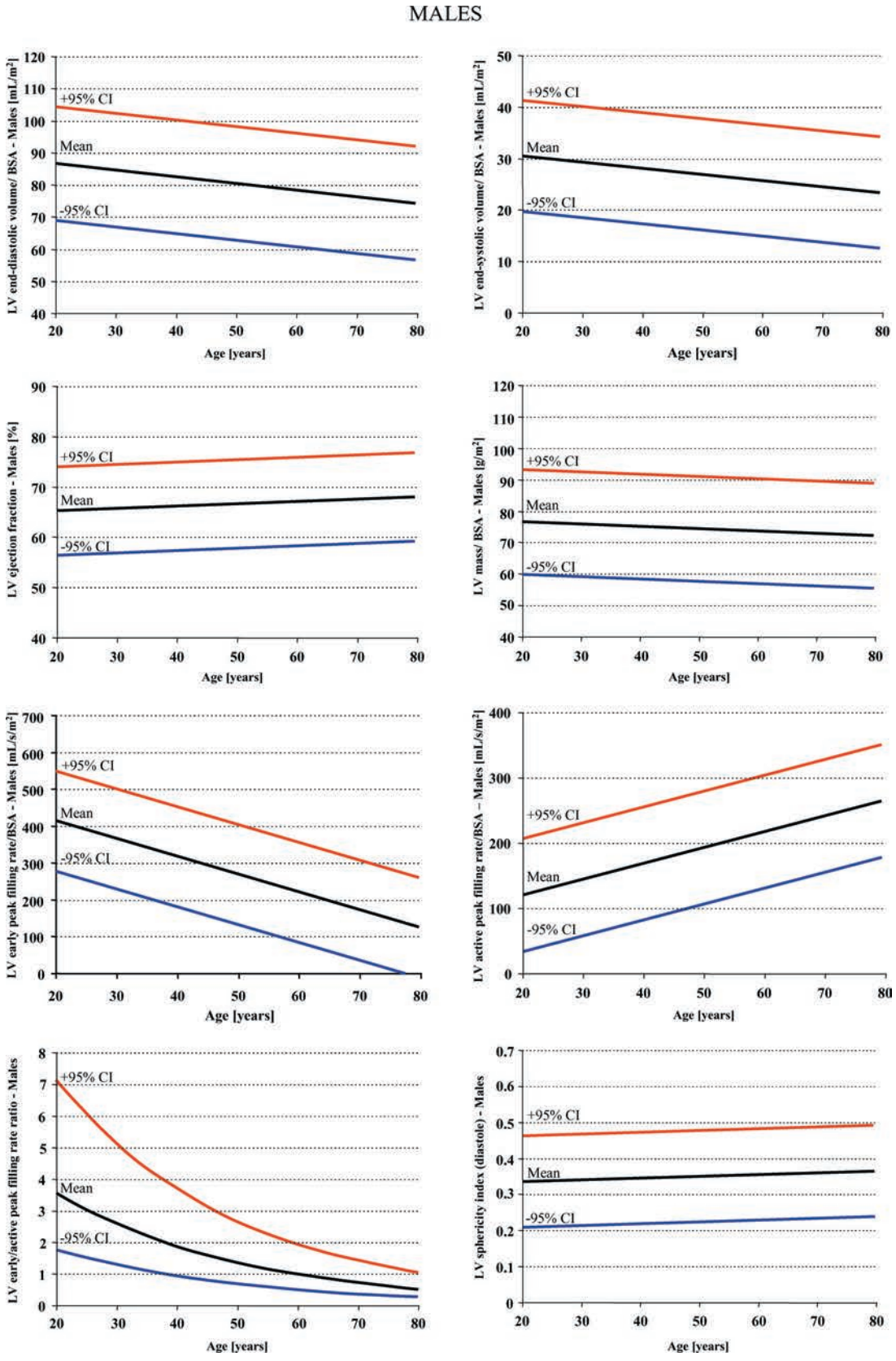

Figure 1. Left ventricular volumes, mass and function in systole and diastole normalized to age and body surface area for males.

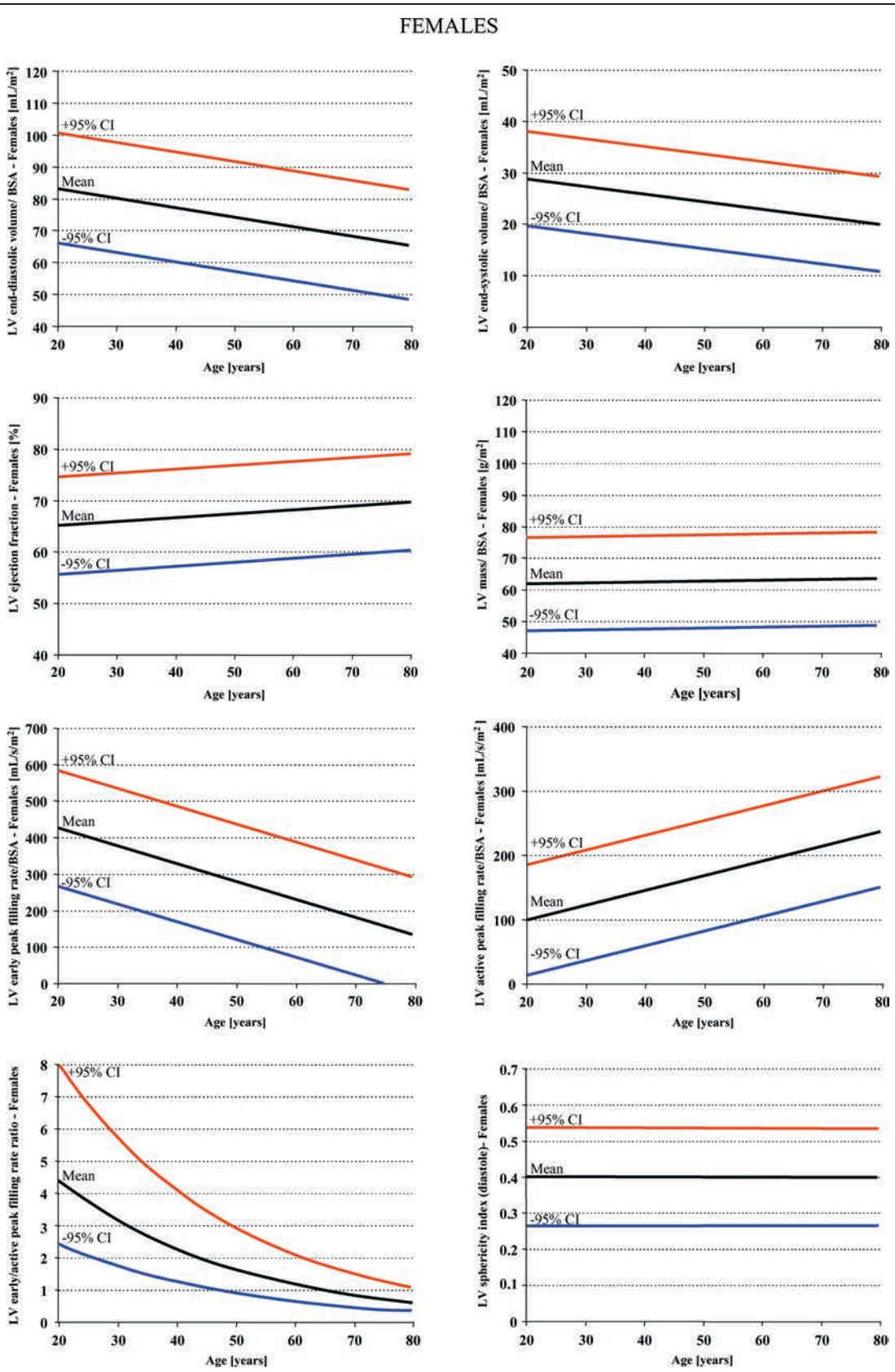

Figure 2. Left ventricular volumes, mass and function in systole and diastole normalized to age and body surface area for females.

Table 8. Left ventricular summary data for all ages (mean ± SD, 95% confidence interval)

	All	Males	Females
EDV [mL]	142 ± 21 (102, 183)	156 ± 21 (115, 198)	128 ± 21 (88, 168)
EDV /BSA [mL/m^2]	78 ± 8.8 (60, 95)	80 ± 9 (63, 98)	75 ± 8.7 (57, 92)
ESV [mL]	47 ± 10 (27, 68)	53 ± 11 (30, 75)	42 ± 9.5 (23, 60)
ESV/BSA [mL/m^2]	26 ± 5.1 (16, 36)	27 ± 5.5 (16, 38)	24 ± 4.7 (15, 34)
SV [mL]	95 ± 14 (67, 123)	104 ± 14 (76, 132)	86 ± 14 (58, 114)
SV/BSA [mL/m^2]	52 ± 6.2 (40, 64)	53 ± 6.1 (41, 65)	50 ± 6.2 (38, 63)
EF [%]	67 ± 4.6 (58, 76)	67 ± 4.5 (58, 75)	67 ± 4.6 (58, 76)
Mass [g]	127 ± 19 (90, 164)	146 ± 20 (108, 184)	108 ± 18 (72, 144)
Mass/BSA [g/m^2]	69 ± 8.1 (53, 84)	74 ± 8.5 (58, 91)	63 ± 7.5 (48, 77)
PFR_E [mL/s]	502 ± 143 (222, 782)	527 ± 140 (253, 802)	477 ± 146 (190, 764)
PFR_E /BSA [mL/m^2]	275 ± 75 (128, 422)	270 ± 70 (134, 407)	279 ± 81 (121, 437)
PFR_E/EDV [/s]	3.6 ± 0.77 (2.1, 5.1)	3.4 ± 0.71 (2.0, 4.8)	3.8 ± 0.83 (2.1, 5.4)
PFR_A [mL/s]	328 ± 76 (180, 477)	373 ± 82 (212, 534)	283 ± 69 (149, 418)
PFR_A/BSA [mL/m^2]	180 ± 44 (95, 266)	193 ± 44 (107, 279)	168 ± 44 (82, 254)
PFR_A/EDV [/s]	2.5 ± 0.53 (1.4, 3.5)	2.6 ± 0.57 (1.5, 3.7)	2.3 ± 0.49 (1.4, 3.3)
PFR_E/PFR_A	1.6 ± 0.32 (0.8, 2.9)	1.4 ± 0.34 (0.7, 2.8)	1.7 ± 0.29 (0.9, 3.1)
Septal AVPD [mm]	15 ± 3.4 (8, 21)	15 ± 3.6 (8, 22)	14 ± 3.2 (8, 21)
Septal AVPD /long length [%]	15 ± 3.2 (9, 22)	15 ± 2.9 (9, 21)	16 ± 3.5 (9, 23)
Lateral AVPD [mm]	17 ± 3.7 (10, 25)	18 ± 4.1 (9, 26)	17 ± 3.2 (11, 24)
Lateral AVPD /long length [%]	18 ± 3.1 (12, 24)	17 ± 3.2 (11, 23)	19 ± 3.1 (13, 24)
Sphericity index, diastole	0.37 ± 0.065 (0.25, 0.50)	0.35 ± 0.06 (0.22, 0.48)	0.40 ± 0.07 (0.27, 0.53)
Sphericity index, systole	0.23 ± 0.059 (0.12, 0.35)	0.20 ± 0.05 (0.10, 0.29)	0.23 ± 0.068 (0.09, 0.36)

EDV, End-Diastolic Volume; ESV, End-Systolic Volume; SV, Stroke Volume; EF, Ejection Fraction; PFR, Peak Filling Rate; E, Early; A, Active; AVPD, Atrioventricular Plane Descent; BSA, Body Surface Area.

blood pressure or impaired LV function with age. Diastolic parameters using echocardiography have been shown to vary by gender (18) and age (19), which is in agreement with our findings. Aging causes a decrease in LV distensibility that increases both the early diastolic filling time, allowing the ventricle more time to fill and the contribution of the atrial kick to LV filling. There are differences between CMR and echocardiography, however. While echocardiography provides peak velocities, CMR provides absolute peak filling rates from the volume/time curves. These are available from radionuclide ventriculography, but CMR has significantly higher spatial resolution.

There have been a number of previous normal ranges published for CMR, but again none have addressed the full scope of the current study. Lorenz published CMR derived LV mass and volumes, utilizing FLASH cines with free breathing (4). Other studies with FLASH cines and breath-holding are from Marcus (61 healthy volunteers aged under 30 years and measured LV volumes and mass) (20), and Sandstede (36 healthy volunteers subdivided in 4 groups of 9 subjects each, according to gender and age greater or less than 45 years) (12). These ranges are now not ideal, because of differences between FLASH and SSFP results (6). Alfakih reported SSFP normal ranges in 60 subjects with an age range of 20–65 years, but subdivided only into 2 subgroups (>40 years, n = 34; <40 years, n = 26) (21). The subjects had a normal examination and ECG with no history of heart disease, but the 10 year risk and BNP was not measured. The data were analyzed manually without AV plane correction, limited to systole, and the results were not divided into age deciles for regression modeling. Therefore, the capacity to compare the results with our current data is limited.

CONCLUSION

LV volumes and function (systolic and diastolic) vary with gender, age and body surface area. Identification particularly of early abnormality requires reference ranges which normalize for all 3 variables. These ranges are supplied with this report in both tabular and graphical form and are of significant clinical and research utility for the interpretation of CMR studies.

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