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VENTRICULAR FUNCTION

Normal human left and right ventricular and left atrial dimensions using steady state free precession magnetic resonance imaging

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Purpose. The aim of this project was to establish a database of left and right ventricular and left atrial dimensions in healthy volunteers using steady-state free precession cardiac magnetic resonance imaging, the clinical technique of choice, across a wide age range. *Methods.* 108 healthy volunteers (63 male, 45 female) underwent cardiac magnetic resonance imaging using steady-state free precession sequences. Manual analysis was performed by 2 experienced observers. *Results.* Left and right ventricular volumes and left ventricular mass were larger in males than females: LV end-diastolic volume 160 ± 29 mL vs. 135 ± 26 mL, LV end-systolic volume 50 ± 16 mL vs. 42 ± 12 mL; RV end-diastolic volume 190 ± 33 mL vs. 148 ± 35 mL, RV end-systolic volume 78 ± 20 mL vs. 56 ± 18 mL ($p < .05$ for all). Normalization of values to body surface area removed the statistical differences for LV volumes, but not for LV mass or RV volumes. With increased age, males showed a significant decrease in volume and mass indices for both ventricles, while female values remained unchanged. Compared to females, males had significantly larger maximal left atrial volumes (103 ± 30 mL vs. 89 ± 21 mL, $p = .01$) and left atrial stroke volumes (58 ± 23 mL vs. 48 ± 15 mL, $p = .01$). There was no difference in left atrial ejection fraction between the sexes. *Conclusion.* We have produced a large database of age-related normal ranges for left and right ventricular function and left atrial function in males and females. This will allow accurate interpretation of clinical and research datasets.

Key Words: Ventricular function; Steady state free precession; Magnetic resonance imaging; Left atrium

1. Introduction

Cardiovascular magnetic resonance imaging (CMR) has become the gold standard method for the characterisation of cardiac anatomy, function and mass (1). It is an accurate and reliable technique for the serial monitoring of patients, particularly in response to therapeutic intervention (2).

CMR is a well-tolerated, non-invasive technique without exposure to radiation with no known side-effects and is becoming increasingly available to the clinician. Establishment of a normal healthy reference database is essential for measurements to be useful and relevant in clinical practice. There are a number of different vendors and acquisition techniques, which may reflect some of the discrepancies in normal values for left and right ventricular parameters published in the literature (3–5). Furthermore, information regarding the left atrial size, volume and function is clinically important in the management of patients, particularly those with atrial fibrillation. Assessment of left atrial volumes using CMR has not yet become routine because it is not straightforward and the standard short-axis method of measuring left atrial volume and ejection fraction is very time-consuming. Echocardiography is currently the gold standard for assessing left atrial volumes but relies on a number of geometric assumptions.

It has been demonstrated that for left atrial measurements, when compared to the short axis method in CMR, the biplane area-length method for ellipsoid bodies is a more rapid alternative in both healthy volunteers and patients which is both accurate and reproducible (6, 7).

We aimed to establish a large database of reference values for left and right ventricles of healthy volunteers using the steady-state free precession technique (SSFP), the preferred technique of choice for assessment of volume data in current clinical practice. Previously only one large series of SSFP

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values has been reported, using one specific vendor, which did not examine right ventricular mass in combination with left and right ventricular volumes in a single clinical examination (3). In addition, we aimed to study left atrial end-systolic and end-diastolic volumes, stroke volume and ejection fraction.

2. Methods

2.1. *Study population*

One hundred eight healthy volunteers (63 male, 45 females; mean age 38 ± 12 years, range 21–68 years) were recruited with no history of cardiac disease, hypertension or cardiac risk factors and a normal baseline electrocardiogram (ECG). Volunteers with contraindications to CMR were not enrolled. The study was carried out according to the principles of the Declaration of Helsinki and was approved by our institutional ethics committee. Each subject gave informed written consent.

Baseline characteristics of the healthy volunteers are shown in Table 1.

2.2. *Cardiovascular magnetic resonance imaging protocol*

All CMR examinations were performed on a 1.5 Tesla MR scanner (Sonata, Siemens Medical Solutions, Erlangen, Germany) with body coil and phased array surface coil, prospective electrocardiographic gating and the patient in the supine position. After piloting using localizers, a horizontal long-axis, vertical long-axis and short-axis pilots, steady-state free precession cine images (TE/TR 1.5/3.0 ms, flip angle 60°, slice thickness 7 mm, 3 mm inter-slice gap, in-plane resolution 1.5 × 1.5 mm^2, temporal resolution 45 ms, breathold duration of 14–17 heartbeats per breathold) were acquired in the horizontal and vertical long axis views during breath holding in end-expiration. The short axis stack was then obtained, parallel to the atrioventricular groove, covering the entire left and right ventricle.

Table 1. Characteristics of healthy volunteers

	Mean ± SD (n = 108)
Age (years)	38 ± 12
Gender	63 male/45 female
Height (cm)	174 ± 9
Weight (kg)	73.4 ± 12.3
Body surface area (m^2)	1.88 ± 0.18
Heart Rate (bpm)	65 ± 10
Systolic blood pressure (mmHg)	123 ± 17
Diastolic blood pressure (mmHg)	81 ± 16

2.3. *Image analysis*

CMR image analysis was performed with Argus software (Version 2002B, Siemens Medical Solutions, Erlangen, Germany). Manual tracing of the endocardial and epicardial borders of successive short-axis slices at end-diastole and end-systole (image with the smallest left and right ventricular cavity) was performed. Both epicardial and endocardial borders were traced on the end-diastolic frame, with only an endocardial border on end-systolic frame. The contour tracing was monitored by reviewing the movie with contours attached.

The basal slice was selected for end-diastole and for end-systole for the left ventricle when at least fifty percent of the blood volume was surrounded by myocardium. The apical slice was defined as the last slice showing intracavity blood pool.

For the right ventricle, volumes below the pulmonary valve were included. From the inflow tract, RV volumes were excluded if the surrounding muscle was thin and not trabeculated, suggestive of right atrium (Fig. 1).

Two experienced observers were free to select the end-systolic and end-diastolic frame. Papillary muscles were included in the mass and excluded from the volume calculations. The interventricular septum was included as part of the left ventricle. From these data, the mass, ejection fraction, end-systolic and end-diastolic volumes could be calculated. Myocardial mass was determined by multiplication of the tissue volume by 1.05 g/cm^3 (specific density of myocardium). Functional parameters, normalised to body surface area were also calculated.

The left atrial volumes, ejection fraction and stroke volume were measured using the biplane area-length method in the horizontal and vertical long axes (7) (Fig. 2). The left atrial appendage was included in the atrial volume, but the pulmonary veins were excluded. Left atrial stroke volume and ejection fraction were calculated from the following formulae:

$$\begin{aligned}\text{Stroke Volume (SV)} &= \text{End–Diastolic Volume (EDV)} \\ &\quad - \text{End–Systolic Volume (ESV)} \\ &\quad \text{and Ejection Fraction (EF)} \\ &= \text{Stroke Volume (SV)}/ \\ &\quad \text{End–Diastolic Volume (EDV)} \\ &\quad \times 100\% \end{aligned} \tag{1}$$

2.4. *Reproducibility*

To assess inter-study reproducibility, 12 subsequent subjects underwent a second identical scan, separated by at least one week from the first study.

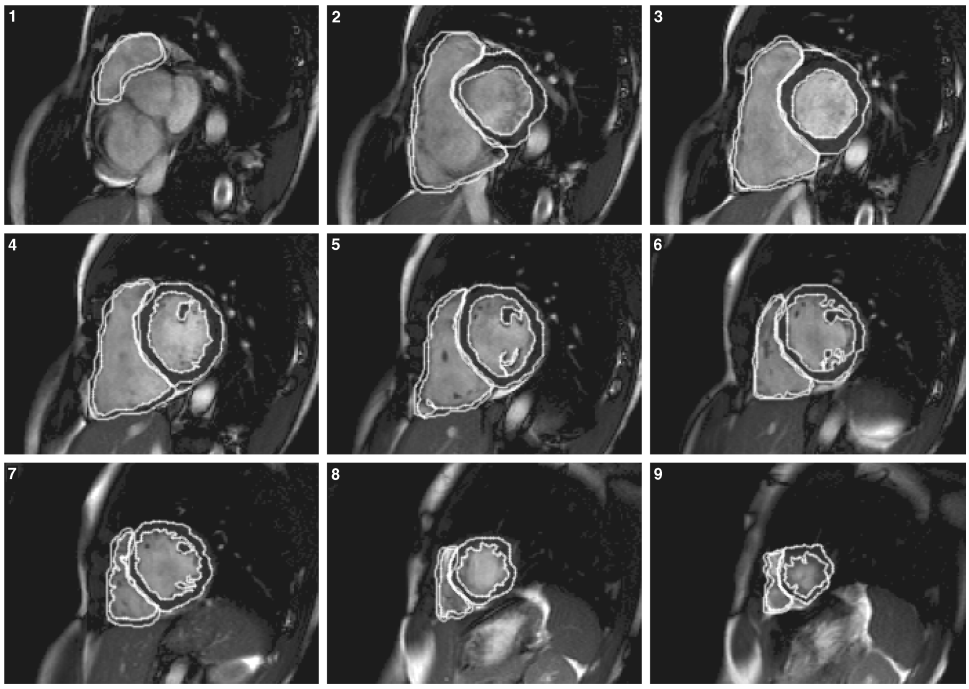

Figure 1. End-diastolic short-axis images from base to apex in a healthy volunteer with endocardial and epicardial contours drawn for both the left and right ventricles. The basal slice was selected for the left ventricle when at least fifty percent of the blood volume was surrounded by myocardium in both end-diastole and end-systole. The apical slice was defined as the last slice showing intracavity blood pool. For the right ventricle, volumes below the pulmonary valve were included. From the inflow tract, RV volumes were excluded if the surrounding muscle was thin and not trabeculated, suggestive of right atrium. Papillary muscles were included in the LV mass.

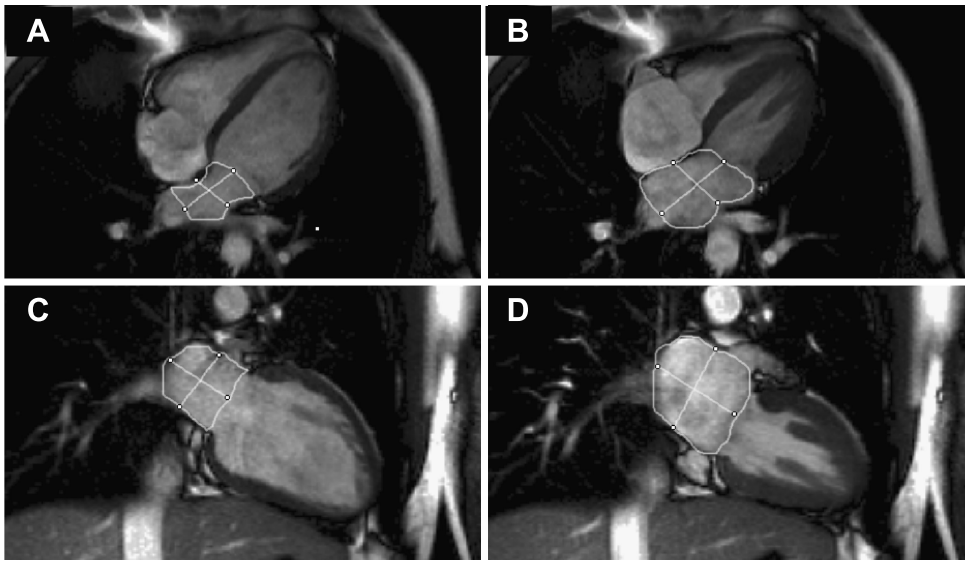

Figure 2. Horizontal long axis (HLA) in end-diastole (A) and end-systole (B), vertical long axis (VLA) in end-diastole (C) and end-systole (D) illustrating contouring for the biplane are-length method for left atrial volumes and ejection fraction. The left atrial appendage was included in the atrial volume but the pulmonary veins were excluded.

Table 2. LV and RV measurements in 108 healthy volunteers

	Mean ± SD (n = 108)	Male (n = 63)	Female (n = 45)	p value
LV ejection fraction (%)	69 ± 6	69 ± 6 (57–81)	69 ± 6 (57–81)	.80
LV mass (g)	112 ± 27	123 ± 21 (81–165)	96 ± 27 (42–150)	< .001
LV mass index (g/m^2)	59.2 ± 11	62.5 ± 9.0 (45–81)	54.6 ± 12 (31–79)	< .001
LV end-diastolic volume (mL)	150 ± 31	160 ± 29 (102–218)	135 ± 26 (83–187)	< .001
LV end-diastolic volume index (mL/m^2)	80 ± 13	82 ± 13 (56–108)	78 ± 12 (54–102)	.16
LV end-systolic volume (mL)	47 ± 15	50 ± 16 (18–82)	42 ± 12 (18–66)	.007
LV end-systolic volume index (mL/m^2)	25 ± 7	25 ± 8 (9–41)	24 ± 6 (12–36)	.53
LV stroke volume (mL)	104 ± 21	112 ± 19 (74–150)	91 ± 17 (57–125)	< .001
LV stroke volume index (mL/m^2)	55 ± 8	56 ± 8 (40–72)	54 ± 9 (36–72)	.12
RV ejection fraction (%)	61 ± 6	59 ± 6 (47–71)	63 ± 5 (53–73)	.002
RV mass (g)	38 ± 8	41 ± 8 (25–57)	35 ± 7 (21–49)	< .001
RV mass index (g/m^2)	20.3 ± 3.6	20.6 ± 3.7 (13–28)	20.0 ± 3.5 (13–27)	.371
RV end-diastolic volume (mL)	173 ± 39	190 ± 33 (124–256)	148 ± 35 (78–218)	< .001
RV end-diastolic volume index (mL/m^2)	91 ± 16	96 ± 15 (66–126)	84 ± 17 (50–118)	< .001
RV end-systolic volume (mL)	69 ± 22	78 ± 20 (38–118)	56 ± 18 (20–92)	< .001
RV end-systolic volume index (mL/m^2)	36 ± 10	39 ± 10 (19–59)	32 ± 10 (12–52)	< .001
RV stroke volume (mL)	104 ± 21	113 ± 19 (75–151)	90 ± 19 (52–128)	< .001
RV stroke volume index (mL/m^2)	55 ± 9	57 ± 8 (41–73)	53 ± 9 (35–71)	.02

Values are given as mean ± SD; reference ranges in brackets, calculated as ± 2SD of the mean.

Table 3. Myocardial mass and function by age and gender

	Male (n = 63)			Female (n = 45)		
	< 35 years (n = 31)	≥ 35 years (n = 32)	p	< 35 years (n = 23)	≥ 35 years (n = 22)	p
LV ejection fraction (%)	67 ± 5 (57–77)	71 ± 6 (59–83)	.01	69 ± 6 (57–81)	69 ± 6 (57–81)	.90
LV mass (g)	131 ± 21 (89–173)	120 ± 23 (74–166)	.05	92 ± 20 (52–132)	92 ± 19 (54–130)	.94
LV mass index (g/m^2)	67 ± 10 (47–87)	60 ± 9 (42–78)	.005	53 ± 9 (35–71)	52 ± 9 (34–70)	.76
LV end-diastolic volume (mL)	173 ± 29 (115–231)	149 ± 25 (99–199)	.001	137 ± 25 (87–187)	128 ± 23 (82–174)	.23
LV end-diastolic volume index (mL/m^2)	90 ± 11 (68–112)	75 ± 11 (53–97)	< .001	80 ± 9 (62–98)	73 ± 11 (51–95)	.03
LV end-systolic volume (mL)	57 ± 15 (27–87)	43 ± 13 (17–69)	< .001	43 ± 11 (21–65)	40 ± 12 (16–64)	.30
LV end-systolic volume index (mL/m^2)	30 ± 7 (16–44)	22 ± 6 (10–34)	< .001	25 ± 6 (13–37)	23 ± 6 (11–35)	.20
LV stroke volume (mL)	118 ± 18 (82–154)	106 ± 19 (68–144)	.015	96 ± 18 (60–132)	89 ± 16 (57–121)	.19
LV stroke volume index (mL/m^2)	60 ± 8 (44–76)	53 ± 8 (37–69)	.001	55 ± 6 (43–67)	51 ± 8 (35–67)	.05
RV ejection fraction (%)	57 ± 5 (47–67)	61 ± 6 (49–73)	.01	61 ± 3 (55–67)	64 ± 7 (50–78)	.20
RV mass (g)	42 ± 8 (26–58)	39 ± 7 (25–53)	.06	36 ± 7 (22–50)	33 ± 7 (19–47)	.13
RV mass index (g/m^2)	22 ± 4 (14–30)	20 ± 3 (14–26)	.03	21 ± 3 (15–27)	19 ± 3 (13–25)	.08
RV end-diastolic volume (mL)	203 ± 33 (137–269)	181 ± 28 (125–237)	.006	152 ± 27 (98–206)	140 ± 37 (66–214)	.23
RV end-diastolic volume index (mL/m^2)	104 ± 15 (74–134)	89 ± 11 (67–111)	< .001	89 ± 11 (67–111)	80 ± 19 (42–118)	.09
RV end-systolic volume (mL)	87 ± 20 (47–127)	71 ± 17 (37–105)	.001	59 ± 12 (35–83)	52 ± 22 (8–96)	.23
RV end-systolic volume index (mL/m^2)	44 ± 9 (26–62)	34 ± 7 (20–48)	< .001	35 ± 5 (25–45)	30 ± 12 (6–54)	.08
RV stroke volume (mL)	116 ± 19 (78–154)	110 ± 18 (74–146)	.20	93 ± 17 (59–127)	93 ± 17 (50–126)	.33
RV stroke volume index (mL/m^2)	59 ± 9 (41–77)	55 ± 8 (39–71)	.06	54 ± 7 (40–68)	54 ± 7 (32–68)	.15

Table 4. Left atrial parameters and comparison between males and females

	Mean ± SD (n = 108)	Males mean ± SD (n = 63)	Females mean ± SD (n = 45)	p value
Maximal LA volume (mL)	97 ± 27	103 ± 30	89 ± 21	.01
Minimal LA volume (mL)	44 ± 13	46 ± 14	41 ± 11	.055
LA ejection fraction (%)	54 ± 12	55 ± 13	53 ± 9	.47
LA stroke volume (mL)	53 ± 21	58 ± 23	48 ± 15	.01

Inter-observer variability was assessed by a second investigator analysing 12 of the data sets. One observer analysed the first 12 volunteer images twice, leaving a 6 week gap and blinded to the previous results, providing intra-observer variability.

2.5. *Statistical analysis*

All data are presented as mean ± standard deviation (SD) unless stated otherwise.

Inter-study reproducibility, inter- and intra-observer variability was assessed using the method of Bland and Altman (8). The coefficient of variability was calculated as the SD of the differences between the two sets of measurements divided by the mean value of the parameter under consideration. All computations were performed with SPSS 11.5 (SPSS Inc., Chicago, IL, US).

3. Results

Cardiovascular magnetic resonance scanning was well tolerated by all participants. All datasets were of sufficient quality to be included in the study. The values for left and right ventricular function and mass are shown in Table 2.

End-diastolic and end-systolic volumes were smaller in females than in males by about 15% for the left and about 25% for the right ventricle ($p < .01$ for all values). Left and right ventricular masses were larger in males than in females (22% for LV mass and 15% for RV mass, $p < .001$ for both). After indexing to body surface area, the differences for the left, but not right, ventricular volumes, and for the right, but not left, ventricular mass were no longer statistically significant. Right ventricular ejection fraction was 7% higher in females ($p = .002$) but left ventricular ejection fraction was not significantly different ($p = .80$).

The normal values for male and female left and right ventricular volumes in older and younger age groups are shown in Table 3. In males, with increasing age, there were significantly smaller right and left ventricular volumes. These differences remained after normalization to body surface area. Left and right ventricular mass and mass indices were also lower with increasing age in males. Both left and right ventricular ejection fractions significantly increased with increasing age in males ($p = .01$ for both). In females, only left ventricular end-diastolic volume index was significantly different ($p = .03$) and stroke volume index showed a trend for smaller values with increasing age ($p = .05$).

The values for end-diastolic (maximal volume), end-systolic (minimal volume), stroke volume and ejection fraction for the left atrium are shown in Table 4. Males showed significantly larger end-systolic left atrial volumes and stroke volumes than females. There was a trend for males to have larger end-diastolic left atrial volumes ($p = .055$). There was no significant gender difference in left atrial ejection fraction.

Intraobserver, interobserver and interstudy variability was higher for right ventricular parameters compared with the left (Table 5). For right and left ventricular parameters, intra-observer variability was lowest, followed by interobserver and then interstudy variability (Fig. 3). Variability was generally larger for left atrial measurements.

Table 5. Reproducibility of measurements

	Intraobserver		Interobserver		Interstudy	
	Bias (95% limits of agreement)	CoV	Bias (95% limits of agreement)	CoV	Bias (95% limits of agreement)	CoV
LV ejection fraction	0.5 (−2.6 to 3.5)	2.3	1.6 (−2.8 to 6.0)	3.3	0.5 (−9.1 to 10.1)	7.5
LV end-diastolic volume index	4.6 (−4.4 to 13.7)	5.6	0.4 (−3.8 to 4.6)	2.7	−1.4 (−9.7 to 6.9)	5.2
LV mass	5.4 (−6.8 to 17.5)	6.1	5.8 (−4.4 to 16.0)	5.2	1.8 (−17.9 to 21.6)	9.4
RV ejection fraction	0.1 (−6.2 to 6.4)	5.3	−2.8 (−15.2 to 9.1)	10.7	1.9 (−11.48 to 15.2)	11.4
RV end-diastolic volume index	−3.2 (−18.8 to 12.5	9.0	−0.1 (−16.7 to 16.5)	9.6	0.7 (−21 to 4.3)	7.4
LA ejection fraction	−1 (−18 to 17)	16.4	4.4 (−6 to 15)	9.6	−3 (−19 to 12)	14.7

CoV = Coefficient of Variability.

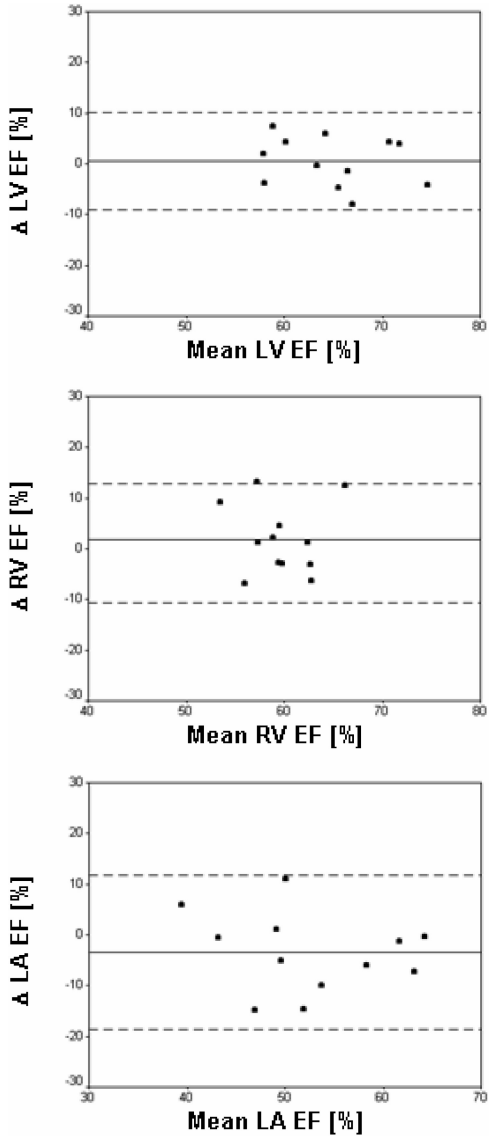

Figure 3. Interstudy reproducibility for LV ejection fraction, RV ejection fraction and LA ejection fraction for 12 healthy volunteers [Bland-Altman plot (8)]. Solid lines represent the mean (bias) and dotted lines represent the limits of agreement (95% limits of agreement).

4. Discussion

Over the past five years, a number of studies have reported on the use of CMR to establish normal values for ventricular function for comparison with clinical patients. These have been limited by the use of free-breathing, the use of small numbers of subjects over a narrow age range, the focussing on either the left or the right ventricle, and the use of different acquisition techniques and vendors (2, 4, 5, 9, 10).

Recently, the steady-state free precession (SSFP) technique has allowed more accurate definition of the endocardial and epicardial borders and a shorter acquisition time.

In this study, we have used this technique to establish a large database of ventricular and left atrial volumes in healthy volunteers in a single, clinically realistic examination.

Our values show volumes, normalized volumes, stroke volumes and ejection fractions for the left ventricle similar to Grothues et al. (2, 9). However, our right ventricular volumes are slightly larger (RVEDV 173 ± 39 vs. 153 ± 34 mL, RVESV 69 ± 22 vs. 58 ± 20 mL) and our masses smaller (38 ± 8 g vs. 60 ± 14 g). These differences may be explained by the use of segmented FLASH breath-hold cines with contiguous 10 mm slices on a Picker Edge 1.5 T Marconi system in Grothues' study of twenty healthy volunteers.

Lorenz et al. published the first normal range of CMR mass and volumes in seventy-five subjects (4). Their data show smaller volumes, which may be explained by the use of acquisition with a conventional cine gradient echo sequence and the inclusion of children. Moon et al. have previously shown significantly higher left ventricular volume measurements using SSFP imaging when compared with FLASH imaging, which is explained as being due to better definition of the endocardial and epicardial borders and improved basal slice selection (10). The normal range published by Alfakih in sixty subjects using a Phillips 1.5 T breath-hold SSFP sequence with 6 mm slices and a 4 mm interslice gap showed left and right ventricular volumes comparable to our study (3). Left ventricular mass index was also similar, males 64.7 ± 9.3 g and females 52.0 ± 7.4 g compared with 62.5 ± 9.0 g and 54.6 ± 11.9 g in our study. However, our study also provides information on right ventricular mass, and left atrial volumes and function.

In the present study, we showed a significant gender difference for left and right ventricular volume indices, left ventricular mass index and right ventricular ejection fraction, similar to previous results (3, 4, 11). We also demonstrated a significant decrease in volume indices of both ventricles with age in males. However, females only showed a statistically significant difference in LV end-diastolic volume and left ventricular stroke volume indices. These observations closely reflect autopsy findings with decreasing left ventricular mass and progressive left ventricular myocyte loss with increasing age in males with values remaining constant in females (12). These findings may reflect gender differences in ventricular remodelling with increasing age in healthy volunteers in agreement with Sandstede et al. (5). Such differences may result from age-related hormonal changes, in particular reduced testosterone levels with increasing age in males, which may explain the reduced ventricular mass. In animal models, supraphysiological testosterone levels have been shown to induce cardiac hypertrophy and increases in left ventricular weight (13). The age-specific gender differences may also be explained by a reduction in physical activity with age. Our data suggest that in clinical practice, indexed age and sex specific values should be used, particularly in males.

Our results confirm that the interstudy reproducibility is lower for the right ventricle than for the left, similar to

previous results (9). This may be explained by the difficulty in defining the most basal slice and in drawing endocardial contours around the increased trabeculations and moderator band of the right ventricle. Our volunteers underwent repeat scans at least one week apart, appropriately reflecting changes in physiology and ensuring repositioning and replanning. The scans within our study were acquired by three operators. This explains why our interstudy variability is slightly larger than other studies where subjects underwent repeat scanning within 15 minutes by a single operator. However, we feel this acquisition reflects real clinical practice more closely.

Intraobserver and interobserver variability was higher for the right than for the left ventricle, again illustrating the complexity of the right ventricle. Our variability measurements were comparable to others reported in the literature (4, 14). The use of axial as opposed to short axis orientation acquisition may have resulted in lower intraobserver and interobserver variability (15).

Left atrial function is impaired in a number of cardiac conditions, including atrial fibrillation, the commonest arrhythmia. Echocardiographic methods of measuring the left atrium rely on geometric assumptions and are user-dependent. The standard acquisition of left atrial volumes and ejection fraction with CMR uses the short-axis stack for which both acquisition and post-processing is time-consuming (6). The biplane area-length method has previously been shown to correlate well with the short axis stack and to be significantly faster, but it requires geometric assumptions similar to echocardiography (6, 16). It also relies upon the use of pilot images acquired to optimise left ventricular imaging rather than primarily focussing on the left atrium in these views.

Our left atrial ejection fractions are similar to those previously reported (6, 16). However, there was a high interobserver variability of these left atrial measurements, reflecting the difficulty in drawing contours, particularly when including the left atrial appendage but excluding the pulmonary veins. A small difference between observers in drawing contours or measuring the left atrial length will have a large effect on left atrial volume when using the biplane area-length method. However, the left atrial ejection fraction variability was acceptable. The interstudy reproducibility for the left atrial measurements was again relatively low, reflecting the additional dependence of the volumes on slice positioning and variable cardiac physiology. However, when using comparable values to those in the literature, our reproducibility values compare favourably (6).

Our study confirms the normal range of left atrial volumes, stroke volumes and ejection fraction using the biplane area-length method in healthy volunteers. These data are routinely obtained from a clinical scan and hence provide a normal range of values for a time-saving method of acquiring left atrial volumes. However, in view of the high observer variability, we would recommend the use of an additional short-axis method for a more reproducible and accurate assessment of the left atrium when this is clinically required.

5. Conclusion

We have produced a large database for left and right ventricular and left atrial volumes of healthy volunteers using SSFP images at 1.5 T. This will be of particular use for reference in both clinical and research studies.

We have shown significantly different volumes with gender and significant differences in age-specific left and right ventricular volumes and mass and ejection fraction in males but not in females. We have also demonstrated the use and limitations of the biplane area-length method to acquire left atrial volumes and ejection fraction.

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