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Original Article

Effect of sex, age and body measurements on heart weight, atrial, ventricular, valvular and sub-epicardial fat measurements of the normal heart ☆,☆☆

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ABSTRACT

Aims: Descriptive morphological studies of the normal heart are lacking. Previous autopsy studies have focused mainly on heart weight. We characterize the normal heart by providing normal dimensions of the atria, ventricles, valves and sub-epicardial fat, comparing the findings in terms of sex, age and body measurements.

Methods: From 3602 referrals to our cardiovascular pathology unit, pathological criteria used for the classification of a morphologically normal heart were a weight of below 500 grams in males, and below 400 grams in females. Diseased hearts were excluded on anatomical and histological evaluation.

Results: We diagnosed 1062 morphologically normal hearts. Mean age at death was 34±12, with a male predominance (701, 66%). Age was similar in females and males (35±13 vs 34±12). Females had a significantly lower heart weight (285±55 vs 374±64). Sex was an independent predictor of most measurements.

The atrial and ventricular cavities were significantly larger in males. All ventricular measurements of muscle thickness were larger in males. All valvular circumferences were larger in males. In contrast, sub-epicardial fat was significantly thicker in females in 6 of 7 regions. This is the first study to provide a calculator to give expected values according to sex, age, height and weight.

Conclusions: Major differences between the sexes exist in the morphologically normal heart. These variations should be considered when assessing cardiac structure in imaging for risk stratification and diagnosis in the cardiomyopathies, as well as in treatment outcomes.

1. Introduction

Sudden cardiac death (SCD) is a leading cause of mortality, accounting for around half of all deaths from cardiovascular disease and the majority are due to coronary artery disease [1]. Sudden adult death syndrome, where the heart is morphologically normal, is an important finding particularly in young individuals dying suddenly [2]. The presence of a normal heart at autopsy, with negative toxicology, points to an underlying electrical abnormality in myocyte channels referred to as channelopathy [3].

Whilst there is rich literature regarding the pathology of structural heart disease [4–6], little has been written on the morphologically normal heart. Previous autopsy studies have focused on organ weights [7–10]. This study is the first to characterize the normal heart in a cohort of individuals dying suddenly in terms of the heart weight, fossa size and patency, coronary artery dominance, dimensions of the atria, ventricular chambers and muscle thickness, valve circumference and sub-epicardial fat and correlate with sex, age, body weight, body height, body mass index (BMI) and body surface area (BSA). This will act as a baseline for future studies as well as correlation with imaging.

2. Methods

The study is undertaken at the Cardiac Risk in the Young (CRY) Cardiovascular Pathology Laboratory based at St George's University of London. The center receives cases of SCD from throughout

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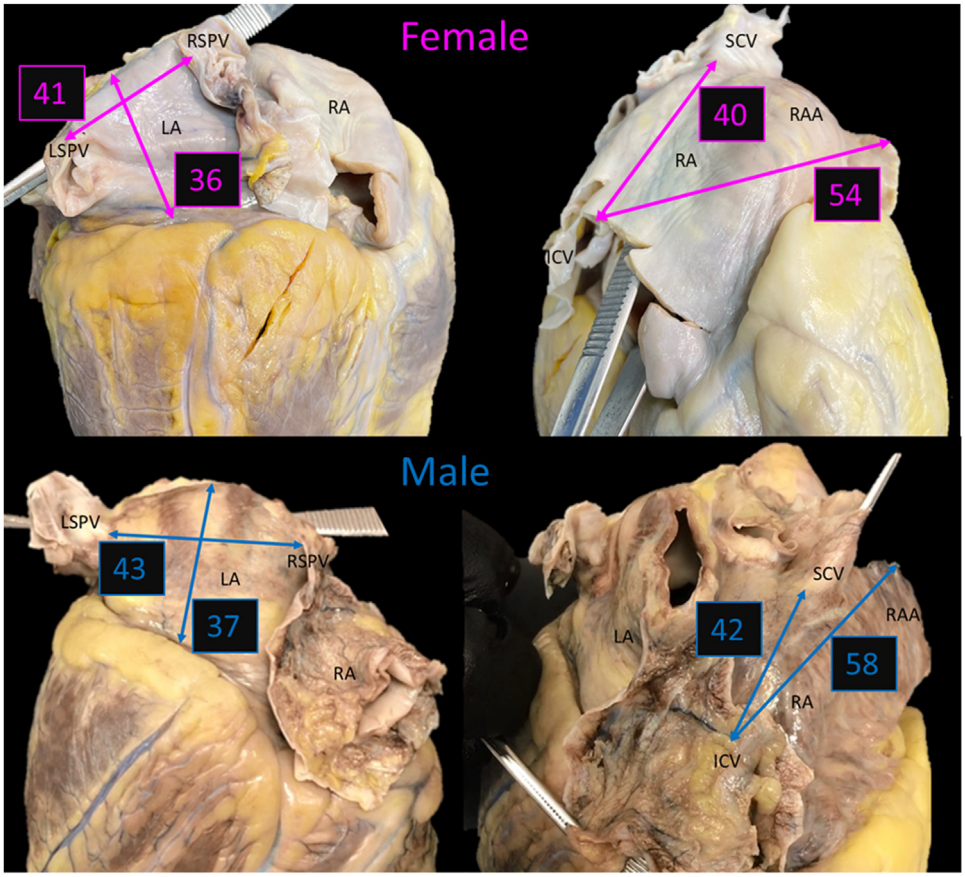

Fig. 1. The atrial measurements for female and male hearts. The left atrium (LA) is measured between the ostia of the left and right superior pulmonary veins (LSPV and RSPV), and from the atrioventricular junction to the superior surface. The right atrium (RA) is measured from the mouth of the inferior caval vein (ICV) to the tip of the appendage (RAA) and between the mouths of the inferior and superior caval veins (SCV). Note the larger measurements in males.

the United Kingdom. Cases with morphologically normal hearts were identified from a cohort of 3602 referrals between 2013 and 2020.

BMI is calculated as weight (kilograms)/height^2 (metres^2). BSA is calculated by square root of (height (centimeters) x weight (kilograms)/3600).

Diagnostic criteria used for the classification of a morphologically normal heart are a heart weight of below 500 g in males, and below 400 g in females. Cases with significant coronary artery disease, valvular disease, congenital disease or hypertension are excluded. Cardiomyopathies, myocarditis and infiltrating diseases, such as amyloid, are excluded on histology.

All hearts were examined macroscopically and microscopically in a formalin fixed state. Coronary artery dominance is judged on the basis of the artery extending to the cardiac crux. The left atrium is measured between the ostia of the left and right superior pulmonary veins, and from the atrioventricular junction to the superior surface (Fig. 1). The right atrium is measured from the mouth of the inferior caval vein to the tip of the appendage and between the mouths of the inferior and superior caval veins (Fig. 1). The fossa ovalis is measured from inferior to superior and from anterior to posterior and a 2 mm^2 probe is introduced to assess for patency (Fig. 2). Macroscopic measurements of the thickness of the ventricular wall and sub-epicardial fat, along with the cavitary diameters, are taken at a midventricular level (Fig. 3). The right ventricular outflow tract wall is measured anteriorly 10 mm below the pulmonary valve. Muscular wall measurements exclude the trabeculae and papillary muscles. The ascending aorta circumference is measured 20 mm above the aortic valve.

All the variables are explored and summarized according to their statistical type; categorical data as frequencies and percentages, and continuous data as means and standard deviations. Two-sided T-test is used to compare normally distributed continuous variables. The Chi-square test is used to assess independency between two categorical variables with Fisher's exact test used when cross tabulations exhibit numbers smaller than 5. The Kruskal-Wallis test is used to assess non-normally distributed or ordinal variables. Multiple linear regression is used to determine the most important predictors of outcome variables. The statistical software package SPSS package 27 is utilized to perform these tests.

Ethical and research governance was prospectively reviewed and approved for this study (10/H0724/38). All examination conforms to the standards set out by the United Kingdom Human Tissue Authority. In coronial autopsies, examination was undertaken under the jurisdiction of her majesty's coroner. In hospital autopsies, informed consent for examination was gained from the highest qualifying relative as set out by the United Kingdom Human Tissue Authority. The investigation conformed to the principles outlined in the Declaration of Helsinki.

3. Results

There are complete measurements taken from 1062 morphologically normal hearts, referred between 2013 and 2020. The mean age at death is 34±12 years with a male predominance (n=701, 66%, ratio 1.9:1). Females died at a similar age to males (35±13 years vs 34±11 years). The mean BMI is 27±6 kg/m^2, which is similar between females and males (27±6 kg/m^2 vs 27±6 kg/m^2). As

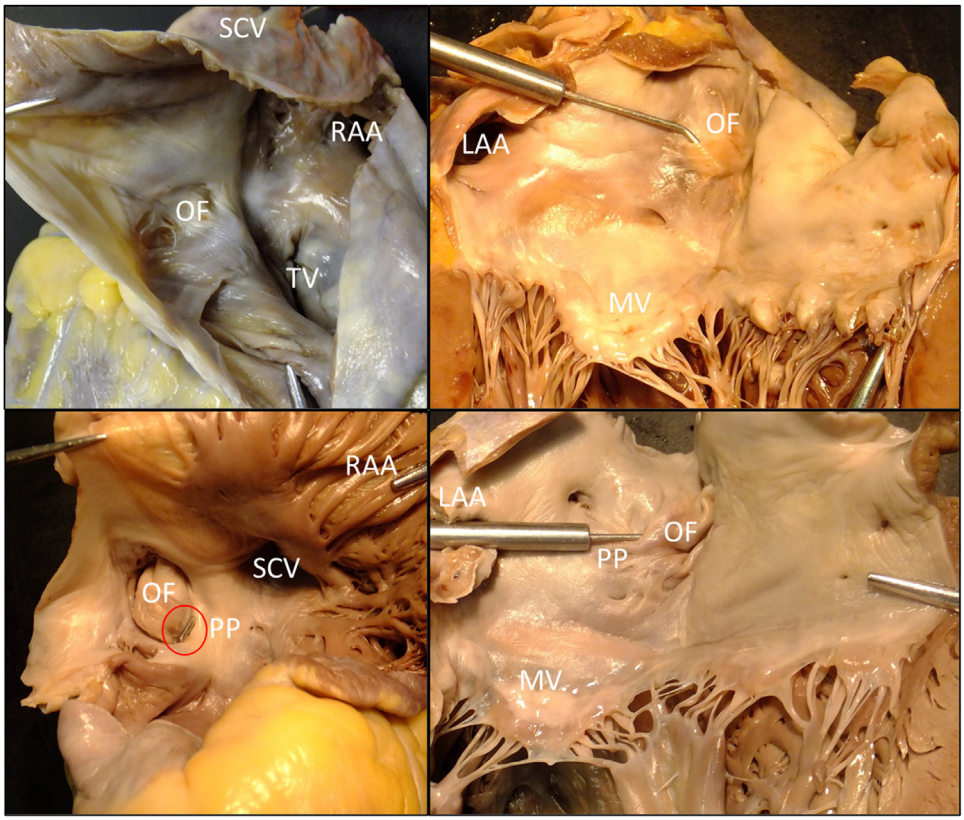

Fig. 2. The normal oval fossa which may be probe patent. The left panels illustrate the oval fossa from the right atrium and the right panels illustrate the oval fossa from the left atrium. The top panels show a case which is not probe patent and the bottom panels show a case where there is probe patency (circled in red). LAA: left atrial appendage; MV: mitral valve; OF: oval fossa; PP: probe patent; RAA: right atrial appendage; SCV: superior caval vein; TV: tricuspid valve.

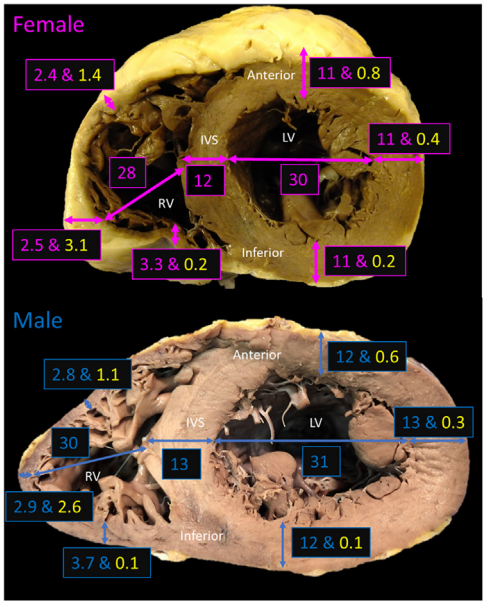

Fig. 3. The ventricular measurements for female and male hearts. Both the subepicardial fat (yellow) and muscle wall thicknesses (pink for females and blue for males) are measured in the anterior, lateral and inferior positions on the right ventricle (RV) and left ventricle (LV). The interventricular septum (IVS) is measured. Muscle wall thickness measurements exclude the trabeculae. Chamber diameters are measured between the mid septum to the lateral wall including the trabeculae. All these measurements are taken at a midventricular level. Note the larger muscle wall thickness and chamber diameters in males and the larger subepicardial fat thickness in females.

expected, BSA is lower in females compared to males (1.83±0.27 m^2 vs 2.04±0.24 m^2, $P<.001$) (Table 1).

3.1. Heart weight

The mean heart weight is 344±74 g. Females have a significantly lower heart weight than males (285±55 g vs 374±64 g, $P<.001$) (Table 2). Sex is the most important predictor of heart weight. We found that heart weight increases with BSA and age (Table 3).

3.2. Coronary artery dominance

The pattern of coronary arterial arrangement is right dominant in 999 (94%), left dominant in 52 (5%), and co-dominant in 11 (1%). These proportions are similar for females and males (Table 2).

3.3. Atrial measurements

In the right atrium, the mean transverse length between the mouth of the inferior caval vein and the tip of the right atrial appendage is 57±12 mm. The mean longitudinal length between the orifices of the inferior and superior caval veins is 41±10 mm.

In the left atrium, the mean transverse length between the left and right superior pulmonary veins is 42±9 mm. The mean longitudinal length between the atrioventricular junction and the superior surface of the left atrium is 37±8 mm.

The measurements of both right and left atria are all significantly smaller in females compared to males (all $P<.011$) (Table 2 and Fig. 1). The atrial measurements all increase with age (Table 3).

Table 1
Demographics for females and males.

Variable	Unit	Summary statistic	Normal hearts (n=1062)	Female (n=361)	Male (n=701)	*P* value
Age	Years	Mean±SD	34±12	35±13	34±11	.119
		Median, Q1–Q3	33, 25–41	33, 25–43	32, 25–40	
		Range	18–100	18–100	18–82	
Sex	Male: Female	Numbers	701:361	361	701	
		Ratio	1.9:1	-	-	
Height	cm	Mean±SD	174±10	166±9	179±8	**<.001**
		Median, Q1–Q3	175, 167–181	166, 161–172	178, 173–184	
		Range	140–208	140–193	150–208	
Weight	kg	Mean±SD	81±20	74±21	85±18	**<.001**
		Median, Q1–Q3	80, 67–91	70, 60–85	83, 73–93	
		Range	29–176	35–160	29–176	
BMI	kg/m^2	Mean±SD	27±6	27±7	27±6	.898
		Median, Q1–Q3	26, 22–30	25, 21–31	26, 23–29	
		Range	10–58	13–53	10–58	
BSA	m^2	Mean±SD	1.96±0.27	1.83±0.27	2.04±0.24	**<.001**
		Median, Q1–Q3	1.97, 1.78–2.13	1.80, 1.65–1.99	2.03, 1.90–2.16	
		Range	1.16–3.02	1.17–2.80	1.16–3.02	

The table gives the age, sex, height, weight, body mass index (BMI) and body surface area (BSA) for the overall cohort and broken down into males and females.

3.4. Oval fossa measurements and patency

The oval fossa has a mean width of 15±5 mm with a mean height of 14±4, and did not show differences between sexes. The fossa is patent in 111 of 917 cases (12%) (Fig. 2). Probe patency is present in a slightly higher proportion of females than males (45, 14% vs 66, 11%) but this did not reach significance (Table 2). The fossa measurements increase with age (Table 3).

3.5. Right ventricular chamber and muscle wall measurements

The mean diameter of the right ventricular chamber is 29±6 mm. The mean right ventricular muscle wall thickness is 2.7±1.0 mm for the anterior wall, 2.8±1.0 mm for the lateral wall, 3.6±1.0 mm for the inferior wall, and 3.2±1.0 mm for the right ventricular outflow tract.

The right cavitary diameter is significantly smaller in females when compared to males ($P<.001$). The diameter increases with BSA (Table 3). The right ventricular muscle wall thickness measurements are all significantly smaller in females when compared to males (all $P<.001$) (Table 2 and Figure 3). Sex is the most important predictor of all muscle wall thickness measurements (Table 3).

3.6. Left ventricular chamber and muscle wall measurements

The mean diameter of the left ventricular chamber is 31±7 mm. The septal wall thickness is 13±3 mm. The mean left ventricular muscle wall thickness is 12±2 mm for the anterior wall, 12±2 mm for the lateral wall, and 12±2 mm for the inferior wall.

The left cavity diameter is significantly smaller in females when compared to males ($P=.007$). The diameter increases with BSA (Table 3). The left ventricular muscle wall thicknesses are all significantly smaller in females when compared to males (all $P<.007$) (Table 2 and Fig. 3). Sex is the most important predictor of all muscle wall thickness measurements (Table 3).

3.7. Sub-epicardial fat measurements

The mean thickness of the right ventricular sub-epicardial fat is 1.2±1.3 mm for the anterior wall, 2.8±2.2 mm for the lateral wall, 0.2±0.6 mm for the inferior wall, and 0.9±1.2 mm for the right ventricular outflow tract.

The mean thickness of the left ventricular sub-epicardial fat is 0.7±1.3 mm for the anterior wall, 0.3±0.8 mm for the lateral wall, and 0.1±0.6 mm for the inferior wall.

All fat measurements are all significantly greater in females when compared to males (all $P<.045$) (Table 4 and Fig. 3). Fat measurements increase with age (Table 3).

3.8. Valvular measurements

The mean tricuspid valvular circumference is 97±14 mm. The mean pulmonary valvular circumference is 54±10 mm. The mean mitral valvular circumference is 77±13 mm. The mean aortic valvular circumference is 52±8 mm and the mean ascending aortic circumference is 53±8 mm. All valvular circumferences, and the ascending aortic circumference, are significantly smaller in females when compared to males (all $P<.001$) (Table 2). All valvular and ascending aorta circumferences increase with age (Table 3).

We attach an excel file which will give expected values and limits for the examined cardiac measurements based upon age, sex, body height and body weight (supplementary file).

4. Discussion

Here, for the first time, we provide comprehensive morphological analysis of a large cohort of normal hearts over a range of ages. The are striking differences between the male and female hearts. Whilst it is well recognized that the male heart is heavier than the female heart (de [8–10]), this is the first study regarding the detailed constitution of the heart chambers.

4.1. Heart weight

Several previous studies have demonstrated that heart weight varies by sex, age and BSA but not correlated with body weight, body height or BMI. Kitzman et al reported on 765 hearts found an average heart weight of 280 g for a 70 kg female and 349 g for an 80 kg male similar to us (female: 285 g; male: 374 g). In contrast to our study, they found body weight was a better predictor of normal heart weight than BSA [7]. De La Grandmaison et al, found an average heart weight of 365 g in males and 312 g in females which correlated best with age and BMI (de [8]). Wingren and Ottoson analyzed 27,645 adult heart weights confirming that males had heavier hearts and was related to BMI, height and sex [10]. Skurdal and Nordrum, found average heart weight to be 316 g in females compared to 395 g in males relating it to sex and body weight [9]. Gaitskell et al, found average heart weight was 388 g in males and 338g in females and related it to sex and BSA [11].

Table 2
The cardiac findings.

Variable	Unit	Summary statistic	Normal heart (n=1062)	Female (n=361)	Male (n=701)	*P* value
Heart weight	g	Mean±SD	344±74	285±55	374±64	**<.001**
		Median, Q1–Q3	347, 291–396	282, 243–328	375, 334–419	
		Range	134–498	134–399	191–498	
Atria						
Right atrium 1	mm	Mean±SD	57±12	54±12	58±13	**<.001**
		Median, Q1–Q3	60, 50–65	55, 45–60	60, 50–65	
		Range	24–100	25–80	24–100	
Right atrium 2	mm	Mean±SD	41±10	40±10	42±10	**.006**
		Median, Q1–Q3	40, 35–50	40, 35–45	40, 35–50	
		Range	20–80	20–80	20–80	
Left atrium 1	mm	Mean±SD	42±9	41±9	43±9	**.002**
		Median, Q1–Q3	40, 35–50	40, 35–45	40, 35–50	
		Range	16–85	20–80	16–85	
Left atrium 2	mm	Mean±SD	37±8	36±8	37±8	**.010**
		Median, Q1–Q3	35, 30–40	35, 30–40	35, 30–40	
		Range	14–70	15–70	14–70	
Oval fossa						
Width	mm	Mean±SD	15±5	15±5	16±4	.337
		Median, Q1–Q3	15, 12–18	15, 12–18	15, 12–18	
		Range	4–40	44–33	5–40	
Height	mm	Mean±SD	14±4	14±5	14±4	.310
		Median, Q1–Q3	14, 10–16	12, 10–16	14, 10–16	
		Range	3–35	3–33	3–35	
Probe patent	Count	Number/Total (percentage)	111/917 (12%)	45/312 (14%)	66/605 (11%)	.122
Right ventricle						
Diameter	mm	Mean±SD	29±6	28±6	30±6	**<.001**
		Median, Q1–Q3	30, 25–35	27, 25–30	30, 25–35	
		Range	10–48	10–45	10–48	
Anterior wall	mm	Mean±SD	2.7±1.0	2.4±1.0	2.8±1.1	**<.001**
		Median, Q1–Q3	3.0, 2.0–3.0	2.0, 2.0–3.0	3.0, 2.0–3.0	
		Range	0.5–8.0	0.5–6.0	1.0–8.0	
Lateral wall	mm	Mean±SD	2.8±1.0	2.5±1.0	2.9±1.1	**<.001**
		Median, Q1–Q3	3.0, 2.0–3.0	2.0, 2.0–3.0	3.0, 2.0–3.0	
		Range	1.0–10.0	1.0–7.0	1.0–10.0	
Inferior wall	mm	Mean±SD	3.6±1.0	3.3±0.8	3.7±1.0	**<.001**
		Median, Q1–Q3	4.0, 3.0–4.0	3.0, 3.0–4.0	4.0, 3.0–4.0	
		Range	1.0–10.0	1.0–6.0	1.0–10.0	
RVOT wall	mm	Mean±SD	3.2±1.0	2.9±1.0	3.4±1.0	**<.001**
		Median, Q1–Q3	3.0, 3.0–4.0	3.0, 2.0–3.0	3.0, 3.0–4.0	
		Range	1.0–7.0	1.0–7.0	1.0–6.0	
Left ventricle						
Diameter	mm	Mean±SD	31±7	30±7	31±7	**.007**
		Median, Q1–Q3	30, 25–35	30, 25–35	30, 27–35	
		Range	8–49	8–49	10–48	
Septal wall	mm	Mean±SD	13±3	12±2	13±3	**<.001**
		Median, Q1–Q3	12, 11–15	11, 10–13	13, 12–15	
		Range	7–21	7–20	8–21	
Anterior wall	mm	Mean±SD	12±2	11±2	12±2	**<.001**
		Median, Q1–Q3	12, 10–14	10, 10–12	12, 11–14	
		Range	7–20	7–20	7–20	
Lateral wall	mm	Mean±SD	12±2	11±2	13±2	**<.001**
		Median, Q1–Q3	12, 11–14	11, 10–12	12, 11–15	
		Range	7–22	7–20	8–22	
Inferior wall	mm	Mean±SD	12±2	11±2	12±2	**<.001**
		Median, Q1–Q3	11, 10–13	10, 10–12	12, 11–14	
		Range	7–20	7–20	7–20	
Valves and aorta						
Tricuspid valve circumference	mm	Mean±SD	97±14	92±13	99±14	**<.001**
		Median, Q1–Q3	95, 90–105	90, 81–100	100, 90–110	
		Range	50–145	55–130	50–145	
Pulmonary valve circumference	mm	Mean±SD	54±10	51±9	56±10	**<.001**
		Median, Q1–Q3	50, 50–60	50, 45–55	55, 50–60	
		Range	25–106	25–80	30–106	
Mitral valve circumference	mm	Mean±SD	77±13	74±11	79±14	**<.001**
		Median, Q1–Q3	75, 70–85	70, 65–80	80, 70–90	
		Range	45–125	45–115	45–125	
Aortic valve circumference	mm	Mean±SD	52±8	50±7	53±8	**<.001**
		Median, Q1–Q3	50, 45–55	50, 45–55	50, 50–60	
		Range	33–90	35–75	33–90	
Ascending aortic circumference	mm	Mean±SD	53±8	51±8	54±8	**<.001**
		Median, Q1–Q3	50, 50–60	50, 45–55	55, 50–60	
		Range	35–85	35–80	35–85	
Coronary artery dominance						
Right	Count	Number/Total (percentage)	999/1062 (94%)	336/361 (93%)	663/701 (95%)	.559
Left	Count	Number/Total (percentage)	52/1062 (5%)	20/361 (6%)	32/701 (5%)	
Codominance	Count	Number/Total (percentage)	11/1062 (1%)	5/361 (1%)	6/701 (1%)	

The heart weight, dimensions of the atria, dimensions of the oval fossa and probe patency, cavity size and muscle wall thickness for right ventricle and left ventricle, valve and ascending aorta circumferences and coronary artery dominance are given for the entire cohort and broken down by sex (RVOT: right ventricular outflow tract). p values are highlighted in bold when considered significant (<0.05).

Table 3
Multiple linear regression analysis results.

Variable	Adjusted R^2	Summary statistic	Intercept	Sex = Female	Body surface area	Age	Body weight	Height	Body mass index
Heart weight	0.525	Coefficient	56.682	68.276	133.053	1.442	-	-	-
	p<.000	Importance		**0.45**	0.42	0.13			
Atria									
Right atrium 1	0.045	Coefficient	30.873	-3.078	21.051	0.068	-0.210	-	-
	p<.000	Importance		**0.43**	0.26	0.16	0.15		
Right atrium 2	0.031	Coefficient	12.305	-	-	0.108	-	14.601	-
	p<.000	Importance				0.46		**0.54**	
Left atrium 1	0.032	Coefficient	15.897	-	21.087	0.086	-0.223	-	-
	p<.000	Importance			**0.43**	0.32	0.25		
Left atrium 2	0.036	Coefficient	12.458	-	-	0.115	-	11.677	-
	p<.000	Importance				**0.60**		0.40	
Fossa	0.041	Coefficient	2.307	-	-	0.072	-	6.098	-
Width	p<.000	Importance				**0.68**		0.32	
Fossa Height	0.041	Coefficient	2.089	-	-	0.072	-	5.384	-
	p<.000	Importance				**0.74**		0.26	
Right ventricle									
Diameter	0.035	Coefficient	22.832	-1.483	3.387	-	-	-	-
	p<.000	Importance		0.44	**0.56**				
Anterior muscle	0.040	Coefficient	2.377	-0.348	-	-	0.005	-	-
	p<.000	Importance		**0.76**			0.24		
Lateral muscle	0.035	Coefficient	2.221	-0.359	-	0.006	-	-	0.018
	p<.000	Importance		**0.69**		0.10			0.22
Inferior muscle	0.047	Coefficient	3.234	-0.401	-	-	-	-	0.019
	p<.000	Importance		**0.76**					0.20
RVOT muscle	0.071	Coefficient	3.007	-0.554	-	-	-	-	0.015
	p<.000	Importance		**0.91**					0.09
Anterior fat	0.056	Coefficient	-0.128	0.244	-	0.025	-	-	0.016
	p<.000	Importance		0.14		**0.79**			0.07
Lateral fat	0.082	Coefficient	0.006	0.399	-	0.052	-	-	0.034
	p<.000	Importance		0.09		**0.83**			0.08
Inferior fat	0.003	Coefficient	0.126	0.075	-	-	-	-	-
	p<.000	Importance		**1.00**					
RVOT fat	0.081	Coefficient	-0.658	-	-	0.029	-	-	0.020
	p<.000	Importance				**0.91**			0.09
Left ventricle									
Diameter	0.047	Coefficient	17.610	-	5.613	0.070	-	-	-
	p<.000	Importance			**0.74**	0.26			
Septal muscle	0.111	Coefficient	11.780	-1.650	-	-	-	-	0.062
	p<.000	Importance		**0.85**					0.15
Anterior muscle	0.110	Coefficient	10.491	-1.332	0.953	-	-	-	-
	p<.000	Importance		**0.89**	0.11				
Lateral muscle	0.086	Coefficient	11.232	-1.246	0.751	-	-	-	-
	p<.000	Importance		**0.92**	0.08				
Inferior muscle	0.084	Coefficient	10.561	-1.105	0.798	-	-	-	-
	p<.000	Importance		**0.89**	0.11				
Anterior fat	0.011	Coefficient	0.289	0.200	-	0.010	-	-	-
	p<.000	Importance		0.44		**0.56**			
Lateral fat	0.041	Coefficient	-0.873	0.136	0.346	0.013	-	-	-
	p<.000	Importance		0.12	0.19	**0.69**			
Inferior fat	0.013	Coefficient	-0.384	0.108	0.175	0.004	-	-	-
	p<.000	Importance		**0.38**	0.25	0.37			
Valves & aortic circumference									
Tricuspid valve	0.082	Coefficient	46.154	-3.940	-	0.162	-	26.452	-
	p<.000	Importance		0.26		0.33		**0.42**	
Pulmonary valve	0.089	Coefficient	16.167	-2.447	-	0.160	-	19.105	-
	p<.000	Importance		0.16		**0.50**		0.34	
Mitral valve	0.059	Coefficient	46.705	-3.587	24.463	0.127	-0.254	-	-
	p<.000	Importance		**0.34**	0.21	0.32	0.13		
Aortic valve	0.210	Coefficient	28.392	-2.982	-	0.279	-	8.673	-
	p<.000	Importance		0.13		**0.83**		0.04	
Ascending aorta	0.281	Coefficient	22.805	-2.702	-	0.343	-	11.059	-
	p<.000	Importance		0.07		**0.88**		0.04	

Multiple linear regression analysis to predict heart weight, atrial measurements, ventricular diameter, muscle thickness, epicardial fat thickness, using age, sex, weight, height, body mass index and body surface area. The most important predictors of heart weight and muscle wall thickness is sex.

The average heart weights in these studies are comparable but higher than in our study of 285 g in females and 374 g in males. This is most likely due to the inclusion of hearts with weights above 400 g in females and 500 g in males which we would consider abnormal.

4.2. Atrial dimensions

This is the first study of atrial dimensions at autopsy. This is a novel method of measurement and these results will provide a reference for future studies as there is increasing emphasis on atrial

Table 4
Epicardial fat thickness.

Variable	Unit	Summary statistic	Normal heart (n=1062)	Female (n=361)	Male (n=701)	*P* value
Right ventricle						
Anterior fat	mm	Mean±SD	1.2±1.3	1.4±1.5	1.1±1.2	**.002**
		Median, Q1–Q3	1.0, 0–2.0	1.0, 0–2.0	1.0, 0–2.0	
		Range	0–8.0	0–8.0	0-7.0	
Lateral fat	mm	Mean±SD	2.8±2.2	3.1±2.5	2.6±2.1	**.002**
		Median, Q1–Q3	2.0, 1.0–4.0	2.0, 1.0–5.0	2.0, 1.0–3.0	
		Range	0–15.0	0–15.0	0–15.0	
Inferior fat	mm	Mean±SD	0.2±0.6	0.2±0.7	0.1±0.5	**.045**
		Median, Q1–Q3	0, 0–0	0, 0–0	0, 0–0	
		Range	0–6.0	0–6.0	0–5.0	
RVOT fat	mm	Mean±SD	0.9±1.2	1.0±1.3	0.8±1.1	**.029**
		Median, Q1–Q3	1.0, 0–1.0	1.0, 0–1.0	0, 0–1.0	
		Range	0–9.0	0–8.0	0–9.0	
Left ventricle						
Anterior fat	mm	Mean±SD	0.7±1.3	0.8±1.4	0.6±1.2	**.011**
		Median, Q1–Q3	0, 0–1.0	0, 0–1.0	0, 0–1.0	
		Range	0–10.0	0–10.0	0–7.0	
Lateral fat	mm	Mean±SD	0.3±0.8	0.4±0.9	0.3±0.8	.082
		Median, Q1–Q3	0, 0–0	0, 0–0	0, 0–0	
		Range	0–9.0	0–9.0	0–6.0	
Inferior fat	mm	Mean±SD	0.1±0.6	0.2±0.8	0.1±0.4	**.027**
		Median, Q1–Q3	0, 0–0	0, 0–0	0, 0–0	
		Range	0–9.0	0–9.0	0–4.0	

The table shows the epicardial fat thicknesses for the anterior, lateral and inferior walls of the right and left ventricular as well as the right ventricular outflow tract (RVOT).

disease including atrial fibrillation and atrial cardiomyopathy [12]. All four atrial measurements are smaller in females and increase with age. A previous imaging study has demonstrated that atrial measurements are smaller in females confirming our findings [13]. Previous imaging studies of healthy living individuals have shown varied results on the effect of age on the atria [14,15]. One previous study using echocardiography has reported that age, height and weight are independent predictors of left atrial width [14] whereas another study has reported that age did not have an effect on atrial size [15]. The European Association of Echocardiography recommends a normal left atrial transverse diameter should be 27–40 mm which is similar to our measurement [16].

4.3. Oval fossa

This is the first study on the size of the oval fossa. There was no difference between sexes. Three anatomical studies of 500–1000 hearts have identified probe patency of the oval fossa in 17–35% of individuals which is very variable [17–19]. Patent oval fossa is a risk factor for paradoxical embolization and ischemic stroke and is therefore important to document in the normal population [20]. An echocardiographic study of 1000 consecutive living patients found a patent fossa in 9.2% similar to our study [21].

4.4. Ventricular chamber and wall measurements

Post mortem ventricular chamber diameter is unique to our study and has not been previously reported. Our findings confirm that males have large cavities with increase with body surface area.

Three large studies of living patients using echocardiography and magnetic resonance imaging have reported greater sizes of both ventricular chambers in males compared to females [22,23]. The European Association of Cardiovascular Imaging provides normal values of cardiac chamber dimensions assessed by resonance imaging which are indexed by body surface area [24]. This supports our finding that body surface area is the most important predictor of both ventricular chamber diameters as well as sex and age.

In contrast to our study, Kitzman et al, found no difference between one ventricular muscle wall measurement of unknown location in males and females and found no correlation with age and body surface area [7]. Their reported means are 3.4–4.0 mm for the RV and 10.8–12.6 mm for the LV. Our measurements are similar to those reported for the younger age group in Kitzman's report.

Echocardiography and resonance imaging demonstrates that both septal and inferior LV wall measurements are larger in males than females [22,25]. A resonance imaging study reported RV mass was greater in males [26]. These reports confirm that males have greater myocardial muscle wall measurements.

4.5. Valve circumference

Kitzman et al, found larger circumferences in males [7]. The tricuspid circumference was largest followed by the mitral circumference. The aortic and pulmonary valve circumferences were the smallest and of similar size. All valves showed increases with age which we confirm.

4.6. Coronary arterial dominance

Coronary artery dominance shows disparity between anatomical and living patient studies and between methods used for assessment. Historical pathological estimates range from 34–71% right dominance, 20–48% left dominance and 9–20% co-dominant in studies of 230–350 hearts [27,28]. There is no explanation for this wide variation. A more precise study of 1453 cases using post mortem coronary angiogram reports 81% right dominance, 9.1% left dominance and 10% codominance similar to us [29].

Our study observed a lower proportion of co-dominance but is within the lower end of the estimates for left dominance examined by angiography. Left dominant circulation has been associated with poorer prognostic outcomes in individuals with and without coronary disease assessed by computed tomography angiography. The presence of a left dominant circulation is an independent risk factor for extensive myocardial infarction and death [30].

4.7. Sub-epicardial fat thickness

Our previous study of 148 normal hearts has demonstrated that RV sub-epicardial fat increased with age and was thicker in females than males. Sub-epicardial fat was greatest in the lateral right ventricle wall, followed by the anterior wall with little or no fat present posteriorly. The lateral wall sub-epicardial thickness ranged from 0–12mm [31]. A post mortem study of 56 cadavers has used photography to quantify the extent of sub-epicardial fat of diseased hearts [32]. They also found that age independently correlated with sub-epicardial fat extent and the presence and stage of coronary artery disease. They do not comment on differences by sex.

4.8. Sub-epicardial fat associations and role in disease

Increased sub-epicardial fat has been related to myocardial mass [33]. Corradi et al, studied 117 hearts comparing normal hearts to those with hypertrophy and/or ischemia and found that there was a preserved ratio of fat to muscle in myocardial hypertrophy suggesting that fat increases with muscle thickness.

Increased sub-epicardial fat has also been related to smoking and elevated heart rate [34]. Miyazawa et al, used computed tomography to examine 623 men aged 40–79 years without a history of cardiovascular disease following them up for an average of 4.7 years finding that current smoker status and increased heart rate were independently associated with increases in sub-epicardial fat volume.

The most established and promising relations, however, are to acute coronary events [35] and atrial fibrillation [36]. Nakanishi et al, examined 517 non-obese patients with coronary disease using computed tomography following them up for 4 years and found that increases in sub-epicardial fat volume, despite risk management, were associated with increased high risk or obstructive plaques. The largest report demonstrating the relationship between atrial fibrillation and sub-epicardial fat derives from the Framingham Heart study. Computed tomography was used to examine 3217 participants, of which 54 developed atrial fibrillation. Pericardial fat volume was found to be associated with prevalent atrial fibrillation following adjustment for risk factors including body mass index [37]. It is therefore surprising that females have greater sub-epicardial fat despite having a lower prevalence of both ischemic heart disease and atrial fibrillation [38,39].

The extent of fat may also play a role in reducing the effects of catheter ablation [40,41]. Nascimento Matos et al, followed up 575 patients undergoing pulmonary vein isolation for atrial fibrillation [40]. Sub-epicardial fat was quantified using computed tomography. They found that sub-epicardial fat was a strong independent predictor of atrial fibrillation relapse outperforming other recognized clinical risk factors. Zipse et al, used bovine myocardium with sub-epicardial fat to assess different radiofrequency ablation strategies [41]. They found that increasingly thick sub-epicardial fat attenuated lesion size regardless of strategy.

There are various reports on the role of sub-epicardial fat in disease. It has been proposed to regulate granulopoiesis, and to serve as a source for inflammatory mediators leading to cardiovascular disease [42]. It has also been linked to fibrosis and function following myocardial infarction as well as myocyte dysfunction in diabetes [43,42]. The differences in sub-epicardial fat between the sexes should be adjusted for when assessing for disease.

4.9. Limitations

Our study will include cases where SCD is due to channelopathies. Future comparison to hearts with a non-cardiac cause of death will be valuable. Our study is based on fixed hearts and future comparison with fresh hearts will be important. Due to the relatively lower numbers of old aged individuals in our sample population, it is uncertain how the calculator will perform in these individuals. Interval between death and postmortem was not available and hearts with death in systole were included. These variables have not been accounted for and may influence cavity diameters.

5. Concluding remarks

When evaluating the abnormal, it is of central importance to understand the normal. Sex is the most important predictor of cardiac anatomy. We provide a calculator to give expected values according to sex, age, height and weight. The fact that sub-epicardial fat is higher in females should be accounted for when examining this population. The fact the female heart is smaller with regard to the measurements of muscle wall thickness, chamber diameters and valvular circumferences should be accounted for so as not to under call pathologic alterations. This is further emphasized by the fact that sex is a modifier of cardiovascular health, disease, and medicine where discrepant outcomes occur for a variety of reasons [44].

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Supplementary materials

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