Reference Ranges for and Determinants of Right Ventricular Area in Healthy Adults by Two-Dimensional Echocardiography

Ekkehard Grünig^a Johanna Biskupek^a Antonello D'Andrea^c Nicola Ehlken^a
Benjamin Egenlauf^a Johannes Weidenhammer^a Alberto M. Marra^{a, c}
Antonio Cittadini^c Christine Fischer^b Eduardo Bossone^d

^aCentre for Pulmonary Hypertension, Thoraxclinic, University Hospital Heidelberg, and ^bDepartment of Human Genetics, University of Heidelberg, Heidelberg, Germany; ^cInternal Medicine Section, Department of Translational Medical Sciences, 'Federico II' University School of Medicine, Naples, ^dCardiology Division, 'Cava de' Tirreni and Amalfi Coast' Hospital, Heart Department, University of Salerno, Salerno, and Cardiac Surgery Department, IRCCS Policlinico San Donato, Milan, Italy

Key Words

Echocardiography · Right ventricular area · Reference ranges · Pulmonary hypertension

Abstract

Background: The right ventricular (RV) area is important for diagnosis and follow-up in patients with various diseases, such as in pulmonary hypertension. **Objectives:** The aim of this study was to define the reference ranges of the end-diastolic RV area in healthy adults and to assess the determining factors. **Methods:** In the first part of the study 860 healthy subjects (37.6% female; mean age 28 ± 5.84 ; 395 endurance athletes, 255 strength athletes and 210 non-athletes) were prospectively assessed. In the second part we performed a pooled analysis of studies published between 1979 and 2014 describing the RV area in healthy subjects ($n = 5,248$). Statistical analysis included the calculation of reference ranges and the analysis of determining factors. **Results:** Mean end-diastolic RV areas in 860 healthy subjects were significantly larger in endurance athletes ($25.1 \pm 2.0 \text{ cm}^2$) compared with strength athletes ($22.9 \pm 1.7 \text{ cm}^2$) and non-athletes ($16.7 \pm 2.0 \text{ cm}^2$, $p < 0.001$). In the synopsis of both data sets, mean end-diastolic RV area was significantly larger

in European/American males (17 cm^2) compared with females (14 cm^2 , $p < 0.001$) and in Asian males (16 cm^2) compared with females (13 cm^2 , $p < 0.001$). The area increased with body surface area and older age. **Conclusion:** This is the largest data set to define RV size in healthy adults aged < 50 years. RV area was determined by age, gender, body surface area, ethnicity and high-level exercise training. High standard deviations resulted in high values for the upper limit of the reference range, which might therefore not be useful as cut-off values for screening purposes. Gender- and ethnicity-specific reference ranges should be used. Further studies in subjects aged > 50 years as well as in children are needed.

© 2015 S. Karger AG, Basel

Introduction

Right ventricular (RV) size is of clinical importance since it reflects the pressure and volume load of the pulmonary circulation and is strongly associated with prognosis in many conditions, such as in pulmonary hyper-

E.G., J.B., A.D'A., C.F. and E.B. contributed equally to this work.

tension (PH) [1–4]. The normal right ventricle of healthy subjects should be a thin-walled crescent-shaped structure, wrapped around the left ventricle [5, 6]. The RV area is a sensitive indicator of volume overload or increasing pulmonary artery pressure resulting in early hypertrophy and enlargement [7].

Transthoracic 2D echocardiography is the most relevant non-invasive method to assess the right heart in clinical practice for diagnosis and follow-up in several diseases, such as cardiomyopathy and PH [8, 9]. The echocardiographic assessment of the RV area is limited by technical difficulties and the complex geometry of the right ventricle [10–12]. Foale et al. [10] first described the technique to assess the right ventricle in the apical 4-chamber view. Routine assessment of the RV area using the apical 4-chamber view would refine measurements of the RV and help to detect early stages of RV hypertrophy, which is common in PH patients [13, 14]. Thus, we set out to establish normal ranges for this measurement from a large population of healthy individuals to serve as reference for clinicians on a daily basis. Since there are only limited publications focusing on the normal size of the right ventricle [6, 7, 13], a robust assessment of RV area is urgently required.

In the current American guidelines for echocardiography a mean of 18 cm² and an upper reference value of 25 cm² are given [7]. However, ranges were not tested for gender specificity or indexed for body surface area (BSA). These values are preliminary and have to be further validated.

The aim of this study was to evaluate the reference ranges of RV area in a large prospectively assessed population of healthy adults and to perform a meta-analysis using previously published studies. Furthermore, we wanted to identify the determining factors of RV area.

Material and Methods

Study Population

From June 2008 to March 2009, 210 healthy, normally active, non-athletic subjects and 650 top-level athletes were prospectively recruited and successively studied by 2D echocardiography at Monaldi Hospital, Naples, Italy, as previously described [15]. The athletes of this study were employed by professional sports organisations and had been exercising intensively for 15–20 h/week for >4 years. The athletes were referred for cardiovascular examination before participation in a sports competition [15]. Volunteer controls were selected from the department of Cardiology in Naples, Italy, and investigated for work eligibility. None of the control subjects suffered from cardiovascular structural or functional abnormalities or were receiving any medication in this regard. The

subjects' screening contained a physical examination, a detailed history, electrocardiography, chest radiography, an exercise test, measuring of BSA and a comprehensive transthoracic echocardiography, including Doppler echocardiography, as described previously [8, 15]. Subjects suffering from cardiopulmonary diseases such as coronary artery disease, systemic arterial hypertension, valvular or congenital heart disease, bicuspid aortic valve, congestive heart failure, cardiomyopathies and diabetes mellitus were rejected from the study. Further exclusion criteria were sinus tachycardia and inadequate echocardiographic image quality. The use of illicit drugs like anabolic steroids was ruled out by medical history and patient interview. This study was approved by the local ethics committee. All subjects enrolled in the study gave their informed consent.

Echocardiographic Assessment

2D and Doppler-echocardiographic images were recorded using 2.5-MHz Duplex probes and conventional tools (Vivid 7, GE Healthcare, Milwaukee, Wis., USA) by experienced cardiac sonographers. The RV size was measured in the apical 4-chamber view. End-diastolic RV area was estimated by planimetry at the end of the ventricular diastole (largest volume), tracing from the lateral aspect of the tricuspid annulus to the septal aspect, excluding the area of the annulus and trabecular structures, following the RV endocardium (fig. 1). The RV area was assessed during passive end-expiration. The subjects had not been fasting before the examination in order to assess the right ventricle with normal hydration status. All studies were reviewed as well as analysed offline by two independent observers, who were blinded to the clinical characteristics of the study population. To provide an example of the measuring technique used, a normal and an enlarged RV area measured by 2D echocardiography are shown in figure 1. A complete echocardiographic assessment including the assessment of pulmonary artery pressures was performed in all subjects to exclude PH or any heart disease able to affect the right heart size through congenital heart defects [16]. A mean of at least 3–5 measurements was used for all calculations. Subjects who had a presumed history of cardiac diseases or increased pulmonary systolic artery pressures (>35 mm Hg) were excluded from the analysis.

Literature Search

We performed a systematic literature search using the Medline and Cochrane Databases for studies describing echocardiographic RV measurements in healthy subjects published between January 1979 and February 2014 either in English or German. Key words or medical subheadings related to RV area or size were used for the literature search. Furthermore, we screened reviews and references of relevant studies as well as practice guidelines to detect further studies. All studies with an unclear status of subjects or non-standardised echocardiographic techniques were excluded.

Statistical Methods

All analyses were performed by two biometricians (C.F. and N.E.).

Calculation of RV Area and Indexing for BSA. All reported values for end-diastolic RV area in the prospective analysis are means of at least three measurements and are presented with the standard deviation (SD). For indexing RV area to BSA we used the formula: end-diastolic RV area (RVEDA) indexed to BSA (cm²/m²) = absolute RVEDA (cm²)/BSA (m²). BSA was calculated using the Mos-

Fig. 1. Echocardiographic measurement of RV area using the apical 4-chamber view. A normal-sized RV area of a healthy subject is shown on the left, and an enlarged RV area of a patient suffering from PH is shown on the right.

Table 1. RV area prospectively obtained in 860 healthy subjects

	Non-athletes	Strength athletes	Endurance athletes
Gender			
Male	126 (14.7)	155 (18.0)	255 (29.7)
Female	84 (9.8)	100 (11.6)	140 (16.2)
RV area, cm ²			
Male	16.8±2.0	22.8±1.8	25.1±2.1
Female	16.6±1.9	23.0±1.6	25.0±2.0
Mixed	16.7±2.0	22.9±1.7	25.1±2.0
RV area index, cm ² /m ²			
Male	9.1±1.0	12.4±1.0	13.5±1.1
Female	9.0±1.1	12.6±0.8	13.5±1.1
Mixed	9.1±1.0	12.5±0.9	13.5±1.1

Values are presented as n (% of total) or mean ± SD.

teller formula: $BSA (m^2) = [height (cm) \times weight (kg)/3,600]^{1/2}$ [17]. In the meta-analysis we calculated the indexed values if possible (table 1).

Prospective Analysis. We calculated correlation coefficients to describe the determinants of end-diastolic RV area. Additionally, groups with a different exercise training status, i.e. endurance and strength athletes or non-athletes, and gender and ethnicity groups were compared by analysis of variance (ANOVA). *p* values <0.05 were considered statistically significant. For these analyses we used IBM SPSS 20 (SPSS Statistics v20, IBM Corporation, Somers, N.Y., USA).

Meta-Analysis. For each study the mean and SD of RV area and sample size were given. Two SD ranges were determined as reference ranges for the subgroups. We combined the results from the meta-analysis with our prospective data for male and female and ethnic groups by pooling the means and SD for each study weighted by sample size, assuming a common underlying normal distribution. Subgroups were compared by *t* tests and ANOVA. *p* values <0.05 were regarded as statistically significant.

Results

Prospective Study

We prospectively evaluated 870 healthy adults in our study. Ten subjects had to be withdrawn, 1 due to hypertrophic cardiomyopathy, 3 for a bicuspid aortic valve, 4 for using anabolic steroids and 2 for inadequate echocardiographic image quality. Thus, the final study cohort included 860 subjects with a mean age of 28 ± 5.84 years (range 18–40), 324 females (37.6%) and 536 males (62.3%; table 1). The cohort included 395 endurance athletes, 255 strength athletes and 210 non-athletes (fig. 2). The non-athletes showed a significantly smaller mean end-diastolic RV area (16.71 ± 1.96 cm², 2 SD range 12.8–20.6 cm²) compared to strength athletes (22.88 ± 1.74 cm², 2 SD range 19.4–26.4 cm², *p* < 0.001) and endurance athletes (25.07 ± 2.04 cm², 2 SD range 21.0–29.2 cm², *p* < 0.001; table 1; fig. 2). Furthermore, the endurance athletes had significantly higher mean end-diastolic RV areas com-

Table 2. Abridgement of studies included in the meta-analysis

Study (first author)	Year	n	Retro/ pro	% female	BSA	Gender distinction	Absolute Index area	Athletes	Non- athletes	Age, years ¹		
										male	total cohort	female
Bommer [11]	1979	25		44			x		x		45 (35–60)	
Cacho [1]	1983	11		27	x		x		x		29.5 (22–37)	
Kaul [27]	1984	10		0			11		x	31.7±1.3		–
Hauser [25]	1985	24		0	x		cal	x	x	33.6±9.6		–
Douglas [23]	1990	41		46			21	x			38±10	
Esch [24]	2007	16		0	cal		x	x	x	25.8±3.8		–
Daimon [21]	2008	700		45	x	x	x		x	43.7±14.5		43.5±14.5
Baggish [19]	2008	40	pro	50	x	x	x	x		19.2±1.2		19.6±1
Chiha [20]	2010	60	retro	53	x		x		x		20–79	
Ogunyankin [28]	2011	1,060		51	x	x	x		x		30±3.5	
Jurcut [26]	2011	21		62			x		x		38±12	
Curren [5]	2011	30		53			x		x		46±14	
van der Zwaan [31]	2011	31	pro	48	x		cal		x		31±7	
D'Oronzio [22]	2012	1,625	retro	53	x	x	x		x		44±14	
Oxborough [29]	2012	102	pro	16	x		x	x			36±11	
Willis [12]	2012	146	pro	47	x	x	x		x		42±12	
Pfaffenberger [30]	2013	622	pro	53	x		x		x	38.3±16.0	41.8±15.5	43.8±14.8
Kou [32]	2014	734	pro	44	x	x	x		x	46.3±13.7	45.8±13.3	45.4±13.1
Total		5,298										

¹ 'x' indicates values provided by the original manuscript. retro = Retrospective study design; pro = prospective study design; cal = calculated.

¹ Presented as either the mean (range), range or mean ± SD.

pared to strength athletes ($p < 0.001$). The differences considering the training status could also be seen in the indexed values.

The analysis showed a weak correlation of RV area with age (strength athletes $r = 0.23$, endurance athletes $r = 0.29$, non-athletes $r = 0.12$) and BSA (strength athletes $r = 0.20$, endurance athletes $r = 0.21$, non-athletes $r = 0.18$) in all three groups. Subjects with higher ages or higher BSA had slightly higher RV areas. Mean RV areas were similar in males and females of the non-athletic group [$16.77 \pm 1.98 \text{ cm}^2$ (2 SD range 14.8–18.8) vs. $16.62 \pm 1.93 \text{ cm}^2$ (2 SD range 14.7–18.5); mixed gender: $16.7 \pm 2.0 \text{ cm}^2$, $p > 0.05$). RV areas indexed for BSA in non-athletic males and females (9.1 ± 1.0 vs. $9.0 \pm 1.1 \text{ cm}^2/\text{m}^2$) as well as mixed gender ($9.1 \pm 1.0 \text{ cm}^2/\text{m}^2$) were also similar.

Meta-Analysis Results

Twenty studies were detected by screening the Medline and Cochrane databases for RV size. Two of the 20 studies were excluded [2, 18] due to lack of information concerning the characteristics of the 'healthy' subjects [2] and due to an unclear training status, as the study included 'non-athletes' scheduled for a marathon run [18].

Thus, 18 studies published between 1979 and 2014 with 5,248 healthy subjects were included in the meta-analysis (table 2) [1, 5, 11, 12, 19–31]. Further subgroups,

Fig. 2. Training status as a determinant of the RV area. In this figure the data of our prospective study is shown. The RV areas of non-athletes compared with strength athletes, non-athletes compared with endurance athletes, and endurance athletes compared with strength athletes differed significantly ($p < 0.001$).

Table 3. Mean absolute and BSA-indexed RV areas: pooled values in males and females

		Absolute RV area, cm ²				p values (gender)	Indexed RV area (BSA), cm ² /m ²				p values (gender)
		male		female			male		female		
		n	mean ± SD	n	mean ± SD		n	mean ± SD	n	mean ± SD	
<i>Non-athletes: EU/USA</i>											
D'Oronzio [22], 2012	EU	764	16.90±3.55	861	13.50±3.03	<0.0001	764	8.58±1.80	861	7.8±1.75	<0.00001
Esch [24], 2007	Canada	8	16.60±3.10	–	–		8	8.68±1.62	–	–	
Hauser [25], 1985	USA	12	24.30±3.40	–	–		12	12.75±1.78	–	–	
Kaul [27], 1984	USA	10	10.50±0.60	–	–		–	–	–	–	
Ogunyankin [28], 2011	USA	533	17.20±4.20	527	13.90±3.60	<0.0001	533	8.73±2.13	527	8.15±2.11	0.00001
Willis [12], 2012	EU	18	20.75±4.53	18	16.16±2.54	0.0007	18	10.59±2.31	18	9.34±1.47	0.06188
Kou [32], 2014	EU	414	18.2±4.3	320	14.8±3.5	<0.001	414	9.4±2.1	320	8.8±1.9	<0.001
D'Andrea (prospective data)	EU	126	16.77±1.98	84	16.62±1.93	0.59	126	9.07±1.07	84	9.23±1.07	0.29
n/weighted mean		1,885	17.31±3.78	1,810	14.01±3.22	<0.0001	1,749	8.82±1.93	1,726	6.61±1.51	<0.0001
<i>Non-athletes: Asia</i>											
Willis [12], 2012	China	26	16.15±2.60	27	13.14±2.86	0.0002	26	8.83±1.42	27	8.26±1.80	0.21461
Willis [12], 2012	India	15	14.30±2.84	12	12.91±2.19	0.1754	15	8.17±1.62	12	7.64±1.30	<0.0001
Willis [12], 2012	Malaysia	19	14.26±2.36	11	13.66±2.94	0.5446	19	7.92±1.31	11	8.43±1.82	0.38041
Daimon [21], 2008	Japan	383	16.00±4.00	317	13.0±3.0	<0.0001	383	9.13±2.28	317	8.72±2.01	0.01159
n/weighted mean		443	15.88±3.81	370	13.03±2.96	<0.0001	443	9.03±2.17	370	8.64±1.97	<0.00001
p values (ethnicity): EU/USA vs. Asia			<0.0001		<0.0001		0.0635		<0.0001		
<i>Endurance athletes: EU/USA</i>											
Esch [24], 2007	Canada	8	18.6±3.9				8	9.73±2.04			
Baggish [19], 2008	USA	20	30.2±5.0	20	26.1±2.7	0.0004	20	14.63±2.42	20	14.48±1.5	0.0013
Hauser [25], 1985	USA	12	30.5±4.7				12	16.11±2.48			
D'Andrea (prospective data)	EU	255	25.1±2.1				255	13.49±1.08			
n/weighted mean		295	25.5±2.4				295	13.57±1.26			
p values (training status): non-athletes vs. endurance athletes			<0.0001				<0.0001				

such as RV areas of strength athletes [19] and of different American ethnicities [20] were excluded from the meta-analysis due to a lack of further data.

The assessed subjects had been classified as 'healthy' or 'free of heart diseases' in all studies. As far as was specified, most studies had performed electrocardiograms and a physical examination to exclude any heart disease. One study characterised the status 'healthy' with a high degree of accuracy. They performed right and left heart catheterisation [11] and assessed rubber casts fashioned from the right heart chambers during necropsy in 8 deceased subjects without clinical or anatomical evidence of heart-lung diseases to validate the echocardiographic dimensions of the heart chambers. In general, the included subjects were aged between 20 and 79 years, while most subjects were younger than 50 years (table 2).

The range for the absolute value of the end-diastolic RV area was between 10.5 and 24.3 cm² for the non-athletes, obtained from the two oldest publications included in the study [25, 27]. The absolute values for the endur-

ance athletes went up to 30.5 cm² [25]. The mean values and SD for absolute and indexed values of the end-diastolic RV area of the meta-analysis for each study and for the pooled analysis are shown in tables 3 and 4.

Determining Factors of RV Area: Gender, Exercise Training Status, Age, Ethnicity and BSA

The pooled weighted mean end-diastolic RV areas in non-athletes were significantly greater in males (17.31 ± 3.78 cm², 2 SD range 9.8–24.9) compared to females (14.02 ± 3.22 cm², 2 SD range 7.6–20.5, $p < 0.0001$; table 3). The mixed gender weighted mean RV area was 16.36 ± 3.72 cm² (2 SD range 8.9–23.8 cm²; table 4).

Significantly larger end-diastolic RV areas in males were also observed in Asian subjects with an absolute mean end-diastolic RV area of 15.88 ± 3.81 cm² (2 SD range 8.3–23.5, indexed 9.03 ± 2.17 cm²/m²) for men and 13.03 ± 2.96 cm² (2 SD range 7.1–19.0, indexed 8.64 ± 1.97 cm²/m²) for women ($p < 0.0001$). The mixed gender weighted mean for RV area in Asian subjects was 14.56 ±

Table 4. Mean absolute and BSA-indexed RV areas for mixed gender

		Male, n	Female, n	Absolute RV area mixed gender, cm ²		Indexed RV area (BSA) , cm ² /m ²	
				n	mean ± SD	n	mean ± SD
<i>Non-athletes: EU/USA</i>							
Bommer [11], 1979	USA	14	11	25	18.00±1.20		–
Curren [5], 2011	USA	14	16	30	14.10±4.50		–
Jurcut [26], 2011	EU	8	13	21	14.50±4.20		–
Cacho [1], 1983	USA	8	3	11	10.91±1.25	11	6.16±0.71
van der Zwaan [31], 2011	EU	16	15	31	22.62±3.77	31	12.02±2.00
D’Oronzio [22], 2012	EU	764	861	1,625	15.1±3.27	1,625	8.16±1.71
Ogunyankin [28], 2011	USA	533	527	1,060	15.6±3.9	1,060	8.46±2.03
Willis [12], 2012	EU	18	18	36	18.46±3.53	36	9.85±1.53
Chiha [20], 2010	Australia	28	32	60	20.12±4.05	60	11.00±2.12
Pfaffenberger [30], 2013	EU	294	328	622	19.4±4.7	622	10.78±2.61
Kou [32], 2014	EU	414	320	734	17.1±4.2	734	9.5±2.0
D’Andrea (prospective data)	EU	126	84	210	16.7±2.0	210	9.1±1.0
n/weighted mean		2,237	2,228	4,465	16.36±3.72	4,389	8.80±2.50
<i>Non-athletes: Asia</i>							
Daimon [21], 2008	Japan	383	317	700	14.61±3.55	700	8.91±2.17
Willis [12], 2012	China	26	27	53	14.62±2.73	53	8.50±1.59
Willis [12], 2012	India	15	12	27	13.68±2.55	27	7.91±1.47
Willis [12], 2012	Malaysia	19	11	30	14.04±2.57	30	8.26±1.51
n/weighted mean		443	367	810	14.56±3.43	810	8.82±2.08
p values (ethnicity): Caucasian vs. Asian					<0.0001		0.81
<i>Endurance athletes: EU/USA</i>							
Douglas [23], 990	USA	22	19	41	21.4±5.3		
Oxborough [29], 2012	EU	86	16	102	26.0±5.0	102	13.88±2.67
Baggisch [19], 2008	USA	20	20	40	28.15±3.85	40	14.56±1.99
D’Andrea (prospective data)	EU	140	0	140	25.1±2.0	140	13.48±1.07
n/weighted mean		268	55	323	25.25±3.60	282	13.78±1.95
p values (training status): non-athletes vs. endurance athletes					<0.0001		<0.0001

3.43 cm² (2 SD range 7.7–21.4, indexed 8.82 ± 2.08 cm²/m²).

Furthermore, RV areas significantly differed between the different ethnicities (Asian vs. Europeans/Americans, $p < 0.0001$) within each gender (table 3) and for mixed gender (table 4). However, there was no significant difference between ethnicities for males and for mixed gender when the values were indexed.

RV area means were also significantly different between non-athletes and endurance athletes (non-athletes 16.36 ± 3.72 vs. endurance athletes 25.25 ± 3.60 cm², 2 SD range 18.1–32.5, $p < 0.0001$; table 4). Figure 3 depicts the weighted means (and confidence intervals) of the end-diastolic RV areas allotted to the examined studies and subcategories.

Discussion

To the best of our knowledge, this is to date the largest data set on RV size in healthy adults ($n = 5,248$) aged between 18 and 79 years (most of them aged below 50 years). The calculated reference ranges for RV size obtained by 2D echocardiography in the apical 4-chamber view are based on a large prospective study in healthy adults ($n = 860$) which was performed by our group and on a meta-analysis of published prospective and retrospective studies. The study provides reference ranges for end-diastolic RV area and confirms for the first time that the reference ranges used should be not only gender specific, but also ethnicity specific and adapted in athletes. Mean end-diastolic RV areas in non-athletes were significantly different between females (14 cm²) and males (17 cm²; 16 cm²

Fig. 3. Forest plot of mean echocardiographically measured RV areas with 95% confidence intervals for each study, organised by gender and ethnicity. Dark symbols with corresponding vertical lines represent the pooled mean estimates of the RV area in the respective subgroup of studies.

in mixed gender), even when indexed for BSA (females $6.6 \text{ cm}^2/\text{m}^2$; males $8.8 \text{ cm}^2/\text{m}^2$). Additionally, they were significantly different between Asians (13 cm^2 in females, 14 cm^2 in males) and Europeans/Americans (14 cm^2 in females, 17 cm^2 in males). Age, gender, BSA and a high level of endurance exercise training have been identified as confounding factors of RV area.

Given the high variability of RV area values obtained by echocardiography, which values should be used for cut-offs? If we consider the mean ± 2 SD of our pooled data (prospective study + data from the meta-analysis),

we identified 20.5 cm^2 in females and 25 cm^2 in males as the upper limit of reference ranges for healthy adult European/Americans, and 19 and 24 cm^2 in healthy Asian females and males, respectively. Very similar reference ranges have recently been seen in other large studies [30, 32] that did not analyse ethnic differences. The high upper limits of reference ranges result from the high SDs and reflect the large variability of RV area when assessed by echocardiography. In previous studies mean values of end-diastolic RV area ranged from 10.5 to 24.3 cm^2 for non-athletes, and went up to 30.5 cm^2 in endurance ath-

letes [25, 27]. The large variation of RV areas within healthy subjects underlying the data used for the meta-analysis in this study might also be due to methodical pitfalls when measuring the RV area. RV area can be largely overestimated if assessed by deep inspiration. Therefore, the assessment of RV area during passive end-expiration needs to become standardised. Another important factor for RV size which could not be considered is the hydration status. A longer fasting period or dehydration can lead to a significant underestimation of RV area.

In clinical practice, absolute RV area is of high relevance to detect or to follow up right heart diseases and to assess treatment effects in diseases such as in PH [2, 3, 26, 33, 34]. Unfortunately, echocardiographic assessment of the right heart is still not standardised and not uniformly adopted in routine clinical practice. There is a high need for an updated consensus statement on cut-off values. If we used the ranges of mean values ± 2 SD obtained in this study for normal RV area, most patients with early PH would probably be overseen by screening with echocardiography. In the first screening study which was able to identify early PH using echocardiography and right heart catheterization, patients with manifest disease had a mean RV area of $19.3 \pm 6.84 \text{ cm}^2$ (median 18.4; 16.6–19.8) compared to $15.0 \pm 5.41 \text{ cm}^2$ (median 14.7; 12.0–17.4) in non-PH patients [35]. Due to the high variability of RV area, RA area cut-off values [8] might be even more useful for screening for PH. Compared to multiple tomographic imaging planes, the obtained values of the RV area appear to be more reliable than the assessment of RV sizes measuring only diameters or inferring the volume.

Determinant Factors of RV Area

The influence of gender on absolute values was detectable in most of the presented studies. Therefore, mixed gender values for absolute RV areas should no longer be used. Moreover, we recommend indexing the measured values for BSA to account for individual physical differences. This study confirms for the first time that there are significant ethnical differences.

Our findings with significantly higher values for end-diastolic RV area in athletes than in non-athletes are in line with previous studies that described the ‘athlete’s heart syndrome’ with chamber enlargements of the left and the right heart [15, 19, 23–25, 29]. Even a singular, exhausting, sportive activity could already lead to a temporarily enlarged RV size [5, 25]. This finding was observed for marathon runners as well as in volunteers on a treadmill exercise test [23, 25]. Besides the temporary RV dilatation caused by a single marathon run, further effects on the heart, such as the re-

lease of cardiac troponin I [36], B-type natriuretic peptides [18, 37], increased pulmonary pressures, RV dysfunction [18], as well as a reduction of RV ejection fraction found by magnetic resonance imaging can be detected. One explanation for the possibly stronger effect of endurance training on the right ventricle compared to the left ventricle could be the thin-walled structure of the right ventricle [38]. The larger RV areas in athletes compared to non-athletes may be the result of higher volume loads (for endurance athletes) or higher pressure (for strength athletes) the right heart has to deal with during exercise [39, 40].

Absolute RV area was weakly correlated with age. We observed subjects with older age to have slightly larger RV areas. However, most subjects of this study were younger than 50 years of age. This finding is confirmed by other recent studies [30, 32] which showed a significant positive impact of age on RV size. However, other studies showed no effect of age on RV area [20, 28], while D’Oronzio et al. [22] observed a weak negative correlation with age. Older age was associated with lower RV volumes in healthy subjects [41].

Limitations

The meta-analysis of our study has some limitations. The definition of ‘healthy’ subjects differed in the individual studies. A right heart catheterisation was mentioned in only one study as part of the clinical examination [11]. We cannot exclude selection bias since not all studies focused on the reference ranges of end-diastolic RV area in healthy subjects, whilst others were designed retrospectively. However, most recent studies on RV area [30, 32] showed similar estimates of reference ranges compared to our pooled meta-analysis, and the results were only slightly changed when these were omitted. The overall mean RV values of the analysed studies differed quite widely. Therefore, we estimated the pooled values for subgroups according to ethnicity and gender. To be able to compare the values with the literature, we also included the reference ranges for mixed gender, although we recommend using gender-specific ranges. For discrimination of PAH patients, a specific cut-off has still to be evaluated, depending on the screening population.

Conclusions

To the best of our knowledge, this is the largest data set to analyse RV area reference ranges in healthy adult subjects (aged <50 years). Mean values for end-diastolic RV area were significantly larger in European/American

males (17 cm²) compared to females (14 cm²), and in Asian males (16 cm²) compared to females (13 cm²). Thus, gender- and ethnicity-specific reference ranges should be used. The end-diastolic RV area significantly increased with a larger BSA, older age and high-level endurance training. High SDs resulted in high values for the upper limit of reference ranges, which might therefore be less useful for cut-off values, especially for screening assessments in clinical practice. Further studies in subjects aged >50 years and in children are needed.

Acknowledgements

We thank all subjects who participated in the study.

Financial Disclosure and Conflicts of Interest

No funding was received for this study. The authors declare that they have no conflict of interest.

References

- 1 Cacho A, Prakash R, Sarma R, Kaushik VS: Usefulness of two-dimensional echocardiography in diagnosing right ventricular hypertrophy. *Chest* 1983;84:154–157.
- 2 Raymond RJ, Hinderliter AL, Willis PW, Ralph D, Caldwell EJ, Williams W, Ettinger NA, Hill NS, Summer WR, de Boisblanc B, Schwartz T, Koch G, Clayton LM, Jobsis MM, Crow JW, Long W: Echocardiographic predictors of adverse outcomes in primary pulmonary hypertension. *J Am Coll Cardiol* 2002;39:1214–1219.
- 3 Vonk Noordegraaf A, Galie N: The role of the right ventricle in pulmonary arterial hypertension. *Eur Respir Rev* 2011;20:243–253.
- 4 Davlouros PA, Niwa K, Webb G, Gatzoulis MA: The right ventricle in congenital heart disease. *Heart* 2006;92(suppl 1):i27–i38.
- 5 Curren M, Lopez-Candales A, Edelman K, Gulyasy B: Normal parameters of right ventricular mechanics with exertion in healthy individuals: a tissue Doppler imaging study. *Am J Med Sci* 2011;341:23–27.
- 6 Lang RM, Bierig M, Devereux RB, et al: Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;18:1440–1463.
- 7 Rudski LG, Lai WW, Afilalo J, Hua L, Hand-Schumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB: Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010;23:685–713; quiz 786–688.
- 8 Grünig E, Henn P, D'Andrea A, Claussen M, Ehlken N, Maier F, Naeije R, Nagel C, Prange F, Weidenhammer J, Fischer C, Bossone E: Reference values for and determinants of right atrial area in healthy adults by 2-dimensional echocardiography. *Circ Cardiovasc Imaging* 2013;6:117–124.
- 9 Grünig E, Barner A, Bell M, Claussen M, Dandel M, Dumitrescu D, Gorenflo M, Holt S, Kovacs G, Ley S, Meyer JF, Pabst S, Riemekasten G, Saur J, Schwaiblmair M, Seck C, Sinn L, Soricter S, Winkler J, Leuchte HH: Non-invasive diagnosis of pulmonary hypertension: ESC/ERS guidelines with updated commentary of the Cologne Consensus Conference 2011. *Int J Cardiol* 2011;154(suppl 1):S3–S12.
- 10 Foale R, Nihoyannopoulos P, McKenna W, Kleinebenne A, Nadazdin A, Rowland E, Smith G: Echocardiographic measurement of the normal adult right ventricle. *Br Heart J* 1986;56:33–44.
- 11 Bommer W, Weinert L, Neumann A, Neef J, Mason DT, DeMaria A: Determination of right atrial and right ventricular size by two-dimensional echocardiography. *Circulation* 1979;60:91–100.
- 12 Willis J, Augustine D, Shah R, Stevens C, Easaw J: Right ventricular normal measurements: time to index? *J Am Soc Echocardiogr* 2012;25:1259–1267.
- 13 Grapsa J, Gibbs JS, Cabrita IZ, Watson GF, Pavlopoulos H, Dawson D, Gin-Sing W, Howard LS, Nihoyannopoulos P: The association of clinical outcome with right atrial and ventricular remodelling in patients with pulmonary arterial hypertension: study with real-time three-dimensional echocardiography. *Eur Heart J Cardiovasc Imaging* 2012;13:666–672.
- 14 Bogaard HJ, Abe K, Vonk Noordegraaf A, Voelkel NF: The right ventricle under pressure: cellular and molecular mechanisms of right-heart failure in pulmonary hypertension. *Chest* 2009;135:794–804.
- 15 D'Andrea A, Riegler L, Golia E, Cocchia R, Scarafile R, Salerno G, Pezzullo E, Nunziata L, Citro R, Cuomo S, Caso P, Di Salvo G, Cittadini A, Russo MG, Calabro R, Bossone E: Range of right heart measurements in top-level athletes: the training impact. *Int J Cardiol* 2013;164:48–57.
- 16 Yock PG, Popp RL: Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation. *Circulation* 1984;70:657–662.
- 17 Mosteller RD: Simplified calculation of body-surface area. *N Engl J Med* 1987;317:1098.
- 18 Neilan TG, Januzzi JL, Lee-Lewandrowski E, Ton-Nu TT, Yoerger DM, Jassal DS, Lewandrowski KB, Siegel AJ, Marshall JE, Douglas PS, Lawlor D, Picard MH, Wood MJ: Myocardial injury and ventricular dysfunction related to training levels among nonelite participants in the Boston marathon. *Circulation* 2006;114:2325–2333.
- 19 Baggish AL, Wang F, Weiner RB, Elinoff JM, Tournoux F, Boland A, Picard MH, Hutter AM Jr, Wood MJ: Training-specific changes in cardiac structure and function: a prospective and longitudinal assessment of competitive athletes. *J Appl Physiol* 2008;104:1121–1128.
- 20 Chiha J, Boyd A, Thomas L: Does normal ageing alter right ventricular relaxation properties? A tissue Doppler study. *Heart Lung Circ* 2010;19:406–412.
- 21 Daimon M, Watanabe H, Abe Y, Hirata K, Hozumi T, Ishii K, Ito H, Iwakura K, Izumi C, Matsuzaki M, Minagoe S, Abe H, Murata K, Nakatani S, Negishi K, Yoshida K, Tanabe K, Tanaka N, Tokai K, Yoshikawa J, Investigators JS: Normal values of echocardiographic parameters in relation to age in a healthy Japanese population: The JAMP study. *Circ J* 2008;72:1859–1866.
- 22 D'Oronzio U, Senn O, Biaggi P, Gruner C, Jenni R, Tanner FC, Greutmann M: Right heart assessment by echocardiography: gender and body size matters. *J Am Soc Echocardiogr* 2012;25:1251–1258.
- 23 Douglas PS, O'Toole ML, Hiller WD, Reichel N: Different effects of prolonged exercise on the right and left ventricles. *J Am Coll Cardiol* 1990;15:64–69.
- 24 Esch BT, Scott JM, Haykowsky MJ, McKenzie DC, Warburton DE: Diastolic ventricular interactions in endurance-trained athletes during orthostatic stress. *Am J Physiol Heart Circ Physiol* 2007;293:H409–H415.

- 25 Hauser AM, Dressendorfer RH, Vos M, Hashimoto T, Gordon S, Timmis GC: Symmetric cardiac enlargement in highly trained endurance athletes: a two-dimensional echocardiographic study. *Am Heart J* 1985;109:1038–1044.
- 26 Jurcut R, Giusca S, Ticulescu R, Popa E, Amzulescu MS, Ghiorghiu I, Coman IM, Popescu BA, Voigt JU, Ginghina C: Different patterns of adaptation of the right ventricle to pressure overload: a comparison between pulmonary hypertension and pulmonary stenosis. *J Am Soc Echocardiogr* 2011;24:1109–1117.
- 27 Kaul S, Tei C, Hopkins JM, Shah PM: Assessment of right ventricular function using two-dimensional echocardiography. *Am Heart J* 1984;107:526–531.
- 28 Ogunyankin KO, Liu K, Lloyd-Jones DM, Colangelo LA, Gardin JM: Reference values of right ventricular end-diastolic area defined by ethnicity and gender in a young adult population: the CARDIA study. *Echocardiography* 2011;28:142–149.
- 29 Oxborough D, Sharma S, Shave R, Whyte G, Birch K, Artis N, Batterham AM, George K: The right ventricle of the endurance athlete: the relationship between morphology and deformation. *J Am Soc Echocardiogr* 2012;25:263–271.
- 30 Pfaffenberger S, Bartko P, Graf A, Pernicka E, Babayev J, Lolic E, Bonderman D, Baumgartner H, Maurer G, Mascherbauer J: Size matters! Impact of age, sex, height, and weight on the normal heart size. *Circ Cardiovasc Imaging* 2013;6:1073–1079.
- 31 van der Zwaan HB, Geleijnse ML, McGhie JS, Boersma E, Helbing WA, Meijboom FJ, Roos-Hesselink JW: Right ventricular quantification in clinical practice: two-dimensional vs. three-dimensional echocardiography compared with cardiac magnetic resonance imaging. *Eur J Echocardiogr* 2011;12:656–664.
- 32 Kou S, Caballero L, Dulgheru R, et al: Echocardiographic reference ranges for normal cardiac chamber size: results from the NORRE study. *Eur Heart J Cardiovasc Imaging* 2014;15:680–690.
- 33 Galiè N, Hinderliter AL, Torbicki A, Fourme T, Simonneau G, Pulido T, Espinola-Zavaleta N, Rocchi G, Manes A, Frantz R, Kurzyna M, Nagueh SF, Barst R, Channick R, Dujardin K, Kronenberg A, Leconte I, Rainisio M, Rubin L: Effects of the oral endothelin-receptor antagonist bosentan on echocardiographic and Doppler measures in patients with pulmonary arterial hypertension. *J Am Coll Cardiol* 2003;41:1380–1386.
- 34 Grünig E, Tiede H, Enyimayew EO, Ehlken N, Seyfarth HJ, Bossone E, D’Andrea A, Naeije R, Olschewski H, Ulrich S, Nagel C, Halank M, Fischer C: Assessment and prognostic relevance of right ventricular contractile reserve in patients with severe pulmonary hypertension. *Circulation* 2013;128:2005–2015.
- 35 Coghlan JG, Denton CP, Grunig E, Bonderman D, Distler O, Khanna D, Muller-Ladner U, Pope JE, Vonk MC, Doelberg M, Chadha-Boreham H, Heinzl H, Rosenberg DM, McLaughlin VV, Seibold JR; DETECT Study Group: Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. *Ann Rheum Dis* 2014;73:1340–1349.
- 36 Trivax JE, Franklin BA, Goldstein JA, Chinaiyan KM, Gallagher MJ, deJong AT, Colar JM, Haines DE, McCullough PA: Acute cardiac effects of marathon running. *J Appl Physiol* 2010;108:1148–1153.
- 37 La Gerche A, Claessen G, van de Bruaene A, Pattyn N, van Cleemput J, Gewillig M, Bogaert J, Dymarkowski S, Claus P, Heidbuchel H: Cardiac MRI: a new gold standard for ventricular volume quantification during high-intensity exercise. *Circ Cardiovasc Imaging* 2013;6:329–338.
- 38 Ector J, Ganame J, van der Merwe N, Adrienssens B, Pison L, Willems R, Gewillig M, Heidbuchel H: Reduced right ventricular ejection fraction in endurance athletes presenting with ventricular arrhythmias: a quantitative angiographic assessment. *Eur Heart J* 2007;28:345–353.
- 39 Roy A, Doyon M, Dumesnil JG, Jobin J, Landry F: Endurance vs strength training: comparison of cardiac structures using normal predicted values. *J Appl Physiol* 1988;64:2552–2557.
- 40 Baggish AL, Wood MJ: Athlete’s heart and cardiovascular care of the athlete: scientific and clinical update. *Circulation* 2011;123:2723–2735.
- 41 Maffessanti F, Muraru D, Esposito R, Gripari P, Ermacora D, Santoro C, Tamborini G, Galderisi M, Pepi M, Badano LP: Age-, body size-, and sex-specific reference values for right ventricular volumes and ejection fraction by three-dimensional echocardiography: a multicenter echocardiographic study in 507 healthy volunteers. *Circ Cardiovasc Imaging* 2013;6:700–710.