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ORIGINAL PAPER

Decoding right ventricular geometry: novel 3D echocardiography-derived global shape analysis across health and disease states

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Aims

While pre-defined reference shapes have been used to assess morphological changes in the left ventricle, standardized methods for evaluating right ventricular (RV) remodelling are lacking. This study aimed to develop and test a new 3D echocardiography (3DE)-based method for quantifying RV shape in a large cohort of healthy individuals and across various disease states.

Methods and results

3DE-derived RV mesh models were reconstructed in 1043 healthy subjects from the World Alliance of Societies of Echocardiography (WASE) study and in 581 patients with severe aortic stenosis, heart failure with reduced ejection fraction (HFrEF), post-heart transplantation, severe primary mitral regurgitation (MR), atrial secondary tricuspid regurgitation (A-STR), tetralogy of Fallot (TOF), and pulmonary hypertension (PH). To assess global RV shape, hemi-sphericity volume ratio (HSVR) and hemi-conicity angle (HCA) were calculated, where a higher HSVR and a more acute HCA reflect more spherical and conical shapes, respectively. In the WASE population, females had more spherical RVs, whereas males had more conical RVs ($P = 0.028$). Considering age, younger females had more conical RVs, while older individuals in both sexes showed spherical remodelling ($P < 0.05$). Comparing disease groups with WASE controls, MR, HFrEF, and A-STR patients had more spherical RVs compared with controls (both $P < 0.001$), while PH and TOF patients showed conical remodelling (both $P < 0.001$). In A-STR, a more conical remodelling was associated with adverse clinical outcomes.

Conclusion

The proposed 3DE-based method comprehensively characterizes RV geometry, demonstrating demographic variation in healthy individuals and disease-specific alterations in patients, with important prognostic implications.

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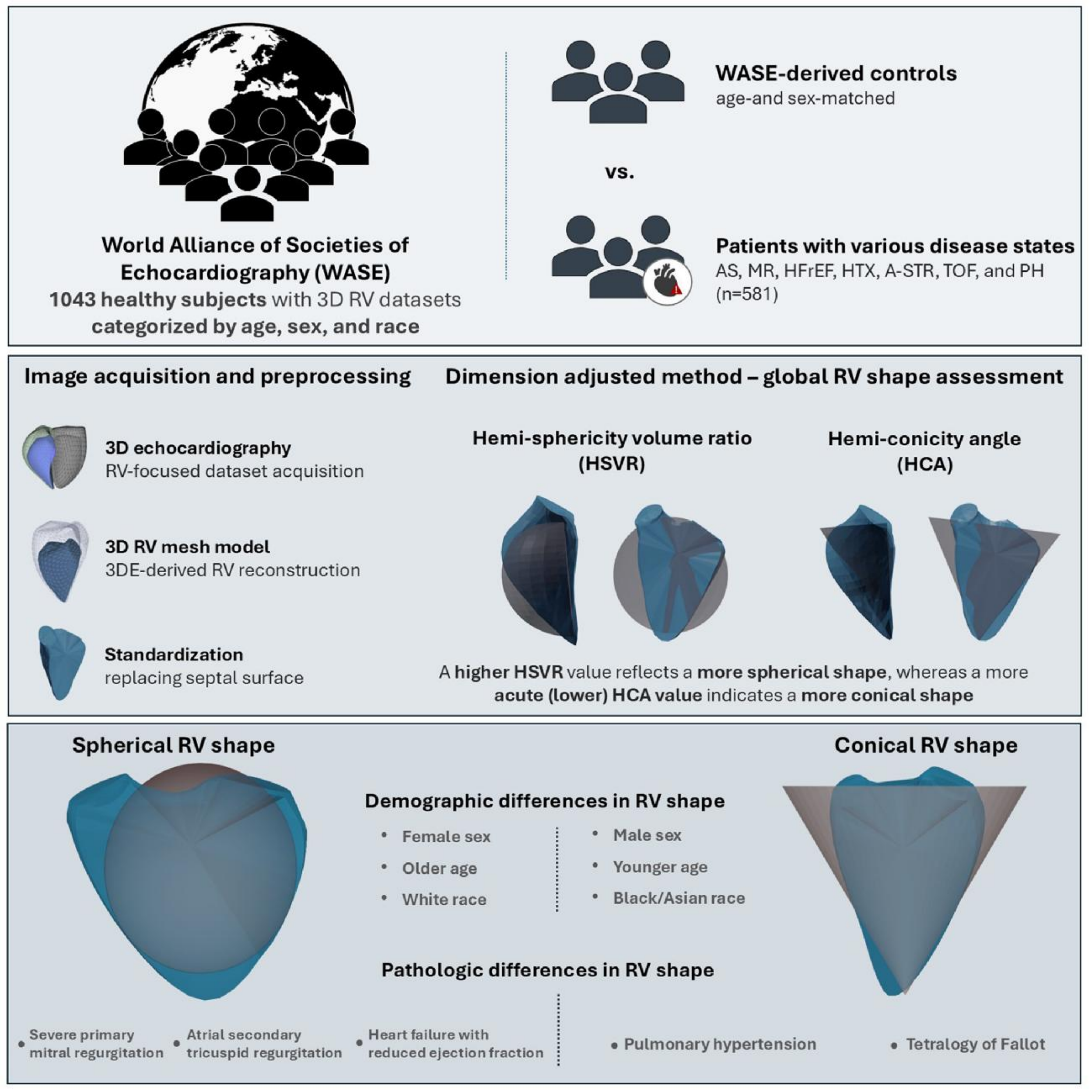
§ The authors wish to dedicate this work to the memory of Professor Roberto M. Lang, whose lifelong commitment to advancing cardiovascular imaging, pioneering contributions to 3D echocardiography, and unwavering dedication to education and patient care continue to inspire generations of clinicians and researchers.

Graphical Abstract



A novel 3D echocardiography-derived approach to analyse global right ventricular shape A total of 1043 healthy individuals from the WASE cohort were analysed across demographic subgroups, along with 581 patients representing various cardiac disease states. A novel 3DE-derived approach was implemented to calculate HSVR and HCA, allowing the assessment of global right ventricular shape. RV shape analysis revealed characteristic sex-, age-, and race-related physiological differences in healthy individuals. In predominantly left-sided cardiac diseases, the RV exhibited a more spherical remodelling, whereas in right-heart conditions, a more conical RV shape was observed. 3DE, 3D echocardiography; A-STR, atrial secondary tricuspid regurgitation; AS, aortic stenosis; HCA, hemi-conicity angle; HFrEF, heart failure with reduced ejection fraction; HSVR, hemi-sphericity volume; HTX, post-heart transplantation; MR, mitral regurgitation; PH, pulmonary hypertension; RV, right ventricle; TOF, tetralogy of Fallot; WASE, World Alliance of Societies of Echocardiography.

Keywords right ventricle • three-dimensional • echocardiography • right ventricular shape

Introduction

Describing changes in right ventricular (RV) shape across different cardiac diseases and physiological conditions has proven challenging, resulting in less attention compared with the more established value of shape analysis in understanding left ventricular (LV) geometry and function.[1,2] Research indicates that processes following functional or haemodynamic load variations involve adaptive mechanisms not only in chamber size, wall thickness, and function,[3] but also in changes to ventricular shape,[4,5] which have been identified as predictors of outcomes in different clinical scenarios.[6] While the size and function of all cardiac chambers have been thoroughly researched, changes in the shape of these chambers, particularly the RV, have not been frequently reported.

Research on LV shape has suggested that ventricular morphology reflects physiological information that is independent of size and function.[1,3] So far, changes in LV geometry have been studied more extensively than those in the RV, partially due to the complex structure of this ventricle compared with its left counterpart. Nevertheless, recent studies suggest that the analysis of three-dimensional echocardiography (3DE)-derived regional curvature indices enables the quantification of regional changes in RV shape.[5] Furthermore, RV shape can also be partially assessed by evaluating cardiovascular magnetic resonance (CMR) imaging and the changes in the curvature of the interventricular septum using two-dimensional transthoracic echocardiography (2DE), which have been associated with the severity of pulmonary hypertension (PH).[3,7,8] However, this approach only focuses on one relevant anatomical region of the RV. A more comprehensive analysis of global RV shape and its variations across different demographic and pathological conditions could provide a better understanding of RV remodelling processes.

Accordingly, the aim of this study is two-fold: (i) to develop a new 3DE-based method to quantify global RV shape and assess the impact of sex-, age-, and race-related differences in normal RV shape using the World Alliance of Societies of Echocardiography (WASE) cohort, and (ii) to identify novel clinical insights by assessing global RV shape across different disease states using a large patient population from multiple centres.

Methods

Study population

To assess the normative changes in RV shape, an established subset ($n = 1043$) of the WASE cohort with available 3DE-derived RV datasets was used.[9] This cohort was further categorized by sex (male and female), race (white, black, and Asian), and age groups (18–40 years, 41–65 years, and >65 years). As previously described in detail, all subjects from the WASE cohort underwent a comprehensive 2DE and 3DE examination using commercial ultrasound imaging systems (GE Healthcare, Philips Medical Systems, and Siemens Healthineers).[10] All image acquisitions followed a standardized protocol established by the American Society of Echocardiography (ASE)/European Association of Cardiovascular Imaging (EACVI) guidelines and were analysed by WASE core laboratories (University of Chicago and MedStar Health Research Institute).[11]

To obtain a clinical perspective, we also analysed RV geometrical remodelling in 581 patients with different cardiac disease states enrolled from 2 tertiary centres. The disease groups included patients with severe aortic stenosis (AS, $n = 86$), severe primary mitral regurgitation (MR, $n = 68$), heart failure with reduced LV ejection fraction (HFrEF, $n = 101$), and post-heart transplantation (HTX, $n = 94$) derived from the RVENet dataset (Heart and Vascular Center, Semmelweis University, Budapest, Hungary).[12] Patients with PH ($n = 38$), atrial secondary tricuspid regurgitation (A-STR, $n = 166$), and tetralogy of Fallot (TOF, $n = 28$) were enrolled from the Department of Cardiology, Istituto Auxologico Italiano, IRCCS, San Luca Hospital (Milan, Italy). All patients underwent an extensive 2DE and 3DE protocol adhering to current guidelines.[11,13] To evaluate RV morphology changes in each disease state, patient groups were compared with sex- and age-matched controls derived from the WASE healthy cohorts. Additionally, as follow-up data were available for the A-STR population, we explored associations between the target global shape metrics and adverse clinical outcomes, defined as the composite of heart failure hospitalization and all-cause death.

Consent

The study adhered to the principles outlined in the Declaration of Helsinki and received approval from the Regional and Institutional Committee on Science and Research Ethics of Semmelweis University and from the ethics committee of the Istituto Auxologico Italiano, Istituto di Ricovero e Cura a Carattere Scientifico. Obtaining informed consent was waived due to the retrospective nature of the study.

3D echocardiography

In the total cohort of 1624 subjects/patients, ECG-gated, wide-angle 3DE-derived RV datasets were recorded from an RV-focused view reconstructed preferably over 4–6 cardiac cycles. Subsequently, all 3DE-derived RV datasets were analysed offline using a commercial, vendor-independent software package (Image Arena; '4D RV-Function', TOMTEC, Unterschleissheim, Germany).

Briefly, after manual identification of landmarks edited on multiple short- and long-axis planes throughout the entire cardiac cycle, the software automatically generates dynamic RV endocardial contours. Firstly, end-diastole and end-systole were identified as the frames in which the RV volumes were the largest and the smallest, respectively. Then, the software automatically performed dynamic tracking of the endocardial border throughout the cardiac cycle, which could be manually corrected if necessary. Finally, the rendered 3DE-derived RV endocardial mesh model was exported for further analysis.

RV global shape analysis

Firstly, the 3DE-derived RV endocardial meshes were imported into the commercially available ReVISION (Right VentrIcular Separate wall motion quantification; Argus Cognitive, Lebanon, NH, USA) software package to quantify RV end-diastolic, end-systolic, and stroke volumes indexed to body surface area [end-diastolic volume indexed to body surface area (EDVi), end-systolic volume indexed to body surface area (ESVi), and stroke volume indexed to body surface area (SVi), respectively] along with RV ejection fraction (EF) as previously described in detail.[14]

Then, to quantify RV global shape, custom-developed software (Argus Cognitive) was used (*Figure 1*). Using the dimension-adjusted method, end-diastolic hemi-sphericity volume ratio (HSVR) and the hemi-conicity angle (HCA) metrics were calculated as follows. Firstly, each RV mesh underwent pre-processing steps, where the 3DE-derived RV endocardial mesh models were standardized by removing the septum and replacing it with an approximately flat surface achieved by introducing a new vertex into the mesh, calculated as the average position of the septum's edge vertices. Then, these edge vertices were connected to the newly added vertex, forming new faces that reconstructed and sealed the septal surface of the ventricle. Next, the respective longitudinal height of each 3DE-derived RV mesh was defined. To calculate HSVR, reference hemi-sphere shapes were created with their dimensions adjusted to each individual RV (the reference hemi-sphere's radius was half the height of the 3DE-derived RV mesh). Then, the reference hemi-sphere's volume and the RV mesh's volume were compared as follows:

$$HSVR = \frac{V_{RV\ mesh}}{V_{Hemi-sphere}}$$

HSVR refers to the hemi-sphericity volume ratio, and V refers to volume.

To calculate HCA, reference hemi-cone shapes were defined as those whose height equals each RV mesh's height and whose volume equals

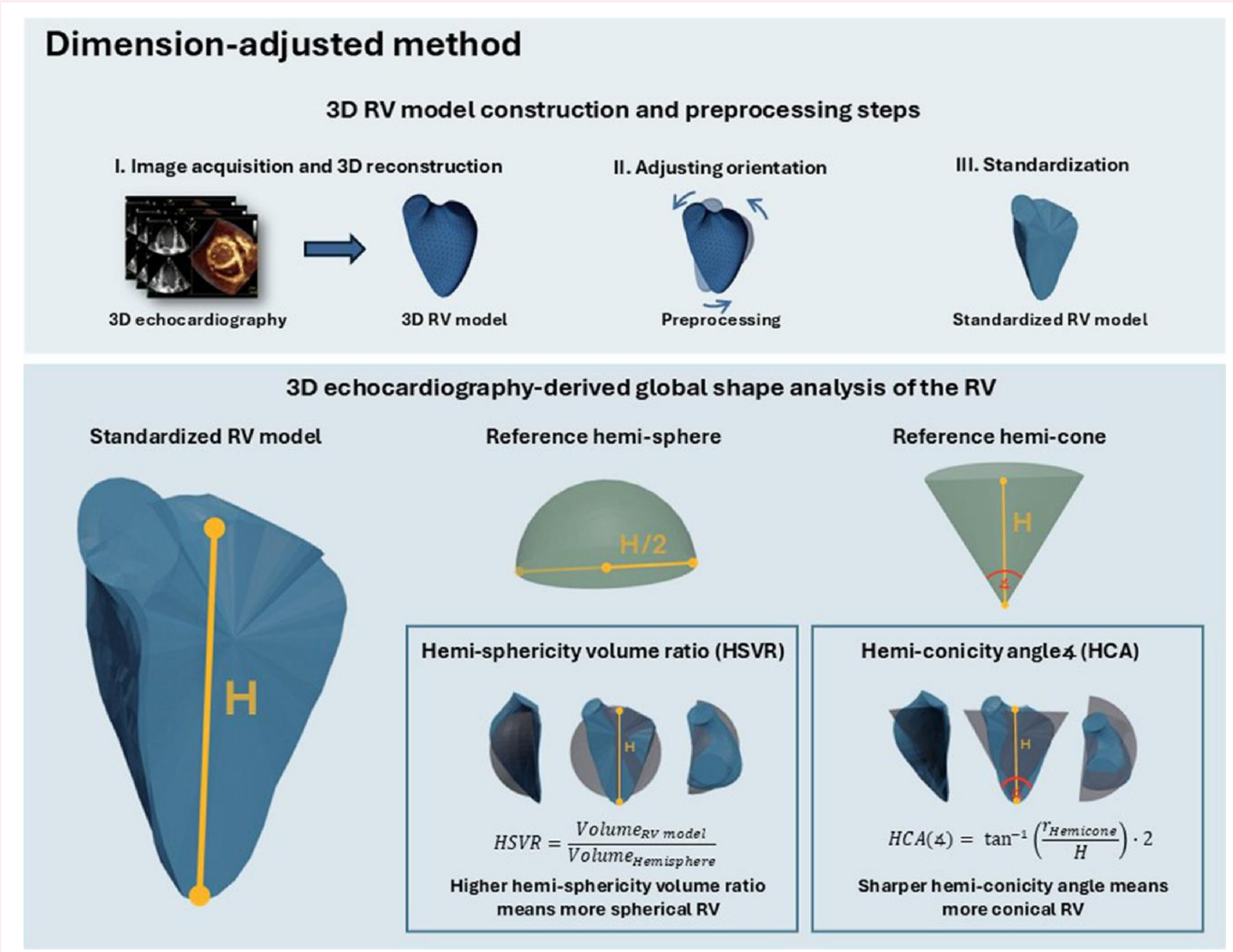


Figure 1 Workflow of the dimension-adjusted method for 3DE-derived global RV shape analysis.

each RV mesh's volume. Then, to calculate HCA, the angle at the apex of each dimension-adjusted reference hemi-cone was evaluated as follows:

$$HCA = \tan^{-1}\left(\frac{r_{Hemi-cone}}{H_{Hemi-cone}}\right) \cdot 2$$

HCA refers to the hemi-conicity angle, *r* refers to the radius, and *H* refers to the height of the hemi-cone.

When assessing the 3DE-derived RV global shape, although an HSVR value of 1 indicates perfect alignment with the volume of the fitted hemisphere, higher HSVR values reflect a more bulging, spherical shape, whereas a more acute (lower) HCA value indicates a more conical shape (*Figure 1*).

Statistical analysis

All statistical analyses were performed using dedicated software (StatSoft Statistica, v12, Tulsa, OK, USA and SPSS v22, IBM, Armonk, NY, USA). Continuous variables were presented as mean ± standard deviation, whereas all categorical variables were reported as frequencies and percentages. The normal distribution of the variables was verified using the Shapiro–Wilk normality test. In the WASE cohort, group differences were evaluated using unpaired two-tailed Student's *t*-tests or, in the case of multiple-group comparisons, one-way analysis of variance (ANOVA, with Fisher's least significant difference *post hoc* test). The disease groups and the corresponding age- and sex-matched WASE controls were also evaluated using unpaired two-tailed Students *t*-tests. To evaluate associations with the composite endpoint, we performed univariable and multivariable Cox regression analyses in the A-STR population, reporting hazard ratios (HRs) with 95% confidence intervals (CIs). In all cases, a *P*-value of <0.05 was considered statistically significant. To assess the reproducibility of HSVR and HCA metrics, intra- and interobserver variability were evaluated in 20 subjects by 2 experienced readers in a blinded fashion, using intraclass correlation coefficients (see Supplementary data online, *Table S1*).

Results

Normative changes of global RV shape in the WASE cohort

Basic anthropometric and demographic data of the WASE cohort with datasets available for 3DE-derived RV analysis were previously described (see Supplementary data online, *Table S1*).[9]

3DE-derived RV global shape analysis was feasible in all 1043 subjects. Sex-related differences in 3DE-derived RV morphology, function, and global shape are summarized in *Table 1*. As expected, 3DE-derived RV EDVi, ESVi, and SVi showed significantly larger values in males

Table 1 Sex-related differences in 3DE-derived RV morphological, functional, and global shape parameters in the WASE cohort

	Male ($n = 533$)	Female ($n = 510$)	*P*
3D morphology and function			
RV EDV index (mL/m^2)	82.2 ± 21.4	70.5 ± 16.9	<0.001
RV end-systolic volume index (mL/m^2)	37.6 ± 11.3	30.7 ± 8.8	<0.001
RV stroke volume index (mL/m^2)	44.6 ± 11.8	39.7 ± 9.9	<0.001
RV EF (%)	54.5 ± 5.4	56.5 ± 5.9	<0.001
3D global shape analysis			
HSVR	1.13 ± 0.32	1.17 ± 0.34	0.025
HCA (°)	72.9 ± 7.7	73.9 ± 7.9	0.028

compared with females, whereas RV EF was lower in males. Interestingly, females had significantly higher values of HSVR and HCA, both of which indicated a more spherical RV shape.

Table 2 shows the age-related differences in 3DE-derived RV morphology, function, and global shape in both sexes. Regarding RV volumes, EDVi, ESVi, and SVi showed similar values in all three age categories in both sexes. In males, RV EF also did not differ significantly among the age groups. However, in females, RV EF was lower in subjects aged over 65 years compared with the two younger groups. Concerning global shape analysis, the youngest male group exhibited significantly lower HSVR values, reflecting a less spherical RV shape compared with the two older age groups, whereas, in males, HCA values did not differ with age. In females, the RV shape showed a progressively more spherical shape in association with increasing age, as both HSVR and HCA values were significantly higher in each age group.

Race-related differences in the WASE cohort are summarized in *Table 3*. In both sexes, RV volumes differed significantly, with the black

Table 2 Age-related differences in morphological, functional, and global shape parameters of the right ventricle in the WASE cohort

	Male ($n = 533$)				Female ($n = 510$)			
	18–40 years ($n = 234$)	41–65 years ($n = 194$)	>65 years ($n = 105$)	ANOVA *P*	18–40 years ($n = 199$)	41–65 years ($n = 197$)	>65 years ($n = 114$)	ANOVA *P*
3D morphology and function								
RV EDV index (mL/m^2)	83.1 ± 19.4	80.6 ± 21.9	82.3 ± 24.3	0.399	71.1 ± 17.03	70.02 ± 16.5	70.04 ± 17.2	0.782
RV end-systolic volume index (mL/m^2)	37.9 ± 10.5	36.7 ± 11.6	38.4 ± 12.4	0.381	30.7 ± 8.9	30.2 ± 8.7	31.5 ± 8.7	0.457
RV stroke volume index (mL/m^2)	45.4 ± 10.9	43.8 ± 11.9	43.8 ± 13.1	0.293	40.3 ± 9.9	39.8 ± 9.5	38.5 ± 10.3	0.309
RV EF (%)	54.7 ± 5.5	54.7 ± 5.4	53.5 ± 5.1	0.106	56.9 ± 5.9§	57.1 ± 5.9§	54.9 ± 6.1$^{*\#}$	0.007
3D global shape analysis								
HSVR	1.08 ± 0.27$^{\#§}$	1.17 ± 0.37*	1.16 ± 0.32*	0.016	1.10 ± 0.33$^{\#§}$	1.18 ± 0.30*§	1.30 ± 0.4$^{*\#}$	<0.001
HCA (°)	71.9 ± 6.9	73.6 ± 8.4	73.6 ± 7.8	0.056	72.1 ± 7.8$^{\#§}$	74.3 ± 7.1*§	76.6 ± 8.4$^{*\#}$	<0.001

*$P < 0.05$ vs. 18- to 40-year age group, #$P < 0.05$ vs. 41- to 65-year age group, §$P < 0.05$ vs. >65 year age group.

Table 3 Race-related differences in morphological, functional, and global shape parameters of the right ventricle in the WASE cohort

	Male ($n = 510$)				Female ($n = 495$)			
	White ($n = 235$)	Black ($n = 69$)	Asian ($n = 206$)	ANOVA *P*	White ($n = 253$)	Black ($n = 73$)	Asian ($n = 169$)	ANOVA *P*
3D morphology and function								
RV EDV index (mL/m^2)	85.7 ± 21.6$^{\#§}$	95.4 ± 23.6*§	74.3 ± 16.7$^{*\#}$	<0.001	70.8 ± 16.7$^{\#§}$	81.2 ± 16.7*§	65.6 ± 15.4$^{*\#}$	<0.001
RV end-systolic volume index (mL/m^2)	38.6 ± 12.07$^{\#§}$	45.4 ± 11.8*§	34.08 ± 8.8$^{*\#}$	<0.001	30.4 ± 8.7$^{\#§}$	36.8 ± 9.3*§	28.7 ± 7.7$^{*\#}$	<0.001
RV stroke volume index (mL/m^2)	47.1 ± 11.5§	50.08 ± 13.3§	40.3 ± 9.5$^{*\#}$	<0.001	40.4 ± 9.8$^{\#§}$	44.3 ± 9.1*§	36.9 ± 9.6$^{*\#}$	<0.001
RV EF (%)	55.4 ± 5.9$^{\#§}$	52.4 ± 4.5*§	54.2 ± 4.9$^{*\#}$	<0.001	57.2 ± 6.1$^{\#}$	54.9 ± 5.1*	56.2 ± 6.1	0.009
3D global shape analysis								
HSVR	1.21 ± 0.32$^{\#§}$	1.05 ± 0.33*	1.05 ± 0.28*	<0.001	1.22 ± 0.33$^{\#§}$	1.13 ± 0.32*	1.12 ± 0.36*	0.005
HCA (°)	74.9 ± 7.3$^{\#§}$	70.7 ± 8.4*	70.9 ± 7.3*	<0.001	75.2 ± 7.2$^{\#§}$	72.8 ± 7.9*	72.5 ± 8.7*	0.001

*$P < 0.05$ vs. white race, #$P < 0.05$ vs. black race, §$P < 0.05$ vs. Asian race.

race having the highest values of RV EDVi, ESVi, and SVi, followed by the white race, whereas Asian women and men had the smallest RV volumes. In terms of function, black males had significantly lower RV EF compared with the other races, whereas white males exhibited the highest values of RV EF. Similarly, in females, the black race was associated with lower values of RV EF than the white race. Global shape analysis revealed that HSVR and HCA values were significantly higher in both white males and females, indicating a more spherical RV shape, whereas the RV shape of black and Asian subjects appeared to be similar.

Assessment of global RV shape across different disease states

Clinical implications were also assessed by comparing various cardiac diseases with age- and sex-matched controls derived from the WASE cohort (*Table 4*).

Patients with HFrEF had similar RV EDVi compared with the matched controls. However, RV ESVi was significantly larger, while RV SVi and RV EF were lower in HFrEF patients compared with controls. In terms of RV shape, HFrEF patients exhibited a more spherical RV remodelling, represented by the higher values of both HSVR and HCA. In patients with severe primary MR, only the values of RV SVi were significantly lower, whereas the other RV volumes did not differ from controls. RV EF values were slightly lower in MR patients. Despite similar RV volumes, in patients with severe primary MR and WASE controls, HSVR and HCA values were significantly higher, reflecting a pronounced spherical RV remodelling in MR patients. In severe aortic valve stenosis, RV EDVi, RV SVi, and RV EF were all smaller compared with healthy subjects, while HSVR and HCA did not differ, implying a similar global RV shape between AS patients and WASE controls. Similarly, HTX patients exhibited markedly lower volumes along with RV EF. However, the shape-related metrics did not differ between HTX patients and controls. Compared with matched controls, A-STR patients demonstrated comparable RV EDVi and SVi, but lower ESVi with a correspondingly higher RV EF. With respect to shape parameters, both HSVR and HCA were significantly elevated, indicating spherical remodelling in A-STR patients. In patients with ToF, all RV volumes were significantly larger than those of controls, while RVEF was lower in ToF patients. Interestingly, both HSVR and HCA values were markedly lower in ToF patients, indicating a more conical RV shape. In PH patients, although RV EDVi values were comparable with controls, RV ESVi was significantly higher, whereas RV SVi and RV EF were decreased in PH patients. Regarding RV global shape, PH patients exhibited a pronounced conical RV shape, as reflected by the lower values of both HSVR and HCA.

Prognostic implications of RV global shape assessment

The A-STR cohort included 52 (31%) patients with mild, 59 (36%) with moderate, and 55 (33%) with severe tricuspid regurgitation. Over a median follow-up of 1.4 years (interquartile range, 0.9–1.9 years), 35 patients (21%) met the composite endpoint. In univariable Cox regression analyses, both HSVR [HR 0.339 (95% CI 0.146–0.783), $P = 0.011$] and HCA [HR 0.955 (95% CI 0.921–0.991), $P = 0.014$] were significant predictors of the composite endpoint, indicating that a more conical remodelling was associated with worse clinical outcomes. In multivariable models including age and tricuspid regurgitant volume as covariates, both HSVR and HCA remained independent predictors of the composite endpoint, whereas the other covariates were not (*Table 5*).

Discussion

To the best of our knowledge, this study is the first to provide a comprehensive assessment of global RV shape using unique 3DE-derived metrics in a large cohort of healthy subjects across a wide range of ages and ethnicities and patients with different cardiac disease states (Graphical Abstract). By quantifying HSVR and HCA metrics, characteristic demographic differences were identified; the female sex was associated with a more spherical RV shape, similar to what occurs with ageing, as subjects in the oldest groups of both sexes exhibited more spherical remodelling. Interestingly, black females and white males had more spherical RV geometry compared with other race groups in their respective sex categories. When assessing different pathological conditions, in predominantly left-sided cardiac diseases, the RV exhibited more pronounced spherical remodelling, specifically in the HFrEF and severe primary MR subgroups, compared with controls, despite having similar RV EDVi values. Conversely, in both ToF and PH patient subgroups, a more conical RV shape was observed compared with matched controls (*Figure 2*). Notably, when assessing subgroups from both physiological and pathological spectra, differences in RV shape were still apparent even in the absence of significant differences in RV EDVi, underscoring the potential added value of shape analysis in a more targeted characterization of RV morphology and function. Importantly, both HSVR and HCA emerged as independent predictors of adverse outcomes in the A-STR population. These findings align with recent studies recognizing that ventricular shape may bear further clinically relevant physiologic information that is independent of size and function, supporting its role in detecting subtler structural alterations.[1,2,15]

Physiologic changes of RV shape

In recent years, research focusing on the echocardiographic assessment of ventricular morphology has gained momentum due to the lack of conventional markers that could portray ventricular shape, particularly in the RV, due to its complex 3D anatomy.[16] In the LV, morphological changes can be defined using pre-determined reference shapes, such as the cone and sphere.[17] Additionally, LV shape indices derived from 2DE, such as the ratio of short- to long-axis cavity dimensions, have been utilized to demonstrate that a more spherical remodelling is linked to a poorer prognosis,[3] and that LV shape provides additional physiological insights beyond conventional metrics, such as EF.[2,18] The advent of 3DE has further enabled shape assessment, improving our understanding of the pathophysiological mechanisms underlying LV remodelling in different cardiac disease states and offering additional valuable prognostic information.[2,19–21] In contrast, research on RV shape remains limited, particularly in relation to physiological factors such as ageing, sex, and race, as well as pathological conditions involving changes in haemodynamic load on the RV. This may be due to the difficulty in assessing RV geometry in its complexity using 2DE, given the unique anatomical structure of this chamber.[3,4] Differently from the LV, the shape of the RV is harder to define; when observed from the coronal view, it is more triangular, whereas it has a crescent-like shape in axial cross-section.[22] Due to its peculiar anatomical architecture with a longitudinally arranged subendocardial and circumferentially oriented superficial layer partially intertwined with LV myofibers, responsible for biventricular interdependence,[23] portraying RV structure and function with routine echocardiographic metrics is challenging. Indeed, subtle changes in myofiber meshwork and orientation, wall stress, and ventricular compliance arising from physiological differences such as ageing, sex, or race could potentially influence RV shape. These changes may not be reflected by conventional 3DE-derived metrics of morphology and function. Although prior 3DE studies within the framework of the WASE investigations provided comprehensive results on normative changes in RV size, function, and contraction patterns,[9,24] characterizing the global RV shape is still essential for understanding 'the normal RV geometry' first.

When assessing normative changes of 3DE-derived RV size and function in relation to sex, our results were consistent with previous

Table 4 Morphological, functional, and global shape parameters of the RV in various cardiac disease states compared with matched WASE-derived controls

	HFrEF		
	HFrEF (*n* = 101)	**WASE (*n* = 101)**	***P***
Age (years)	67.8 ± 11.3	66.3 ± 10.4	0.305
Male, *n* (%)	81 (80.1)	81 (80.1)	0.859
3D morphology and function			
RV EDV index (mL/m^2)	83.3 ± 30.8	78.3 ± 27.0	0.420
RV end-systolic volume index (mL/m^2)	51.9 ± 25.8	34.8 ± 13.6	<0.001
RV stroke volume index (mL/m^2)	31.4 ± 8.5	43.4 ± 14.6	<0.001
RV EF (%)	40.1 ± 10.0	55.2 ± 6.5	<0.001
3D global shape analysis			
HSVR	1.44 ± 0.47	1.23 ± 0.35	0.001
HCA (°)	79.45 ± 8.40	75.25 ± 7.91	<0.001
	Severe primary MR		
	MR (*n* = 68)	**WASE (*n* = 68)**	***P***
Age (years)	62.1 ± 11.1	62.0 ± 11.0	0.987
Male, *n* (%)	46 (67.6)	46 (67.6)	0.854
3D morphology and function			
RV EDV index (mL/m^2)	72.2 ± 17.6	78.7 ± 25.4	0.157
RV end-systolic volume index (mL/m^2)	34.9 ± 10.3	34.9 ± 13.8	0.840
RV stroke volume index (mL/m^2)	37.3 ± 9.7	43.8 ± 12.8	0.004
RV EF (%)	51.7 ± 6.3	56.1 ± 5.8	<0.001
3D global shape analysis			
HSVR	1.58 ± 0.55	1.22 ± 0.33	<0.001
HCA (°)	82.02 ± 8.48	76.07 ± 7.48	<0.001
	Severe AS		
	AS (*n* = 86)	**WASE (*n* = 86)**	***P***
Age (years)	78.3 ± 6.3	74.6 ± 4.9	<0.001
Male, *n* (%)	45 (52.3)	45 (52.3)	0.878
3D morphology and function			
RV EDV index (mL/m^2)	62.1 ± 16.01	74.5 ± 21.9	<0.001
RV end-systolic volume index (mL/m^2)	32.04 ± 11.6	34.4 ± 11.01	0.179
RV stroke volume index (mL/m^2)	30.08 ± 7.4	40.07 ± 12.4	<0.001
RV EF (%)	48.8 ± 9.08	53.9 ± 6.07	<0.001
3D global shape analysis			
HSVR	1.35 ± 0.332	1.31 ± 0.39	0.401
HCA (°)	78.06 ± 6.68	76.94 ± 8.55	0.262
	HTX		
	HTX (*n* = 94)	**WASE (*n* = 94)**	***P***
Age (years)	51.2 ± 11.4	51.3 ± 11.4	0.969
Male, *n* (%)	71 (75.5)	71 (75.5)	0.865
3D morphology and function			
RV EDV index (mL/m^2)	61.2 ± 16.4	78.9 ± 21.6	<0.001
RV end-systolic volume index (mL/m^2)	29.6 ± 9.3	34.2 ± 12.3	0.002

Continued

Table 4 Continued

	HTX		
	HTX ($n = 94$)	**WASE ($n = 94$)**	**P**
RV stroke volume index (mL/m^2)	31.9 ± 8.4	44.7 ± 11.07	<0.001
RV EF (%)	52.1 ± 5.3	57.3 ± 6.3	<0.001
3D global shape analysis			
HSVR	1.17 ± 0.49	1.23 ± 0.33	0.374
HCA (°)	73.04 ± 9.96	75.21 ± 7.79	0.120
	A-STR		
	A-STR ($n = 166$)	**WASE ($n = 166$)**	**P**
Age (years)	79.4 ± 7.8	71.5 ± 5.1	<0.001
Male, *n* (%)	47 (28.3)	47 (28.3)	1.000
3D morphology and function			
RV EDV index (mL/m^2)	72.4 ± 15.7	72.6 ± 20.4	0.923
RV end-systolic volume index (mL/m^2)	30.6 ± 10.1	32.9 ± 10.3	0.038
RV stroke volume index (mL/m^2)	41.7 ± 9.3	39.6 ± 11.6	0.074
RV EF (%)	58.2 ± 8.0	54.7 ± 5.8	<0.001
3D global shape analysis			
HSVR	1.43 ± 0.45	1.27 ± 0.36	<0.001
HCA (°)	79.23 ± 9.09	75.99 ± 8.03	0.001
	TOF		
	ToF ($n = 28$)	**WASE ($n = 28$)**	**P**
Age (years)	21.8 ± 7.3	23.7 ± 6.4	0.318
Male, *n* (%)	16 (57.1)	16 (57.1)	0.787
3D morphology and function			
RV EDV index (mL/m^2)	130.2 ± 33.07	86.5 ± 16.6	<0.001
RV end-systolic volume index (mL/m^2)	72.07 ± 19.6	38.2 ± 11.4	<0.001
RV stroke volume index (mL/m^2)	58.1 ± 14.9	48.3 ± 8.5	0.003
RV EF (%)	44.6 ± 4.2	56.3 ± 7.09	<0.001
3D global shape analysis			
HSVR	1.01 ± 0.19	1.21 ± 0.40	0.024
HCA (°)	70.52 ± 5.04	74.66 ± 8.24	0.027
	PH		
	PH ($n = 38$)	**WASE ($n = 38$)**	**P**
Age (years)	69.4 ± 9.3	55.9 ± 7.1	<0.001
Male, *n* (%)	13 (34.2)	13 (34.2)	0.808
3D morphology and function			
RV EDV index (mL/m^2)	73.0 ± 22.8	71.06 ± 25.3	0.728
RV end-systolic volume index (mL/m^2)	44.4 ± 18.6	31.3 ± 12.6	<0.001
RV stroke volume index (mL/m^2)	28.5 ± 7.1	39.6 ± 14.2	<0.001
RV EF (%)	40.9 ± 9.3	55.9 ± 7.1	<0.001
3D global shape analysis			
HSVR	0.98 ± 0.31	1.36 ± 0.39	<0.001
HCA (°)	68.60 ± 9.64	78.01 ± 7.77	<0.001

large-scale studies,[24,25] as males exhibited larger volumes and slightly lower EF. Interestingly, although females had smaller RV volumes, female sex was associated with a more spherical RV, as reflected by the higher values of HSVR and HCA. Generally, the female sex has been markedly underrepresented in research studies, even in contemporary literature, hindering the understanding of the exact mechanisms underlying these sex-related differences. It is important to emphasize that the female heart is not simply a scaled-down version of the male heart, but that, in addition, also has a different microstructural architecture. As suggested by recent publications, females have less elongated ventricles with a distinct roundness of the RV, along with a reduced anterior–posterior RV width.[26]

As a physiological process, healthy ageing also induces significant changes in terms of RV shape. Ageing is associated with a progressive shift towards spherical RV remodelling without any change in RV volumes, suggesting subtle morphological alterations that volumetric measures cannot capture. This shift may reflect the increase in pulmonary arterial stiffness, along with myocardial fibrosis or impaired ventriculo-arterial coupling observed with ageing.[23,27] Although age- and sex-related differences in RV shape have not yet been investigated thoroughly, regional RV shape analysis by Addetia and colleagues has reported the absence of sex differences but distinct age-associated alterations.[5] Specifically, they found that in older healthy subjects, analysing regional curvature indices revealed a flatter RV-free wall and outflow tract, suggesting RV stiffening with

Table 5 **Association of RV global shape metrics with the composite endpoint of all-cause mortality and heart failure hospitalization in patients with a-STR**

Multivariable Cox regression analysis	Model 1		Model 2	
	HR [95% CI]	***P***	**HR [95% CI]**	***P***
Age (years)	1.033 [0.981–1.087]	0.220	1.032 [0.981–1.086]	0.226
Regurgitant volume (mL)	1.024 [0.998–1.052]	0.072	1.024 [0.997–1.051]	0.080
HSVR	0.404 [0.183–0.893]	0.025	—	
HCA (°)	—		0.963 [0.929–0.998]	0.037

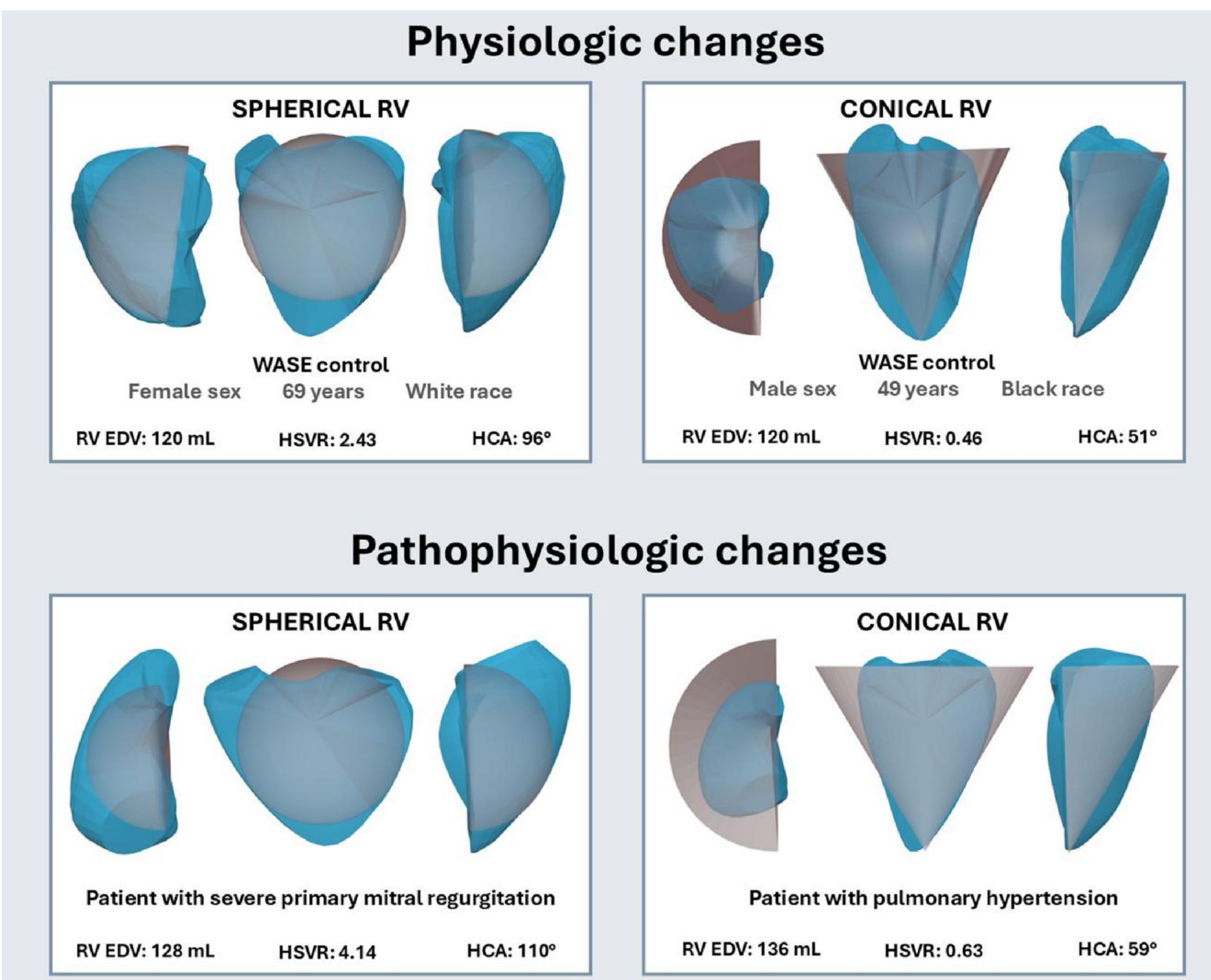


Figure 2 Representative cases of physiologic and pathophysiologic variations in global RV shape.

normal ageing.[5] These results further confirm the added value of shape assessment.

The impact of race on RV size and function in a large cohort of healthy individuals assessed by 3DE was first described in the WASE study by Addetia and colleagues, demonstrating that Black individuals exhibit larger RV volumes and slightly lower RV EF.[24] Interestingly, the CMR-based, large-scale Multi-Ethnic Study of Atherosclerosis study preceding WASE showed conflicting results with black males having smaller RV end-diastolic volume (EDV).[28] Although not fully understood, these inconsistencies might be partially explained by inter-modality disagreements and more so by the relative underrepresentation of the black race in the WASE cohort. Despite vastly different RV volumetrics, the RV shape of black males and females was rather similar to the RV shape seen in the Asian race, both exhibiting markedly less spherical geometry compared with the white race, which showed a more pronounced spherical shape. When interpreting these physiological alterations of RV shape, it is important to emphasize that in most cases, the observed distinct geometrical differences occurred seemingly independently of RV volumes, highlighting the potential sensitivity of global shape metrics in capturing even subtle structural changes of the RV.

Pathophysiologic changes of RV shape

In recent years, prior research has emerged describing regional differences in RV shape in selected patient subgroups (such as PH and ToF)[3,4] and in a smaller cohort of healthy subjects.[5] Still, our study is the first to comprehensively characterize the global RV shape variations in relation to physiological determinants, establishing normative changes that provide the necessary context for interpreting the effects of pathological stimuli. Furthermore, the assessment of RV morphological remodelling across a broader spectrum of cardiac diseases with different haemodynamic and pathophysiological profiles remains lacking. To mitigate this, left- and right-sided cardiac diseases were also examined under both volume- and pressure-overload conditions, likely imposing a combined haemodynamic burden on the RV.

Effect of left-sided cardiac diseases on RV shape

In patients with HFrEF and severe primary MR, a more pronounced RV spherical remodelling was observed, with both having similar RV EDVi values compared with controls. While both conditions dominantly affect the LV with left-sided congestion, still, through backward failure and interventricular dependence, the RV and its shape could be affected earlier than volumetric differences would manifest. In parallel, when assessing the shape of the left counterpart, it has been previously described that the LV undergoes a similar spherical remodelling, which is associated with a poor prognosis.[29] Highlighting the added value of shape analysis, Maffessanti and colleagues demonstrated earlier changes in global LV sphericity in MR patients that preceded alterations in functional metrics. Notably, 6 months after mitral valve repair, LV shape had normalized, despite a transient reduction in systolic function, which subsequently recovered,[2] highlighting shape as an early and potentially reversible marker of remodelling.

Capturing a different haemodynamic condition, severe AS poses a substantial pressure overload, mainly to the LV, while the RV often remains less affected until the later stages of the disease course. In fact, recent research highlighted that the main predictor of RV dysfunction in AS was LV dysfunction, possibly arising from ventriculo-ventricular interactions.[30] In our cohort, severe AS patients had slightly lower RV volumes and mildly reduced yet still maintained RV EF. However, the RV shape was similar to that of the controls, suggesting a potentially limited structural involvement of the RV.

In terms of unaltered RV shape, similar findings were observed in post-HTX patients, for whom, despite lower but still preserved RV volumes and EF, no differences in shape were noted. Possibly, in a stable post-HTX patient, having a relatively 'healthy' donor heart that maintained normal RV geometry could account for this finding. Still, the RV's mechanical adaptive mechanisms cannot be forgotten, as distinct contraction patterns develop post-HTX to maintain normal systolic function with reduced longitudinal function compensated by an increase in radial contraction.[31,32]

A-STR patients represent a newly recognized form of secondary tricuspid regurgitation, predominantly characterized by dilation of the right atrium and tricuspid annulus, with a preserved LV and RV systolic function.[13] This subgroup is clinically important, as both prognosis and therapeutic decision-making diverge in the era of transcatheter tricuspid valve interventions.[33] In contrast to 2DE data,[6,13] we found that this population demonstrates predominantly spherical and not conical remodelling when assessed by 3DE compared with healthy controls. This apparent contradiction arises only at first glance. When assessed in a 2D apical four-chamber view, the RV does appear more triangular ('conical') because of the dominant annular enlargement, particularly when compared with patients with ventricular secondary tricuspid regurgitation. Our 3DE approach captures the entire 3D structure, including the anterior portion of the RV. Interestingly, this increased sphericity was not associated with worse outcomes; instead, a more conical remodelling pattern correlated with the composite endpoint. Further prospective studies are warranted to delineate the distinct types and natural history of STR and to identify prognostic determinants.

Effect of right-sided cardiac diseases on RV shape

Conversely, in PH and repaired TOF, both representing conditions with primarily right-sided heart involvement, a remarkably different RV geometrical remodelling was observed. In both patients with PH and TOF, the RV exhibited markedly conical RV remodelling despite having different RV volumetric measures. In ToF, as expected due to volume overload, the RV volumes were significantly larger, with a mildly reduced RV EF compared with controls, in contrast to findings in the PH population. Although the remodelling processes are driven by different haemodynamic stimuli (noted that realistically, both volume and pressure overload are present but to a different extent) and underlying mechanisms, both pathologies show a conical shape compared with normal controls. Geometrical similarities between ToF and PH were also described by Bidviene and colleagues, as regional curvature analysis revealed that both patient subgroups had a flatter free wall and inflow tract, along with a more convex septum.[4]

Nevertheless, understanding the RV's complex remodelling processes in context with different pathophysiological conditions warrants further studies. Longitudinal assessment of different disease courses and corresponding alterations in RV structure and shape may help better characterize the RV.

Limitations

Differences in image acquisition at the different institutions might have occurred. However, to minimize this, all echocardiography examinations were performed using a standardized protocol established by current ASE/EACVI guidelines[11] and by research groups specialized in 3DE imaging. Although the multi-centric nature of our study provides strength to the results, it could also have been affected by interobserver variability. However, the utilized post-processing tools are semi-automatic, vendor-independent, thoroughly validated software solutions that have likely minimized these issues effectively, further confirmed by good intra- and interobserver variabilities, highlighting the reliability of the key measurements. Furthermore, the quantitation of the 3DE-derived global RV shape metrics is performed entirely using custom-developed, automated software, thus less affected by interobserver changes. Importantly, these advances also carry the potential for integration with AI-based analysis to fully automate RV shape recognition and further reduce operator dependence.

Conclusions

The proposed method of 3DE-derived global shape analysis allows a unique assessment of the complex RV geometry. The quantification of RV HSVR and HCA revealed characteristic sex-, age-, and race-related physiological differences in a large cohort of healthy individuals. Furthermore, global shape analysis offered potentially valuable insights into RV remodelling in response to different disease states, as in predominantly left-sided cardiac diseases, the RV exhibited predominantly spherical remodelling, whereas in right-heart conditions, a more conical remodelling was observed. Importantly, our novel metrics not only enable the detection of pathological changes but are also associated with adverse clinical outcomes, thereby potentially informing patient prognostication. Nevertheless, large-scale prospective studies are warranted to establish longitudinal changes across the disease course and confirm their prognostic value.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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Data availability

The data underlying this study will not be publicly available.

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