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ORIGINAL PAPER

Age-changes in right ventricular function–pulmonary circulation coupling: from pediatric to adult stage in 1899 healthy subjects. The RIGHT Heart International NETwork (RIGHT-NET)

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Abstract

The present study analyzes age-specific changes in RV function and RV–PA coupling in a large cohort of apparently healthy subjects with a wide age-range, to identify reference values and to study the influence of clinical and echocardiographic cofactors. 1899 Consecutive healthy subjects underwent a standardized transthoracic echocardiographic examination. Tricuspid annular plane systolic excursion (TAPSE) and systolic pulmonary artery pressure (SPAP) were measured. Ventriculo-arterial coupling was then inferred from the TAPSE/SPAP ratio. A quantile regression analysis was used to estimate quantiles 0.05, 0.10, 0.50 (median), 0.90, and 0.95 of TAPSE, SPAP and TAPSE/SPAP. The association between age and each of these values was determined. The mean age of the group was 45.2 ± 18.5 years (range 1 to 102 years), 971 were males. SPAP increased with age, whereas TAPSE and TAPSE/SPAP ratio decreased. Upon multivariate modeling, the most significant positive associations for TAPSE were body surface area (BSA) driven by the pediatric group, stroke volume (SV), E/A and negatively heart rate and E/e′ ratio. SPAP was positively associated with increasing age, SV, E/A, E/e′ and negatively with BSA. TAPSE/SPAP ratio was negatively associated with age, female sex, and E/e′ and positively with BSA. A preserved relationship between TAPSE and SPAP was found across the different age groups. TAPSE, SPAP and TAPSE/SPAP demonstrate important trends and associations with advancing age, impaired diastolic function, affected by female sex and BSA However the relationship between TAPSE and SPAP is relatively well preserved across the age spectrum.

Keywords Echocardiography · Normal subjects · Tricuspid annular plane systolic excursion · Pulmonary artery systolic pressure · Right ventricular–arterial coupling

Abbreviations

BMI	Body mass index
BSA	Body surface area
HR	Heart rate
LV	Left ventricle
MAP	Mean arterial pressure
PA	Pulmonary artery
RAP	Right atrial pressure
RV	Right ventricular
SPAP	Systolic pulmonary artery pressure
SV	Stroke volume
TTE	Transthoracic echocardiographic
TAPSE	Tricuspid annular plane systolic excursion
TRV	Tricuspid regurgitation velocity

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Introduction

Age-related changes in the left ventricle (LV) and their significant effect on systemic vascular function have been extensively described in literature. In a healthy ageing population, the LV and the arterial vascular tree stiffen proportionally, giving rise to a conserved relationship between the two [1, 2]. Much less is known about normal age-related changes in right ventricular (RV) function

and its coupling to the PA vascular bed. Population-based studies have clearly identified the predictive value of RV function and PA hypertension in heart failure, HF [3–9]. Across the entire lifespan, in a disease-free state, it is reasonable to assume that RV–PA coupling functions at optimal or near-optimal levels. However, pathophysiologic changes occur during the ageing process that emerge as a manifestation of the senescent phenotype, such as a progressive elevation in PA pressures [10, 11], and resistance and a relative reduction in RV function [12, 13]. Currently the reference standard to estimate the normality of RV contractility against its PA afterload is achieved by transcatheter pressure–volume analysis, an invasive procedure. Recently however, 2D RV speckle tracking and 3D echo deformation analysis [14] have been developed to better quantify RV function. However, their use is often limited to experts working in large centers, in part due to lack of readily available normal values. While two-dimensional speckle-tracking strain analysis can be used, tricuspid annular plane systolic excursion (TAPSE) has been shown to be reproducible, validated, and commonly used in clinical practice [15]. TAPSE is also predictive of clinical outcomes across a variety of disease states [16, 17].

Given heart structure and function are inter-related and are affected by age, BSA and gender, the aims of the present study were (a) evaluate age-specific changes for RV function and RV–PA coupling, (b) to study the influence of clinical (age, sex and BSA), and echocardiographic cofactors [E/e′, E/A, stroke volume (SV), mean arterial pressure, heart rate] in a large cohort of apparently healthy subjects with a wide age-range and (c) establish normal reference values using quantile regression analysis [quantiles 0.05, 0.10, 0.50 (median), 0.90, and 0.95].

Methods

Study population

The study enrolled 2040 subjects from 10 centers participating to the RIGHT-NET Study, without overt cardiovascular (CV) disease or risk factors [18]. Healthy subjects were selected from volunteers (mainly hospital staff, relatives, friends, blood donors) and individuals referred to our hospital for work ability assessment. After the exclusion of subjects with inadequate echocardiographic image quality, the final study population of 1899 healthy subjects were considered (Fig. 1). The RIGHT-NET Study methodology has been previously described [19–21]. A standardized transthoracic echocardiographic (TTE) examination with continuous ECG recording was performed in accordance with current American Society of Echocardiography/European Association of Cardiovascular Imaging guidelines [19, 22]. The LV ejection fraction (EF) was calculated by modified Simpson's equation in the apical 4 and 2 chamber views. Valvular regurgitation was quantified from color Doppler imaging by standard criteria and categorized as absent, minimal (within normal limits), mild, moderate or severe. Stroke volume (SV) was derived from $SV = (LVOT_{area} \times LVOT\ VTI)$ where LVOT is left ventricular outflow tract. LVOT was measured in mid-systole at the aortic annulus level. Spectral Doppler LVOT VTI was obtained by the pulse wave Doppler and then SV was corrected by the BSA. Doppler-derived LV diastolic inflow was recorded in the apical 4-chamber view by placing the sample volume at the tip of the mitral valve leaflets. The early (e′) diastolic velocities were measured by tissue Doppler imaging (TDI) at the septal and lateral corner of the mitral annulus and the mean between the two values was calculated. All examinations were reviewed and analyzed

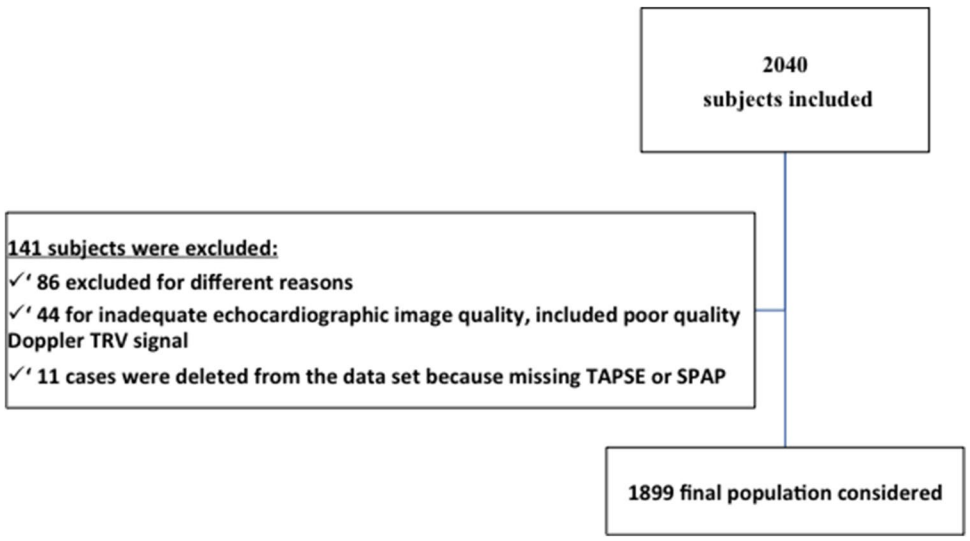

Fig. 1 Summary patient selection

offline by certified operator experts in TTE at an image processing workstation. Each parameter was assessed in three to five consecutive cardiac cycles, and mean values were used for data recording and analysis. Quality control assessments were performed at the Echo Core lab by three certified cardiologists experienced in pulmonary hypertension to reduce variability, and both maintain and/or improve the quality of data collection [19, 21]. Blood pressure, height and weight were measured before the echocardiographic examination [10].

Pulmonary artery systolic pressure and tricuspid annular plane excursion

Peak tricuspid regurgitation velocity (TRV) was measured from multiple views. An agitated saline solution was used in cases of poor Doppler signal of the TRV, such as in the presence of incomplete spectral wave envelope and/or artifacts as previously reported [10]. SPAP estimation was based on the simplified Bernoulli equation applied to TRV, with the addition of estimated right atrial pressure (RAP), based on IVC size and collapse [23]. TAPSE was measured from the four chamber views by placing an M-mode cursor through the tricuspid annulus, measuring the excursion distance between end-diastole and end-systole (in mm) and with optimal image orientation and alignment to avoid underestimation (Fig. 2). The TAPSE/SPAP ratio was estimated, and both TAPSE and TAPSE/SPAP were indexed by body surface area (BSA) in order to reduce the effect of anthropometric differences. This ratio defines the cardiac length–force relationship, and gives insight into the contractile state of the RV and its interaction with the pulmonary vascular bed [19, 24, 25]. Tissue Doppler velocities of the tricuspid annulus were recorded from the apical four-chamber view, by placing the sample volume at the level of lateral corner of the tricuspid annulus, adjusting the spectral pulsed Doppler signal filters within Nyquist limit of 15–20 cm/s, and using the minimal sufficient gain setting to avoid signal blurring. All measurements were performed according to the recommendations for echocardiographic assessment of the right heart published by the American Society of Echocardiography (ASE)/European Association of Cardiovascular Imaging (EACVI) [22, 26]. Furthermore a quality control process was designed and implemented among RIGHT-NET laboratories and operators as previously reported [21].

Statistical analysis

Data are expressed as mean ± SD or/and percent for frequency data. The cohort was divided by age into nine groups. Children were defined as 1–10 years old, adolescents as 11 to 17 years old, adult subjects as 18 to 74 years

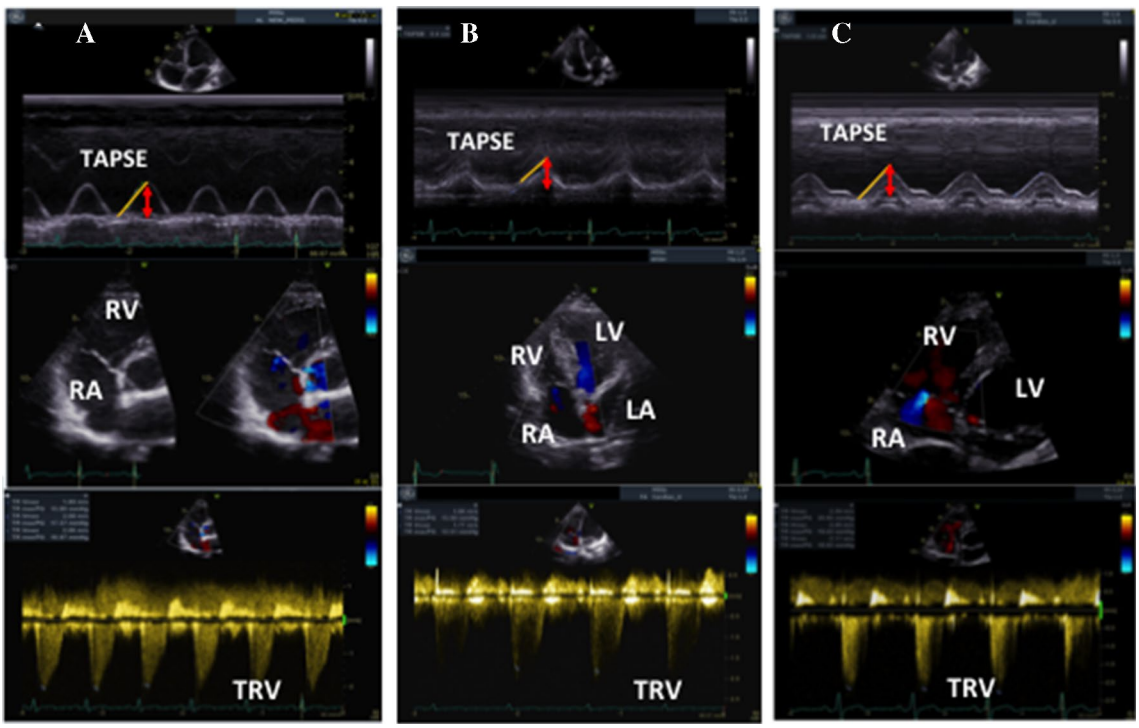

Fig. 2 Apical 4-chamber view and M-mode cursor placement at the tricuspid lateral annulus (top). Color signal of TR (middle). Maximal velocity by continuous wave (CW) Doppler signal of TRV from 4-chamber or short axis (bottom). *TAPSE* tricuspid annular plane systolic excursion, *RV* right ventricle, *RA* right atrium, *LV* left ventricle, *LA* left atrium, *TRV* tricuspid regurgitation velocity

old and elderly subjects as greater than 74 years of age. As previously reported, the groups had 10 year increments in age [27].

The difference within each group variable was tested by ANOVA and the difference between gender–age group for each variable was evaluated by unpaired T-Test. The Pearson partial correlation test was used to assess the relationship between clinically relevant variables such as TRV, TAPSE, SPAP, TAPSE/SPAP and age, body mass index (BMI), BSA (body surface area), SV, E/A, E/e′, mean arterial pressure (MAP), heart rate (HR), and sex. These variables were then incorporated into the multivariate model ($p < 0.05$). Multiple regression analysis was performed first on the whole group, and then subjects were analyzed in three separate age groups in order to test the weight of these variables in different age classes: the pediatric group (aged 1–10 years), adolescence–adult group (aged 11–75 years) and the elderly (aged more than 75 years).

A quantile regression analysis was used to describe quantiles 0.05, 0.10, 0.50 (median), 0.90, and 0.95. The association between age and each RV function value was described by restricted cubic splines regressions analysis with one internal knot at the median age to better represent non linear relationships between variables. Missing values were considered to be missing completely at random. Statistical analyses were performed using Stata version 10.0 (StataCorp LP, College Station, TX).

Ethical considerations

The study protocol followed the principles of the Declaration of Helsinki and each participating center had obtained both approval from its Local Research Ethics Committee and informed consent from each subject or, in case of minors, from the parent. Clinicaltrials Gov Identifier: NCT03041337.

Results

General study population characteristics

Age and gender related characteristics of the population are summarized in Table 1S. There were 979 males (51.5%) and 920 females (48.5%). Mean age was of 45.2 ± 18.5 years with a range from 1 to 102 years. The cohort of 1899 subjects was divided in 9 groups: group 1: 59 pediatric subjects aged 1–10 years; group 2: 96 adolescents aged 11–17 years; group 3: 267 subjects aged 18–29 years; group 4: 284 subjects aged 30–39 years; group 5: 373 aged 40–49 years; group 6: 395 subjects aged 50–59 years; group 7: 237 subjects from 60 to 69 years; group 8: 92 subjects from 70 to 75 years; group 9: 96 > 75 years. Blood pressure increased with age, whilst BMI and BSA reached a plateau during the adult years and then decreased again, as expected, in the older age groups. Heart rate was highest in the younger subject groups, and remained stable during the adult and older age groups.

Among the adult population (more than 17 years of age) 80.3% were non smokers.

Echocardiographic characteristics

Echocardiographic characteristics of the various groups are summarized in Table 1. Absolute LV SV increased with advancing age until the seventh decade when it stabilized, while LV SV/BSA slowly increased in the elderly group. The E/A ratio decreased and E/e′ ratio increased with age. TRV and SPAP increased with age, whereas TAPSE and TAPSE/SPAP ratio decreased with increasing age (Table 1; Fig. 3). In particular SPAP was stable until the fifth decade and then increased with advancing age. In men, SPAP did not change substantially during the first four decades and then increased with age; in women, the relationship between age and SPAP was closer (Fig. 1S). TAPSE/SPAP ratio decreased with age in both genders but in men we observed a bimodal trend, the ratio was low in the pediatric and young age-group, increased in the adult phase and then decreased again in the elderly. In women there was a constant decreased from the youngest subjects to the elderly group (Fig. 1S). There was no difference for TAPSE/SPAP/BSA between sex and significantly decrease with advancing age (Table 1).

TAPSE, as absolute number, tended to be higher in men for each age group except for the very elderly and showed a reverse U shape which peaks during the 30s and then decreases with advancing age in both, the whole group and in males and females separately (Figs. 3, 2S). When TAPSE was indexed by BSA, the highest value was observed in the pediatric group (TAPSE/BSA 23.7 ± 7.3 in pediatric subjects, 13.4 ± 2.6 in adults and 13.5 ± 2.4 in the elderly) and was higher in women compared with men (13.2 ± 3.4 vs 14.2 ± 3.3, $p < 0.0001$), in particular from the third to the sixth decade (Table 1), and then declines progressively with ageing in both sexes (Fig. 2S).

Estimated values according to quantile regression analysis

Reference values are reported in Supplementary Tables 2S, 3S, 4S, 5S and percentiles 0.05, 0.10, 0.50 (median), 0.90, 0.95 for TAPSE, SPAP, TAPSE/SPAP and TAPSE/BSA respectively are described. For example, at age 50, the predicted median of SPAP is about 21.3. The 5th percentile is around 11.5, meaning that only 5% of the patients are predicted to have a value less than 11.5. Similarly, the 95th

Table 1 Echocardiographic characteristics of the group of normal subjects

Group	LV E/A	Mean LV E/e′	LV SV (ml)	SV/BSA	RV S′ (cm/s)	SPAP (mmHg)	TAPSE (mm)	TAPSE/BSA	TAPSE/SPAP (mm/mmHg)	TAPSE/SPAP/BSA (mm/mmHg)
All groups										
1: 59 (1–10)	2.9 ± 1.4	6 ± 1.9	31.6 ± 12.9	32.7 ± 7.4	13.5 ± 2.2	19.6 ± 3	20.8 ± 3	23.7 ± 7	1.1 ± 0.6	1.3 ± 0.7
2: 96 (11–17)	2.5 ± 1	6.1 ± 1.9	65.4 ± 17.6	37.8 ± 8.7	13.7 ± 2.2	20.5 ± 7.1	24.3 ± 4.1	14.3 ± 3	1.4 ± 0.8	0.8 ± 0.4
3: 267 (18–29)	1.9 ± 0.7	6.1 ± 2.2	65.3 ± 13.6	36 ± 6.5	14.2 ± 2.1	20.2 ± 5.5	24.3 ± 4.1	13.5 ± 2	1.3 ± 0.8	0.7 ± 0.2
4: 284 (30–39)	1.6 ± 0.6	6.4 ± 2	67.9 ± 15	37.2 ± 8.2	13.9 ± 2.3	20.2 ± 5.7	24.4 ± 3.3	13.5 ± 2	1.3 ± 0.6	0.7 ± 0.3
5: 373 (40–49)	1.4 ± 0.4	6.9 ± 2	69.5 ± 14	38.3 ± 7.8	13.6 ± 2.1	21.2 ± 5.8	24.2 ± 3.5	13.4 ± 2	1.2 ± 0.5	0.7 ± 0.3
6: 395 (50–59)	1.2 ± 0.4	7.5 ± 2.4	68.7 ± 13.9	38 ± 7.4	13.6 ± 2.5	22 ± 5.9	23.4 ± 3.4	12.9 ± 2	1.2 ± 0.5	0.6 ± 0.3
7: 237 (60–69)	0.9 ± 0.4	7.3 ± 2.5	71 ± 14.2	39.7 ± 7.4	13.3 ± 2.5	23 ± 5.9	23.4 ± 3.5	13.1 ± 2	1.1 ± 0.3	0.6 ± 0.2
8: 92 (70–75)	0.9 ± 0.3	7.1 ± 2.8	72.2 ± 17.7	40.4 ± 8.7	14.6 ± 3.6	23.6 ± 6.2	23.6 ± 3.7	13.1 ± 2	1.1 ± 0.3	0.6 ± 0.2
9: 96 (> 76)	0.9 ± 0.7	8.1 ± 3.1	72 ± 15.9	42.9 ± 7.5	14.3 ± 3.4	26.1 ± 7.7	22.9 ± 3.9	13.5 ± 2	0.9 ± 0.3	0.6 ± 0.2
Males										
1: 41 (1–10)	3.9 ± 1.4 (ns)	6 ± 1.6 (ns)	34.3 ± 11.7#	34.8 ± 6.7#	13.4 ± 2 (ns)	20 ± 5.2 (ns)	21 ± 3.1 (ns)	23.3 ± 7 (ns)	1.1 ± 0.5 (ns)	1.2 ± 0.5 (ns)
2: 71 (11–17)	2.4 ± 0.9 (ns)	5.9 ± 1.9 (ns)	69.3 ± 17.2*	39.1 ± 9#	13.6 ± 2.2 (ns)	20 ± 7.7 (ns)	24.8 ± 3.9#	14.2 ± 3 (ns)	1.4 ± 0.9 (ns)	0.8 ± 0.5 (ns)
3: 140 (18–29)	1.9 ± 0.7 (ns)	5.9 ± 1.9 (ns)	70.3 ± 13.8*	36.2 ± 6.7 (ns)	14.2 ± 2.2 (ns)	21 ± 6.2#	24.9 ± 3.9#	12.9 ± 2.1*	1.3 ± 0.5 (ns)	0.7 ± 0.3#
4: 152 (30–39)	1.6 ± 0.5#	6.2 ± 1.7 (ns)	72.9 ± 17.9*	37.3 ± 8.2 (ns)	13.8 ± 2.3 (ns)	20 ± 6.1 (ns)	24.6 ± 3.5 (ns)	12.5 ± 2*	1.4 ± 0.7 (ns)	0.7 ± 0.3 (ns)
5: 198 (40–49)	1.4 ± 0.4 (ns)	6.7 ± 2 (ns)	74.9 ± 15.9*	38.8 ± 6.5 (ns)	13.5 ± 2.3 (ns)	21 ± 6.2 (ns)	24.5 ± 3.8 (ns)	12.7 ± 2.2*	1.3 ± 0.6*	0.7 ± 0.3 (ns)
6: 185 (50–59)	1.2 ± 0.4 (ns)	7.3 ± 2.4#	72.3 ± 15.3*	37.7 ± 6.5 (ns)	13.9 ± 2.8#	21 ± 6.3*	23.8 ± 3.7#	12.4 ± 2*	1.3 ± 0.5*	0.7 ± 0.3 (ns)
7: 108 (60–69)	1 ± 0.3 (ns)	7.5 ± 2.4 (ns)	73.1 ± 15.5#	39.2 ± 7.3 (ns)	13.6 ± 2.3 (ns)	23 ± 6.1 (ns)	24 ± 3.4#	13 ± 2 (ns)	1.1 ± 0.4*	0.6 ± 2 (ns)
8: 44 (70–75)	0.9 ± 0.3#	7.4 ± 2.9 (ns)	78.9 ± 17.6*	41.3 ± 8.8 (ns)	15.5 ± 4.1#	23 ± 6.1 (ns)	24.5 ± 3.8#	12.8 ± 2 (ns)	1.2 ± 0.4#	0.6 ± 0.2 (ns)
9: 40 (> 76)	0.9 ± 0.6 (ns)	8 ± 3.8 (ns)	77.6 ± 17.8#	43.3 ± 7.6 (ns)	14.6 ± 3.4 (ns)	26.9 ± 8 (ns)	23.3 ± 4.8 (ns)	13.2 ± 2 (ns)	0.97 ± 0.4 (ns)	0.5 ± 0.2 (ns)
Females										
1: 18 (1–10)	2.4 ± 1.3	6 ± 2.4	25.4 ± 13.1	27.9 ± 7	13.6 ± 2.7	18.9 ± 7	20.1 ± 2.8	24.6 ± 7.3	1.2 ± 0.9	1.5 ± 1
2: 71 (11–17)	2.7 ± 1.2	6.6 ± 4.6	54.5 ± 13.9	34.2 ± 6.5	13.8 ± 2.1	20.2 ± 4.9	22.7 ± 4.1	14.4 ± 2	1.3 ± 0.5	0.8 ± 0.3
3: 127 (18–29)	2 ± 0.7	6.4 ± 2.4	59.7 ± 11	35.8 ± 6.3	14.2 ± 2.1	19.4 ± 4.5	23.6 ± 3.4	14.2 ± 2.2	1.3 ± 0.4	0.8 ± 0.2
4: 132 (30–39)	1.8 ± 0.7	6.5 ± 2.3	61.3 ± 12.6	37.1 ± 7.6	14 ± 2.3	20.6 ± 5.1	24.2 ± 3.0	14.6 ± 2.1	1.2 ± 0.4	0.7 ± 0.2
5: 175 (40–49)	1.4 ± 0.4	7.1 ± 2.1	63.3 ± 14	37.7 ± 7.4	13.8 ± 2	21.8 ± 5.3	23.8 ± 3	14.2 ± 2	1.1 ± 0.3	0.7 ± 0.2
6: 210 (50–59)	1.2 ± 0.4	7.8 ± 2.4	64.1 ± 14.7	38 ± 8.2	13.3 ± 2.2	22.9 ± 5.4	23 ± 3	13.5 ± 0.2	1.1 ± 0.4	0.6 ± 0.3
7: 129 (60–69)	0.9 ± 0.4	7.2 ± 2.6	69 ± 14	40.2 ± 7.5	13.4 ± 2.7	23 ± 5.3	22.9 ± 3.5	13.3 ± 2	1 ± 0.3	0.6 ± 0.2
8: 48 (70–75)	0.8 ± 2.2	6.9 ± 2.7	66.1 ± 15.5	39.6 ± 8.5	13.6 ± 2.7	24.2 ± 6.4	22.7 ± 3.4	13.8 ± 2	0.9 ± 0.3	0.6 ± 0.2
9: 56 (> 76)	0.9 ± 0.7	8.2 ± 2.6	68.3 ± 12.5	41.9 ± 7.1	14.2 ± 3.4	25.5 ± 7.4	22.6 ± 3.2	13.9 ± 2	0.9 ± 0.3	0.6 ± 0.2

LV left ventricle, *ns* not significant, *RV* right ventricle, *SV* stroke volume, *BSA* body surface area, *SPAP* systolic pulmonary artery pressure, *TAPSE* tricuspid annular plane systolic excursion

Difference between men and women #$p < 0.05$, *$p < 0.0001$

Difference among groups of age (ANOVA) and by gender is $p < 0.0001$ except for S′ in women ($p = 0.03$)

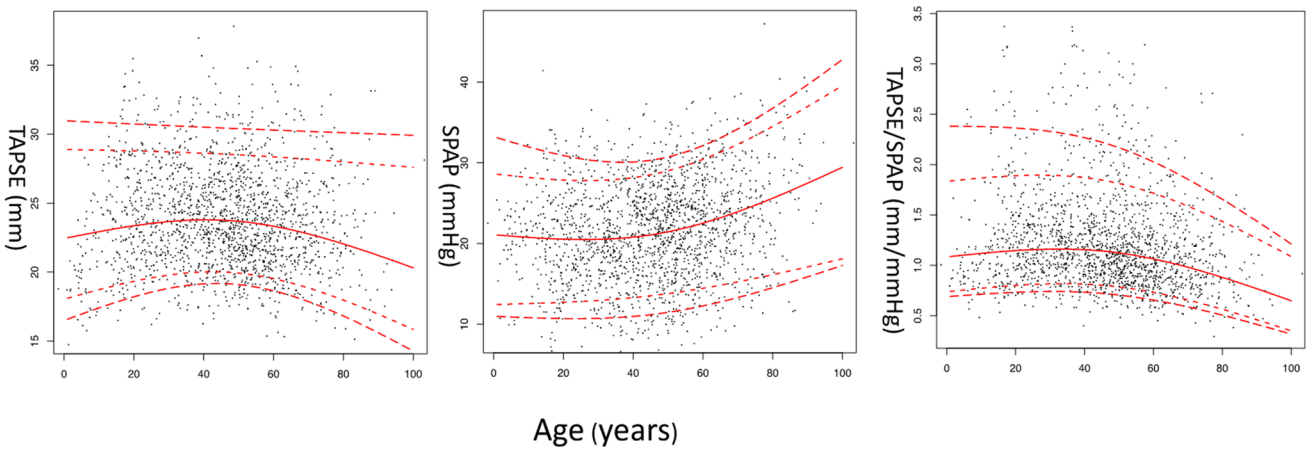

Fig. 3 Scatterplot of age vs TAPSE, SPAP and TAPSE/SPAP with quantile regression lines for the whole group (modeled through natural cubic splines) of order 0.05, 0.10, 0.5, 0.90, 0.95. All group of individuals

percentile is about 30.6, i.e., only 5% of the patients are predicted to have SPAP greater than 30.6.

Clinical and echocardiographic predictors of TAPSE/SPAP, TAPSE, and SPAP

The univariate and independent multivariate determinants of TAPSE, SPAP, and TAPSE/SPAP ratio are summarized in Tables 2 and 3 respectively. On univariate analysis, significant predictors of TAPSE included positive association with BSA, SV, and E/A, HR, E/e′ in a negative fashion (Table 2). In particular, TAPSE had a weak but significant negative correlation with age which became slightly stronger after removing the pediatric group ($r = -0.11$, $p < 0.0001$). SPAP was positively associated with advancing age, BMI, MAP, SV, E/e′ and negatively with E/A. The TAPSE/SPAP ratio was negatively associated with age, BMI, and E/e′ whilst its positive determinants were SV, BSA and E/A (Table 2). The relationship between TAPSE, TAPSE/SPAP and BMI was driven by the female group (Table 2). On multivariate modeling, the independent determinants of TAPSE were BSA, SV, and E/A positively and HR and E/e′ negatively, whereas the independent determinants for SPAP were age, SV, E/A, E/e′ (Table 3). Significant and independent determinants of TAPSE/SPAP were age and E/e′ negatively and BSA positively (Table 3, all groups). Female gender was independently associated with TAPSE/SPAP with females having lower TAPSE/SPAP.

Association of TAPSE/SPAP, TAPSE, SPAP with clinical and echocardiographic predictors by age categories

In the pediatric age group (0–10 years), BSA was independently associated with TAPSE, E/A was independently associated with SPAP whilst mean arterial pressure with TAPSE/SPAP (Table 3). In subjects aged 11–75 years, E/e′, HR, and female sex were negative determinants of TAPSE,

Table 2 Simple correlation between clinical and haemodynamic parameters and RV-PA coupling in all groups

	TAPSE		SPAP		TAPSE/SPAP	
	r	p	r	p	r	p
Age (years)	−0.046	**0.049**	0.225	**0.0001**	−0.162	**0.001**
BMI (kg/m^2)	0.039	0.095	0.096	**0.0001**	−0.049	**0.036**
BSA (m^2)	0.2	**0.0001**	−0.004	0.8	0.1	**0.0001**
MAP (mmHg)	0.048	0.064	0.087	**0.001**	0.004	0.9
Sex (M = 1/F = 2)	−0.13	**0.0001**	0.05	**0.01**	−0.14	**0.0001**
SV (ml)	0.28	**0.0001**	0.1	**0.0001**	0.068	**0.005**
HR (bpm)	−0.18	**0.0001**	−0.03	0.2	−0.049	0.059
E/A	0.103	**0.0001**	−0.06	**0.01**	0.1	**0.0001**
E/e′	−0.099	**0.0001**	0.149	**0.0001**	−0.166	**0.0001**

Bold represents the significant p value

BMI body mass index, *BSA* body surface area, *MAP* mean arterial pressure, *SV* stroke volume, *HR* heart rate, *SPAP* systolic pulmonary artery pressure, *TAPSE* tricuspid annular plane systolic excursion

Table 3 Multiple regression analysis in the whole and different age groups

Independent variable	TAPSE			SPAP			TAPSE/SPAP		
		b	p		b	p		b	p
All group	R^2 0.144			R^2 0.06			R^2 0.06		
Age (years)		−0.002	0.9		0.2	**0.0001**		−0.141	**0.0001**
Sex (M = 1/F = 2)		−0.02	0.9		0.037	0.1		−0.08	**0.002**
BMI (kg/m^2)		0.038	0.09		−0.007	0.8		−0.01	**0.01**
BSA (m^2)		1.6	**0.001**		−2.4	**0.002**		0.28	**0.0001**
MAP (mmHg)		0.01	0.28		−0.001	0.9		0.002	0.12
SV (ml)		0.32	**0.0001**		0.065	**0.03**		0.001	0.4
HR (bpm)		−0.10	**0.0001**		0.03	0.2		−0.9	0.3
E/A		0.134	**0.0001**		0.145	**0.0001**		−0.008	0.8
E/e′		−0.08	**0.001**		0.08	**0.001**		−0.115	**0.0001**
Pediatric	R^2 0.132			R^2 0.2			R^2 0.14		
Age (years)		0.3	0.1		−0.3	0.4		0.06	0.1
Sex (M = 1/F = 2)		−0.7	0.4		−0.06	0.9		0.8	0.4
BMI (kg/m^2)		−0.02	0.8		−0.16	0.3		0.0007	0.9
BSA (m^2)		12.4	**0.015**		−3.9	0.6		1.33	0.2
MAP (mmHg)		−0.01	0.8		0.13	0.15		−0.025	**0.04**
SV (ml)		0.0001	0.9		0.07	0.37		−0.009	0.3
HR (bpm)		0.03	0.3		0.005	0.9		−0.002	0.6
E/A		0.3	0.3		1.47	**0.0087**		−0.06	0.3
E/e′		−0.1	0.5		0.3	0.3		−0.05	0.2
Adult	R^2 0.106			R^2 0.04			R^2 0.06		
Age (years)		0.003	0.5		0.06	**0.0001**		−0.003	**0.008**
Sex (M = 1/F = 2)		−0.4	**0.01**		0.8	**0.006**		−0.07	**0.024**
BMI (kg/m^2)		−0.02	0.3		0.05	0.23		−0.012	**0.01**
BSA (m^2)		1.16	0.079		−1.7	0.13		0.27	**0.008**
MAP (mmHg)		0.01	0.1		−0.001	0.9		0.003	**0.05**
SV (ml)		0.05	**0.0001**		0.02	**0.001**		0.001	0.1
HR (bpm)		−0.01	**0.03**		0.009	0.4		−0.001	0.3
E/A		0.8	**0.0001**		0.6	**0.03**		0.03	0.18
E/e′		−0.09	**0.01**		0.1	**0.01**		−0.02	**0.0001**
Elderly	R^2 0.172			R^2 0.25			R^2 0.23		
Age (years)		0.06	0.3		0.2	**0.029**		−0.006	0.3
Sex (M = 1/F = 2)		−0.6	0.4		−0.6	0.7		−0.04	0.6
BMI (kg/m^2)		0.2	**0.02**		−0.004	0.9		0.01	0.2
BSA (m^2)		−2.5	0.48		1.6	0.8		0.02	0.2
MAP (mmHg)		−0.001	0.9		−0.03	0.6		−0.001	0.7
SV (ml)		0.02	0.3		0.007	0.9		0.0004	0.9
HR (bpm)		−0.02	0.5		−0.03	0.6		0.003	0.3
E/A		0.6	0.29		1.4	0.1		−0.03	0.57
E/e′		−0.3	**0.017**		0.89	**0.008**		−0.03	**0.021**

Bold represents the significant p value

BMI body mass index, *BSA* body surface area, *MAP* mean arterial pressure, *SV* stroke volume, *HR* heart rate, *SPAP* systolic pulmonary artery pressure, *TAPSE* tricuspid annular plane systolic excursion

while LV SV, and E/A were significant positive independent determinants of TAPSE. Independent determinants for SPAP included age, female sex, LVSV, E/A, and E/e′. Age, E/e′, BMI, and female gender were negatively associated with TAPSE/SPAP, while mean blood pressure, BSA were positively and independently associated with TAPSE/SPAP (Table 3). In the elderly group (> 75 years), BMI and E/e′ were significant and independent determinants of TAPSE; age and E/e′ were associated with SPAP, while E/e′ was negatively associated with TAPSE/SPAP ratio (Table 3).

The relationship between TAPSE and SPAP was relatively preserved over the age groups (pediatric group r = −0.248, p = 0.06; adults r = 0.011, p = 0.6; elderly r = −0.09, p = 0.3) with similar TAPSE and SPAP values. We did not find any downshift of the regression line among the three different groups of age (Fig. 4).

Discussion

This is the first large population-based study to outline age, anthropometric and LV stiffness-pressure related changes in right ventricular function and right ventricular-pulmonary vascular coupling using the TAPSE/SPAP ratio in healthy individuals aged 1–102 without overt cardiovascular disease and ultimately to work on the generation of reference values. Specifically, we demonstrate that (i) TAPSE, as absolute value, is low in the pediatric group, increases during adulthood and then slowly declines during the elderly years. TAPSE is also lower in females but its value is higher in both the pediatric and female populations when indexed by BSA; (ii) a strong positive association between SPAP and advancing age was observed. In the adult and elderly groups was noted also a positive associated with LV filling pressure represented by E/e′; (iii) TAPSE/SPAP ratio, as a surrogate for right ventricular pulmonary vascular coupling, declines with ageing but is also affected by LV diastolic filling pressure.

SPAP was low in the pediatric group and then increased significantly during the initial decades of adult life with no significant difference between men and women. SPAP was affected by not only age, and LV end diastolic pressure (E/e′)/stiffness (E/A), but also by LV SV. In this regard, higher pulmonary blood flow is expected to increase systolic and mean pulmonary artery pressure by simple hydrodynamic conservation principles [28, 29]. On the other hand, although BMI was positively associated with SPAP in our univariate analysis, it lost its association in the multiregression analysis. However, contradictory results are reported in the literature regarding the relationship between SPAP and BMI [11, 12]. In a subset of healthy subjects from the Olmsted County (MN), Lam et al. [13] found a significant independent relationship between age, arterial stiffness (pulse pressure) and LV diastolic pressure with SPAP but not with BMI. Interestingly, the effect of BMI on SPAP appears to be mediated by a higher SV [29]. On the other hand, BSA as an index of body size, was independently related not only with SPAP but also with TAPSE and TAPSE/SPAP when the whole group was considered. According to Lam et al. [13], the increase in SPAP also parallels increases in systemic vascular stiffness with ageing. Increase in vascular stiffness, mediated by ageing, could explain the relation between MAP and SPAP in univariate analysis but this relation was not anymore present in multivariate analysis likely because other

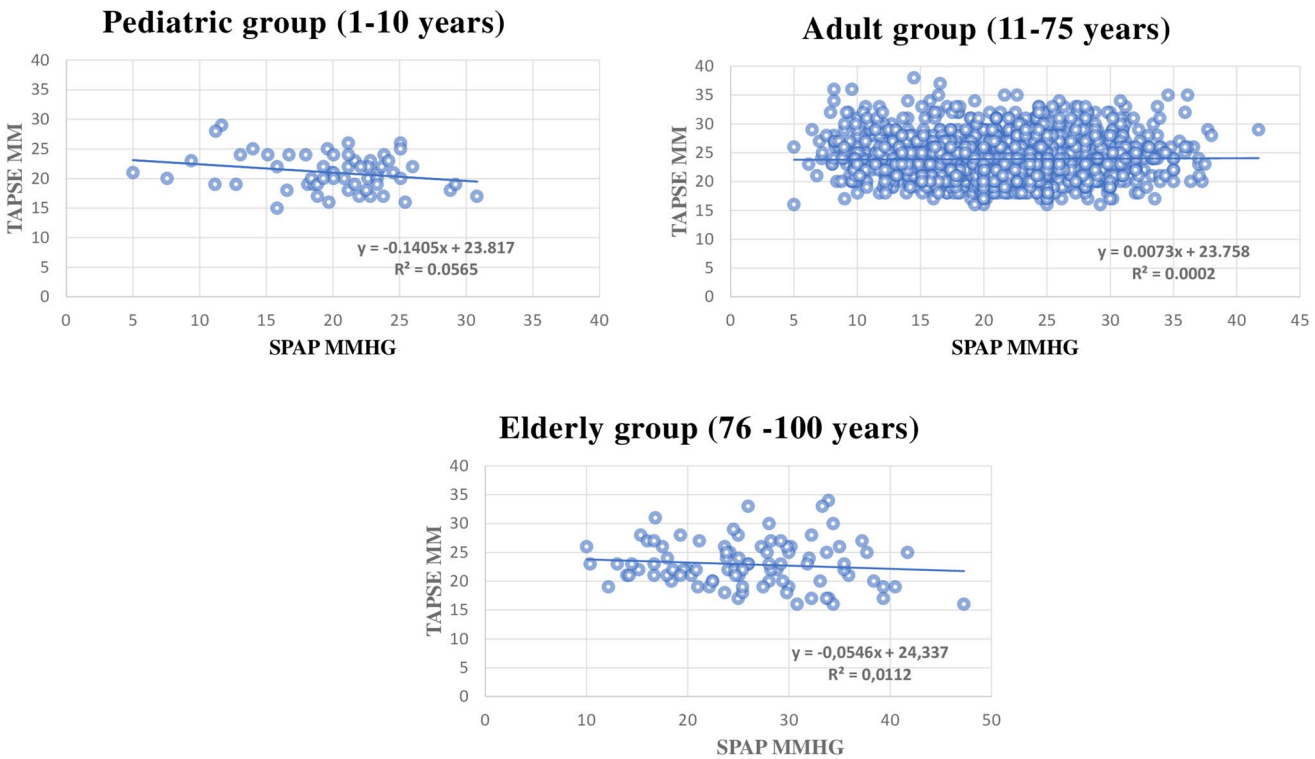

Fig. 4 Correlation between TAPSE and SPAP by age groups

parameters such as LV stiffening and LV diastolic dysfunction overtook the effect of age on RV function. This was particularly clear when the groups of adults and elderly were analyzed separately.

The assessment of RV systolic function is important for risk stratification both in general populations and in specific pathological settings, with TAPSE being a good surrogate of right ventricular long axis function [24, 30] or according to Schmeisser et al. [31] a complex longitudinal RV deformation combined with intrinsic contractility, pulsatile, and non-pulsatile afterload. In the present study, normal TAPSE values were consistent with those described in the 2015 ASE/EACVI Recommendations for cardiac chamber quantification (23.8 ± 3.5 mm versus 24 ± 3.5 mm our results and guidelines respectively) and none of the age subgroups had a TAPSE below the cut-off point of abnormality (17 mm) [22]. Furthermore, the relationship between TAPSE and age was best represented by a reverse U shape with a very weak relation mostly determined by the elderly group. TAPSE increased during childhood and adulthood according to growth in body size, in fact BSA was independently and positively related with TAPSE in the pediatric group, as also reported by Koestenberger et al. [32] and others [33]. Moreover TAPSE was also significantly lower in females compare to males. Interestingly, when TAPSE was normalized by BSA the highest value was found in the pediatric group and in women from the third to sixth decade. We do not have specific data on menopausal status and estrogen replacement therapy of the study subjects but RV seems to be more performing in pre–peri menopause period in women than in men. TAPSE declines later on in life as well as TAPSE/BSA, with no difference in sex, suggesting an attenuation of sex effect due to age. TAPSE/SPAP ratio was low in the pediatric group driven by TAPSE, after that remained relatively stable until middle adult life and then decline in older age. Same trend when TAPSE/SPAP was indexed by BSA. Moreover, TAPSE/SPAP was lower in females than males starting from the fifth decade, but after the adjustment by BSA the RV–PA coupling was similar in the two sexes. This suggests that RV function and RV–PA coupling are in relation to body size that needs to be considered not only in the pediatric phase of life but also when sex characteristics are considered [32, 34]. Sex differences in RV structure and performance were described by the MESA group either in pulmonary hypertension or in study cohort without clinical cardiovascular disease. In particular in postmenopausal women from MESA-RV using hormone therapy, higher levels of estrogens were associated with higher RV performance [34–36]. Using strain methodology, Park et al. [37] showed that RV longitudinal contractility was higher in women than men especially in the younger age.

TAPSE/SPAP ratio also was proposed as a useful clinical index of RV to pulmonary vascular coupling, described initially in heart failure with or without reduced ejection fraction, [38, 39] pulmonary arterial hypertension (PH) (5) and PA hypertension due to immune disease [7]. For example, Guazzi et al. [38] found that a TAPSE/SPAP < 0.35 mm/mmHg and Modin et al. [30] TAPSE/SPAP < 0.38 mm/mmHg was related with higher mortality in HF patients. Ferrara et al. [10] previously described that TAPSE/SPAP decreased with age and it was higher in men than women but the effect of BSA was not considered and the pediatric and adolescent group were not included. More recently Forton et al. [40] described the progressive reduction in TAPSE/SPAP from the group of adolescents to middle-age adults, either at rest or during stress test. On the contrary, S′/SPAP did not change among the groups at rest. Either TAPSE or S′ did not change significantly from the young to the adult groups.

On univariate analysis for the all group, age, sex, SV and LV E/e′ and E/A were related to TAPSE, SPAP and TAPSE/SPAP. Mean arterial pressure was positively related to SPAP suggesting a direct relation between the two and BSA was related to TAPSE and TAPSE/SPAP underline the effect of body size on RV function. On multifactorial regression analysis on the all group, only age was not an independent predictor for TAPSE anymore while was still associated with SPAP and TAPSE/SPAP along with body size and LV end diastolic stiffness ad pressure. Interestingly, the weight of the independent variables vary according to age group. In the pediatric group, age lost its effect while body size affected RV function and E/A was independently related to SPAP. In the adult group, sex, driven by female sex, was the constant independent variable related to TAPSE, SPAP and TAPSE/SPAP suggesting the importance of hormone difference between sexes followed by age and LV end diastolic pressure and diastolic dysfunction. In the group of elderly, the constant parameter related to TAPSE, SPAP and TAPSE/SPAP was LV E/e′ as part of the ageing process.

Interestingly we found a similar relationship between TAPSE and SPAP across the different age-groups. In other words, in healthy population the contractile properties of the RV are adequate for a given pulmonary systolic load included in the group of elderly and TAPSE is always above the limit of normality for all the age-group considered. These findings are the opposite to those reported in pathological settings described by Guazzi et al. [24]. In fact, in patients with heart failure the relationship between TAPSE and SPAP is characterized by a downward shift of the regression line for non-survivors vs. survivors although the slope

of the regression line appears to be similar due to not only to a lower TAPSE for a given SPAP but also to a reduced contractile RV capacity [24].

Limitations

Despite the large number of subjects in this investigation, several limitations have to be acknowledged. (1) In this study the majority of the subjects were Caucasian and the results cannot be applied to other ethnic groups. (2) The distribution of individuals across the age continuum varied with greater representation in the early and middle adult years. Pediatric and elderly age groups were therefore relatively underrepresented. This had the potential to relatively bias our statistical observation, though this was partly mitigated by studying group characteristics by decade. (3) The pediatric subjects were included largely by the ability to measure TRV and therefore may have introduced some element of bias toward higher PA pressures or other pre-disease state confounders. (4) The population of the present study was classified as healthy based on history and the absence of overt CV disease, but not on serological laboratory testing and/or other medical investigations. Moreover, family history of cardiovascular disease was not systematically collected. Though this is a reasonable way to describe normality in younger cohorts, it is certainly fraught with difficulty in elderly populations who more likely have subclinical and pre-disease states. However, this is part of the "normal" ageing process, and until we have more refined definitions and delineations of ageing available, such methodologies will remain inherently suboptimal.

Conclusion

Age-related changes in RV function, as estimated by SPAP, TAPSE, and RV–PA coupling, as estimated by TAPSE/SPAP, can be observed in a cohort of healthy subjects. The relation between TAPSE and SPAP is relatively preserved in the early to late adult years but also that ageing profoundly affects SPAP, TAPSE and TAPSE/SPAP either directly or through LV diastolic dysfunction. Body size significantly affects TAPSE and consequently TAPSE/SPAP and needs to be taken into account not only in the pediatric and adolescent phase, but also when sex is considered. Reference values of TAPSE, SPAP and TAPSE/SPAP derived from this cohort can be used to interpret and track changes in individuals and compare and contrast with pathological states and evolving risk factors.

Appendix

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Declarations

Conflict of interest No conflict of interest.

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