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The impact of ageing on right ventricular longitudinal function in healthy subjects: a pulsed tissue Doppler study

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Aims To evaluate the influence of age on pulsed Tissue Doppler-derived measurements of right ventricular (RV) tricuspid annulus in a population of healthy subjects and to propose reference values according to age decades.

Methods and results Two hundred and ninety-eight healthy subjects (M/F = 186/112) underwent Doppler echocardiography and pulsed Tissue Doppler of tricuspid annulus in apical four-chamber view. Tricuspid annular plane systolic excursion (TAPSE), Doppler indexes of RV outflow tract and of tricuspid inflow, right atrial dimension and inferior vena cava size, and collapsibility were measured. Pulsed Tissue Doppler lateral corner of the tricuspid annulus was also recorded and annular systolic (Sa), early diastolic (Ea), and atrial (Aa) peak velocities and Ea/Aa ratio determined. The ratio of tricuspid E peak velocity and Ea (E/Ea ratio) was calculated as an index of right atrial pressure. The population was divided in seven age decades: 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, and >70 years. TAPSE, Sa, Ea, and Ea/Aa ratio were progressively reduced and both Aa and E/Ea ratio increased with the increasing age groups (all $P < 0.0001$). E/Ea ratio was 4.1 ± 0.9 in the age decade 11–20 years and 5.4 ± 1.5 in subjects >70 years ($P < 0.0001$). By multi-linear regression analyses, after adjusting for heart rate and body mass index, age was the main independent predictor of average Sa, Ea, and Aa velocities and of E/Ea ratio.

Conclusions Ageing shows an independent impact on pulsed Tissue Doppler-derived indexes of RV myocardial function in healthy subjects. Our data provide reference values of pulsed Tissue Doppler of the right ventricle for age decades.

Introduction

Right ventricular (RV) function is an important predictor of exercise capacity and mortality in patients with heart failure and pulmonary arterial hypertension, independently on the impact of left ventricular (LV) function.[1–6] While standard Doppler echocardiography can reliably evaluate LV function, the ultrasound assessment of RV structure and function is often suboptimal, due to its anatomic location and to its particular geometric configuration which precludes an accurate determination of RV volume and wall motion abnormalities.[7] Moreover, RV stroke volume is dependent on the interaction of RV free wall, septal wall, and RV outflow tract (RVOT), which markedly differ in their own geometric and contractile properties. Finally, pulmonary arterial resistances have peculiar characteristics that deeply affect RV function under both normal and pathological conditions.[8]

Several attempts have been performed to measure RV volumes and RV ejection fraction[7,9] but all these methods are not easy to perform in the clinical setting. In 1980s, Kaul *et al*. proposed the simple M-mode measure of tricuspid annular plane systolic excursion (TAPSE) as an accurate index of RV systolic function, taking into account that RV shortening occurs mainly along its longitudinal axis.[10] Further information of RV systolic function may be provided by Doppler-derived RVOT profile since flow velocities and systolic time intervals can be easily measured and are sensitive to changes of pulmonary arterial pressure.[11] With regard to the need of obtaining information of RV diastolic function, Doppler-derived tricuspid inflow pattern is useful for the determination of the homologous velocities currently obtained by LV mitral inflow.[12]

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The application of pulsed Tissue Doppler allows to quantify longitudinal myocardial function of the right ventricle, measuring myocardial velocities, and time intervals throughout the overall cardiac cycle.[13–15] Also the estimation of right atrial pressure (RAP) is possible by this technique, estimating the ratio of tricuspid inflow E velocity to myocardial early diastolic velocity (Ea) of lateral tricuspid annulus.[12,16–17] Pulsed Tissue Doppler of lateral tricuspid annulus has been successfully used to assess RV longitudinal function in several diseases including heart failure,[18] coronary artery disease,[19,20] hypertrophic cardiomyopathy,[21] chronic pulmonary disease,[22,23] and congenital heart diseases.[24] Currently available non-invasive estimation of RAP involve patients after cardiac surgery[25] and heart transplantation.[26]

Previous studies assessed the influence of ageing on pulsed Tissue Doppler of RV tricuspid annulus, generating reference values for age decades only in small series of healthy subjects.[27–30] However, no information is available about the impact of ageing on RV E/Ea ratio as non-invasive estimated RAP. The present study aimed to evaluate the relation between age and pulsed Tissue Doppler-derived measurements of systolic and diastolic function of the right ventricle in a large population of healthy subjects, in relation to demographic and echocardiographic variables, and to propose reference values according to different age groups.

Methods

Study population

We prospectively studied 298 healthy subjects (186 men and 112 women, mean age 41.7 ± 18.0 years, age range 10–82 years) referred to our echo-lab and recruited from the staff and relatives of our Departments into a programme of cardiovascular prevention of the Department of Clinical and Experimental Medicine of the Federico II University of Naples. Exclusion criteria were: smoking, history of chronic obstructive pulmonary disease, and cardiovascular disease including systemic and/or pulmonary arterial hypertension, diabetes mellitus, any kind of endocrinologic disease, connective tissue disease, coronary artery disease and previous acute myocardial infarction, stroke and transient ischaemic events, significant valvular heart disease, or congestive heart failure. Additional exclusion criteria concerned age <10 years, overweight (body mass index >25.9 kg/m^2), dyslipidaemia (total cholesterol >190 mg/dL, and triglycerides >150 mg/dL), any kind of resting ECG abnormalities, and unsatisfactory echocardiographic window. All subjects gave a written informed consent and the study was approved by the Ethical Committee of Federico II University Hospital of Naples.

Procedures

Standard Doppler echocardiography and pulsed Tissue Doppler were performed by Vivid Seven (GE, Horten, Norway) equipped with Tissue Doppler capabilities. A 2.5 MHz transducer was used for Doppler-echo and Tissue Doppler recording. At the end of the study, cuff blood pressure (mean of three measurements) was estimated by a physician blinded to the examination. According to the recommendations of the American Society of Echocardiography and the European Association of Echocardiography,[31] two-dimensional measurements of RV transverse basal and mid-cavity diameters, and longitudinal diameter were obtained at end-diastole in the apical four-chamber view. RV global systolic function was assessed by measuring M-mode-derived TAPSE (cm), according to the original method proposed by Kaul *et al.*[10] Pulsed Doppler of the RV systolic outflow tract was recorded in parasternal short-axis view: RV

Table 1 Clinical characteristics of the population according to age decades

	10–19 years ($n = 40$)	20–29 years ($n = 53$)	30–39 years ($n = 41$)	40–49 years ($n = 52$)	50–59 years ($n = 53$)	60–69 years ($n = 37$)	>70 ($n = 22$)	*P*-value
Men/Women	26/14	30/23	27/14	32/20	35/18	21/16	15/7	NS
Age (years)	15.0 ± 2.5 (14.2–15.8)	24.5 ± 2.8 (23.7–25.3)	34.0 ± 3.1 (32.9–35.0)	44.4 ± 2.9 (43.7–45.3)	54.1 ± 3.0 (53.3–54.9)	63.5 ± 2.9 (62.5–64.5)	73.2 ± 3.4 (71.7–74.8)	<0.0001
BMI (kg/m^2)	22.2 ± 4.1 (20.9–23.5)	22.8 ± 2.3 (21.4–22.7)	23.4 ± 2.4 (22.7–24.2)	24.3 ± 3.4 (23.3–25.3)	24.7 ± 2.4 (24.0–25.4)	23.8 ± 2.7 (22.9–24.7)	24.0 ± 2.0 (23.1–24.9)	<0.0001
Systolic BP (mmHg)	114.6 ± 11.6 (110.9–118.3)	116.1 ± 13.4 (112.4–119.8)	117.0 ± 13.5 (112.8–121.3)	122.1 ± 13.5 (118.3–125.8)	126.5 ± 12.5 (123.0–129.9)	130.5 ± 11.6 (126.6–134.4)	137.9 ± 8.1 (134.3–141.5)	<0.0001
Diastolic BP (mmHg)	71.7 ± 7.6 (69.3–74.1)	73.4 ± 8.7 (71.0–75.8)	73.9 ± 9.1 (71.0–76.7)	75.3 ± 8.6 (72.9–77.7)	77.3 ± 6.9 (75.4–79.2)	75.6 ± 7.2 (73.2–78.1)	78.1 ± 6.0 (75.4–80.8)	<0.0001
Mean BP (mmHg)	86.0 ± 8.3 (83.3–88.7)	87.6 ± 9.5 (85.0–90.3)	88.2 ± 9.8 (85.1–91.4)	90.6 ± 9.4 (88.3–93.5)	93.7 ± 8.0 (91.5–95.9)	93.9 ± 7.8 (91.3–96.5)	98.1 ± 6.1 (95.3–100.8)	<0.0001
HR (bpm)	77.3 ± 8.9 (74.3–80.2)	73.4 ± 10.7 (70.3–76.5)	72.6 ± 9.8 (69.4–75.8)	71.2 ± 12.5 (67.7–74.6)	72.1 ± 13.8 (68.2–76.0)	69.4 ± 11.5 (65.5–73.2)	74.6 ± 11.09 (69.7–79.5)	NS

Data are expressed as mean ± SD (95% confidence interval).
BMI, body mass index; BP, blood pressure, HR, heart rate.

Table 2 Doppler echocardiographic characteristics of the population according to age decades

	10–19 years ($n = 40$)	20–29 years ($n = 53$)	30–39 years ($n = 41$)	40–49 years ($n = 52$)	50–59 years ($n = 53$)	60–69 years ($n = 37$)	>70 ($n = 22$)	*P*-value
RV basal diameter/ BSA (cm/m^2)	1.9 ± 0.4 (1.6–2.1)	1.8 ± 0.5 (1.5–2.2)	1.9 ± 0.29 (1.7–2.0)	1.8 ± 0.28 (1.6–1.9)	1.8 ± 0.30 (1.7–1.9)	1.9 ± 0.33 (1.7–2.1)	1.9 ± 0.23 (1.7–2.07)	NS
RV mid-cavity diameter/BSA (cm/m^2)	1.6 ± 0.3 (1.4–1.8)	1.7 ± 0.3 (1.4–1.9)	1.4 ± 0.2 (1.3–1.6)	1.4 ± 0.3 (1.2–1.5)	1.4 ± 0.2 (1.3–1.5)	1.5 ± 0.2 (1.4–1.7)	1.5 ± 0.3 (1.3–1.6)	NS
RV longitudinal diameter/BSA (cm/m^2)	3.8 ± 0.8 (3.2–4.4)	3.9 ± 0.7 (3.5–4.4)	3.7 ± 0.3 (3.5–3.9)	3.6 ± 0.8 (3.4–3.8)	3.8 ± 0.4 (3.6–4.0)	3.9 ± 0.4 (3.7–4.1)	3.7 ± 0.4 (3.4–4.0)	NS
TAPSE (cm)	2.3 ± 0.4 (2.1–2.5)	2.2 ± 0.3 (2.1–2.3)	2.2 ± 0.3 (2.1–2.3)	2.1 ± 0. 3 (2.0–2.2)	2.0 ± 0.2 (2.0–2.1)	2.0 ± 0.3 (1.9–2.1)	1.8 ± 0.3 (1.7–2.0)	<0.0001
RA diameter (cm)	3.2 ± 0.6 (2.8–3.6)	3.2 ± 0.5 (2.9–3.4)	3.6 ± 0.5 (3.3–3.9)	3.3 ± 0.6 (3.0–3.6)	3.4 ± 0.5 (3.2–3.6)	3.8 ± 0.6 (3.5–4.1)	3.8 ± 0.5 (3.4–4.1)	<0.001
RA diameter/BSA (cm/m^2)	2.0 ± 0.4 (1.7–2.3)	1.8 ± 0.2 (1.7–1.9)	1.9 ± 0.3 (1.7–2.1)	1.8 ± 0.2 (1.7–1.9)	1.8 ± 0.3 (1.7–2.0)	2.1 ± 0.3 (1.9–2.2)	2.0 ± 0.4 (1.8–2.3)	<0.01
IVC diameter (cm)	1.0 ± 0.2 (0.8–1.2)	1.1 ± 0.4 (0.3–2.0)	1.4 ± 0.2 (1.2–1.5)	1.4 ± 0.4 (1.1–1.6)	1.4 ± 0.2 (1.3–1.5)	1.5 ± 0.3 (1.3–1.6)	1.7 ± 0.1 (1.4–1.9)	<0.005
IVC collapsibility index (%)	97.0 ± 1.0 (94.5–99.4)	91.0 ± 2.9 (86.8–95.1)	84.5 ± 6.3 (77.8–91.1)	85.6 ± 4.6 (80.8–90.5)	78.5 ± 4.3 (75.2–81.9)	70.1 ± 5.9 (63.9–76.3)	63.0 ± 6.4 (57.6–68.3)	<0.0001
RVOT systolic velocity (m/s)	0.91 ± 0.1 (0.86–0.95)	0.85 ± 0.1 (0.81–0.89)	0.82 ± 0.1 (0.78–0.87)	0.81 ± 0.2 (0.77–0.85)	0.85 ± 0.1 (0.79–0.88)	0.81 ± 0.1 (0.77–0.85)	0.78 ± 0.1 (0.73–0.82)	=0.009
RVPEP (ms)	67.7 ± 14.2 (63.0–72.3)	74.0 ± 11.9 (70.6–77.3)	75.2 ± 11.7 (71.2–79.1)	77.1 ± 14.2 (73.0–81.1)	78.9 ± 14.3 (74.9–83.0)	78.7 ± 15.0 (74.6–83.4)	78.5 ± 15.9 (71.1–85.7)	=0.008
RVET (ms)	302.7 ± 31.1 (292.4–312.9)	294.6 ± 52.8 (279.9–309.3)	291.9 ± 36.9 (279.6–304.2)	290.7 ± 46.4 (277.5–303.9)	291.7 ± 64.2 (273.6–309.8)	307.7 ± 35.2 (295.6–319.8)	295.2 ± 29.9 (281.5–308.8)	NS
TR E velocity (m/s)	0.63 ± 0.10 (0.59–0.66)	0.60 ± 0.11 (0.57–0.63)	0.57 ± 0.10 (0.54–0.60)	0.54 ± 0.11 (0.50–0.57)	0.53 ± 0.10 (0.50–0.56)	0.50 ± 0.13 (0.46–0.54)	0.57 ± 0.12 (0.5 2–0.63)	<0.0001
TR A velocity (m/s)	0.40 ± 0.08 (0.37–0.43)	0.39 ± 0.09 (0.36–0 42)	0.38 ± 0.07 (0.35–0.40)	0.40 ± 0.09 (0.36–0.42)	0.42 ± 0.07 (0.40–0.44)	0.41 ± 0.12 (0.37–0.45)	0.51 ± 0.15 (0.44–0.58)	<0.0001
TR E/A ratio	1.6 ± 0.3 (1.5–1.7)	1.6 ± 0.4 (1.49–1.7)	1.5 ± 0.3 (1.4–1.6)	1.4 ± 0.3 (1.3–1.5)	1.3 ± 0.3 (1.2–1.3)	1.2 ± 0.2 (1.1–1.3)	1.1 ± 0.2 (1.0–1.2)	<0.0001

Data are expressed as mean ± SD (95% confidence interval).

IVC, inferior vena cava; RA, right atrial; RV, right ventricular; RVOT, right ventricular outflow tract; RVPEP, right ventricular pre-ejection period; RVET, right ventricular ejection time; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid inflow.

Table 3 Pulsed Tissue Doppler measurements of tricuspid annulus according to age decades

	10–19 years ($n = 40$)	20–29 years ($n = 53$)	30–39 years ($n = 41$)	40–49 years ($n = 52$)	50–59 years ($n = 53$)	60–69 years ($n = 37$)	>70 years ($n = 22$)	*P*-value
Lateral tricuspid annulus								
Sa peak velocity (cm/s)	14.8 ± 2.1 (14.2–15.5)	14.8 ± 1.6 (14.3–15.2)	14.2 ± 1.6 (13.7–14.7)	14.6 ± 2.1 (14.0–15.1)	13.5 ± 1.7 (13.0–14.0)	13.2 ± 1.7 (12.7–13.8)	11.7 ± 2.2 (10.7–12.7)	<0.0001
Ea peak velocity (cm/s)	15.7 ± 2.9 (14.8–16.7)	16.1 ± 3.1 (15.2–16.9)	14.9 ± 3.2 (13.8–15.9)	14.0 ± 2.8 (13.4–15.0)	12.4 ± 2.5 (11.7–13.1)	12.5 ± 3.2 (11.4–13.5)	10.8 ± 1.6 (10.1–11.6)	<0.0001
Aa peak velocity (cm/s)	9.0 ± 3.3 (8.0–10.1)	11.0 ± 3.3 (10.1–12.0)	12.1 ± 3.6 (11.0–13.3)	13.7 ± 4.0 (12.6–14.8)	13.8 ± 3.3 (12.9–14.7)	14.8 ± 4.0 (13.4–16.1)	13.3 ± 3.2 (11.9–14.8)	<0.0001
Ea/Aa ratio	1.9 ± 0.8 (1.7–2.2)	1.5 ± 0.4 (1.4–1.6)	1.3 ± 0.38 (1.1–1.4)	1.2 ± 0.9 (0.9–1.5)	0.95 ± 0.3 (0.86–1.04)	0.892 ± 0.2 (0.79–0.98)	0.85 ± 0.2 (0.76–0.93)	<0.0001
E/Ea ratio	4.1 ± 0.9 (3.8–4.4)	3.9 ± 1.1 (3.5–4.2)	3.9 ± 1.0 (3.6–4.3)	3.8 ± 0.9 (3.6–4.1)	4.4 ± 1.1 (4.1–4.7)	4.2 ± 1.4 (3.7–4.7)	5.4 ± 1.5 (4.7–6.1)	<0.0001

Data are expressed as mean ± SD (95% confidence interval).

pre-ejection period (PEP, ms, from the ECG QRS onset to the beginning of RV systolic outflow velocity) and RV ejection time (ET, ms, from the beginning to the end of RV systolic output flow) were determined as RV systolic indexes. The right atrial (RA) minor axis diameter was taken in the apical four-chamber view at ventricular end-systole, in a plane perpendicular to the long axis of the cavity extending the measure from the lateral border to the interatrial septum.[31] The diameter of inferior vena cava (IVC) and its percent decrease during inspiration (collapsibility index) were measured in a subcostal view at 1.0–2.0 cm at the junction with the right atrium using the long-axis view.[31]

Pulsed Doppler RV inflow recording was performed in the apical four-chamber view, placing the sample volume at the tips level: tricuspid inflow was measured for peak early inflow velocity (E), peak atrial velocity (A), and peak velocity E/A ratio.[12] Also pulsed Tissue Doppler was performed in 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 until a Nyquist limit of 15–20 cm/s, and using the minimal optimal gain. By Tissue Doppler, annular systolic velocity (Sa) and both early (Ea) and atrial (Aa) velocities were measured and Ea/Aa ratio was derived. RV E/Ea ratio was also calculated as an index of RAP.[17] All tricuspid inflow and Tissue Doppler parameters represented an average of three consecutive cardiac cycles at end-expiratory apnea. Standard Doppler and pulsed Tissue Doppler methods and reproducibility in our laboratory have been previously described.[32]

Statistical analysis

Data are presented as mean ± SD. Descriptive statistics was obtained by one-factor ANOVA and χ^2 distribution with computation of exact *P*-value by Monte Carlo method. Least squares linear regression was used to evaluate univariate and multivariate correlates of Tissue Doppler measurements. For multiple linear regression models, multicollinearity was also examined by computation of in-model tolerance. Collinearity was considered acceptable and regression model stable for tolerance >0.70. The null hypothesis was rejected for $P < 0.05$.

Results

The study population was divided into seven decades of age: 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, and >70 years. *Table 1* reports the clinical characteristics by dividing the study population according to age groups: as expected, body mass index and blood pressure increased significantly with age, while heart rate was not significantly different among the various age groups.

Table 2 summarizes the main Doppler echocardiographic measurements of the right ventricle according to age decades. No difference of RV transverse (basal and mid-cavity) and longitudinal diameters was found among the groups while TAPSE gradually decreased throughout the age decades. Standard Doppler-derived RVOT systolic velocity and tricuspid inflow peak velocity E/A ratio were progressively reduced, while RVPEP was prolonged with advancing age. Both RA minor axis diameter and IVC diameter were progressively increased and the IVC collapsibility index was reduced with the increasing age decades. However, IVC diameter >1.7 observed in 7 of 298 subjects (three of these were over 70 and two over 60) was always combined with an IVC collapsibility index >50%, this combination being indicative of only marginal RAP increase (=6–10 mmHg).[31]

Table 3 lists the results of pulsed Tissue Doppler measurements of lateral tricuspid annulus. Sa and Ea velocities were

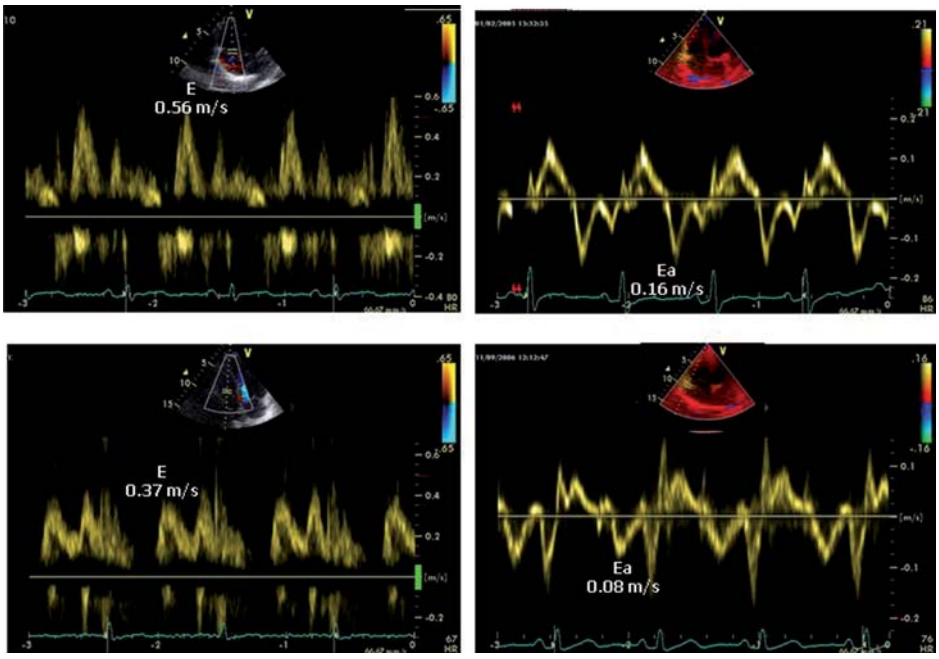

Figure 1 RV E/Ea ratio is 3.5 in a healthy 21-year-old subject (upper panel: left, Doppler tricuspid inflow pattern; right, pulsed Tissue Doppler of lateral tricuspid annulus) and 4.6 in a healthy 64-year-old subject (lower panel: left, Doppler tricuspid inflow pattern; right, pulsed Tissue Doppler of lateral tricuspid annulus).

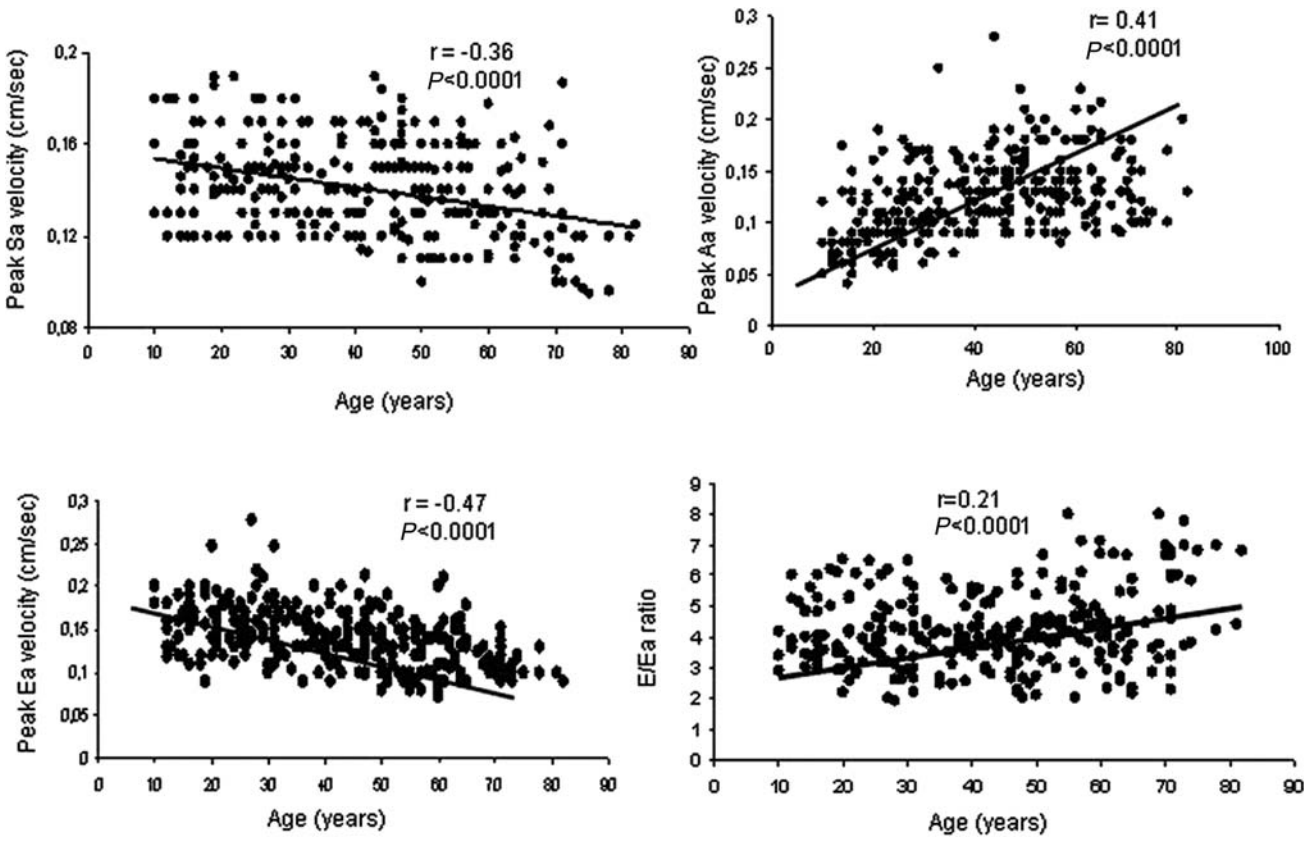

Figure 2 Scatter plot and regression lines of the relation of age with RV Sa peak velocity, Aa peak velocity (upper panel), Ea peak velocity, and E/Ea ratio (lower panel).

progressively reduced and Aa increased with increasing age. RV E/Ea ratio was particularly higher in the last three decades of age (50–59, 60–69, and >70 years). An E/Ea ratio over 6, recognized cut-off point of RAP >10 mmHg,[17] was observed in only 10.1% (30/298) of the study population; 18 of these patients were over 50 and 10 over 70 years.

Table 4 Multiple independent correlates of Tissue Doppler variables in the overall population

	Unstandardized coefficients	Standardized coefficients (beta)	*P*-value	Tolerance
Predictors of tricuspid annulus Sa[a]				
Age	0.000	−0.379	<0.0001	0.75
Body mass index	0.000	0.044	NS	0.92
Heart rate	0.001	0.125	0.02	0.98
Systolic blood pressure	0.000	−0.021	NS	0.75
Predictors of tricuspid annulus Ea[b]				
Age	−0.001	−0.386	<0.0001	0.75
Body mass index	−0.001	−0.108	0.04	0.91
Heart rate	0.000	−0.046	NS	0.96
Systolic blood pressure	0.000	−0.126	0.03	0.75
Predictors of tricuspid annulus Aa[c]				
Age	0.001	0.390	<0.0001	0.74
Body mass index	0.001	0.052	NS	0.92
Heart rate	0.000	0.094	NS	0.98
Systolic blood pressure	0.000	0.039	NS	0.75
Predictors of tricuspid annulus E/Ea ratio[d]				
Age	0.010	0.152	0.02	0.75
Body mass index	0.003	0.007	NS	0.91
Heart rate	0.001	0.007	NS	0.98
Systolic blood pressure	0.014	0.171	<0.01	0.74

[a]Cumulative $R^2 = 0.158$, SE = 0.02 cm/s, $P < 0.0001$.
[b]Cumulative $R^2 = 0.258$, SE = 0.02 cm/s, $P < 0.0001$.
[c]Cumulative $R^2 = 0.180$, SE = 0.04 cm/s, $P < 0.0001$.
[d]Cumulative $R^2 = 0.078$, SE = 1.17, $P < 0.0001$.

Figure 1 depicts an E/Ea ratio in a young (21-year-old) subject and in 64-year old subject, respectively.

Univariate relations of tissue Doppler measurements

Age showed significant correlations with Sa ($r = -0.36$) Aa ($r = 0.41$), Ea ($r = -0.47$), and with E/Ea ratio ($r = 0.21$) (all $P < 0.0001$) (*Figure 2*). Among the other clinical variables, body mass index was significantly related to Ea ($r = -0.23$; $P < 0.0001$), Aa ($r = 0.16$; $P < 0.005$), but not to E/Ea ratio; heart rate was associated with Sa ($r = 0.17$; $P < 0.005$), systolic and diastolic BP were related to Ea ($r = -0.33$; $P < 0.0001$ and $r = -0.19$; $P < 0.001$, respectively) and to Aa ($r = 0.23$; $P < 0.0001$ and $r = 0.12$; $P < 0.02$, respectively).

Among the echocardiographic variables, TAPSE was related to Ea ($r = 0.28$; $P < 0.0001$), Sa ($r = 0.23$; $P < 0.004$), and E/Ea ratio (-0.21; $P = 0.008$). RVPEP was related to Ea and Sa ($r = -0.17$; $P < 0.003$ and $r = -0.18$; $P < 0.002$, respectively). RVET was related to Aa ($r = -0.16$; $P < 0.007$) and RVOT systolic velocity was related to Sa ($r = 0.211$, $P < 0.0001$).

Multiple linear regression analyses

Multiple linear regression analyses were performed to identify the independent association between the main demographic, clinical, and echocardiographic variables and pulsed Tissue Doppler measurements. By these analyses, age was the main independent predictor of Ea, Aa, Sa, and E/Ea ratio, while systolic blood pressure was a contributor of Ea and E/Ea ratio (*Table 4*).

Discussion

The walls of the right ventricle include superficial layers where the fibers are arranged more or less circumferentially, in a direction that is parallel to the atrio-ventricular groove, and deep layers where the fibers are longitudinally aligned base to apex.[33] RV shortening and lengthening are greater longitudinally than radially and, in disagreement with the left ventricle, twisting and rotational motions do not contribute significantly to RV function.[34] In this view, pulsed Tissue Doppler can be considered an optimal technique for the assessment of age-related changes of RV function since it quantifies the longitudinal shortening and lengthening of this chamber. While confirming and extending previously few published data on the impact of age of pulsed Tissue Doppler-derived longitudinal systolic and diastolic measurements of the right ventricle,[27–29] the present study is the first to demonstrate the impact of ageing on RV E/Ea ratio.

Four previous experiences analysed the impact of age on RV myocardial velocities, by using pulsed Tissue Doppler[27–29] or off-line colour Tissue Doppler analysis.[30] Three of these studies[27–29] did not find any relation between age and S_a velocity but age was related with Sa in the study of Kukulski *et al.*[30] This finding is in agreement with the present study where the age-dependent reduction of Sa paralleled the analogous reduction determined by the simple M-mode assessment of the tricuspid annulus (TAPSE). Of note, in our study Tissue Doppler sample volume was placed at the level of the lateral tricuspid annulus, a location which allows a reliable estimate of global RV longitudinal motion, whereas Lindqvist *et al.*[27] and Kjaergaard *et al.*[29] analysed multiple segments of RV lateral wall and Alam *et al.* took into account a small population sample of only 62 subjects. It is conceivable that the

recognized gradual increase of pulmonary arterial systolic pressure developing with age[33,35,36] might exert a significant impact on longitudinal systolic function of the right ventricle. An age-dependent predominant rotational motion with less longitudinal motion of the right ventricle has been already shown by MRI.[37]

A significant negative relation between age and Ea of RV tricuspid annulus had been found in the report of Lindqvist *et al.*[27] and of Alam *et al.*,[28] while Lindqvist *et al.*,[27] Kjaerjaard *et al.*,[29] and again Alam *et al.*[28] showed a positive relation between age and Aa velocity. Kukulski *et al.*[30] observed a negative relation of age with Ea/Aa ratio of RV free wall. Our study confirmed these results since Ea velocity was progressively reduced and Aa velocity increased with advancing age decades. In addition, in the pooled population age was strongly related with Ea (negative relation) and with Aa (positive relation). Age-related changes of RV diastolic function have been demonstrated also by the simple assessment of Doppler tricuspid inflow indices.[38] The age-dependent changes of RV diastolic properties can be attributed to the increase of the arterial stiffness of the pulmonary vessels occurring with ageing.[33,35,36]

To the best of our knowledge, the present study is the first to provide information about the changes of E/Ea ratio of the right ventricle occurring with ageing. This measurement is a well know indicator of invasive RAP, as demonstrated in patients with coronary and other cardiovascular disease undergoing cardiac catheterization,[17] in transplanted patients[26] and in anaesthetized, paralyzed, and mechanically ventilated patients.[39] In the healthy subjects of the present study we found an age-dependent increase of RV E/Ea ratio, which, however, rarely (10%) exceeded the value of 6, an established cut-off value for an invasively measured RAP >10 mmHg,[17] 3% (10/298) of these being over 70 years. Of interest, also the other echocardiographic indexes of RAP (RA minor axis diameter, IVC diameter, and collapsibility index) changes significantly with ageing but the abnormal increase of IVC size (>1.7) observed in five elderly subjects (two over 60 and three over 60) was always combined with an IVC collapsibility index $>50\%$. This combination has been demonstrated to be equivalent to a RAP ranging between 6 and 10 mmHg.[31]

The age-dependent increase of RAP can be attributed to RV overload developing with advancing age.[33,35,36] It is, however, worthy of note that the age-dependence of RV E/Ea ratio observed in the present study was less evident than that previously reported for LV E/Ea ratio.[40] The different loading conditions of the right ventricle in comparison with those occurring in the left ventricle might explain this difference.[41]

Our multiple linear regression analyses provided additional information. Age emerged as the strongest contributor of Sa and Ea reduction and of Aa and E/Ea ratio increase. The association of age with these measurements was independent on the influence exerted by clinical confounders including systolic BP, heart rate, and body mass index. We had found similar results when analysing the impact of age on pulsed Tissue Doppler measurements of the mitral annulus.[40] All together, these data suggest that the physiologic, age-related changes of longitudinal LV and RV (systolic and diastolic) functions, and filling pressures occurs irrespective of changes in commonly used clinical variables.

In conclusion, our findings demonstrate an independent impact of ageing on RV myocardial diastolic and systolic indices and of non-invasively estimated RAP, obtained by pulsed tissue Doppler of tricuspid annulus in a highly selected population of normal subjects. The present study also provides normal values of RV tissue Doppler variables for age decades, which can be used as reference data in order to interpret appropriately the quantitative assessment of longitudinal RV function in patients with cardiac disease.

Conflict of interest: none declared.

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