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ORIGINAL INVESTIGATIONS

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Right ventricular total isovolumic time: Reference value study

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Abstract

Background: There is lack of noninvasive indices to detail the right side cardiovascular physiology. Total isovolumic time (tIVT) is a sensitive marker of left ventricular electromechanical efficiency and systolic-diastolic interaction. The aim of the study was to evaluate normal reference value of the right ventricular tIVT with increasing age.

Methods and results: One hundred and eighty-one healthy volunteers (51% male) underwent transthoracic echocardiography. The population was divided into four categories according to age: A < 30 years; B 30–39 years; C 40–49 years; and C ≥ 50 years old. tIVT was computed in seconds/minutes as: 60 − (tET + tFT). tET and tFT are the total ejection and filling time adjusted by the heart rate, measured, respectively, from the onset to the end of the right ventricle (RV) forward flow through the pulmonary valve and from the onset of the E-wave and the end of the A-wave at the level of the tricuspid valve. The mean RV tIVT was 7 ± 1.1 s/min and increased significantly with age, from a 3.4 to 9.7 s/min($P < 0.0001$). Significant correlation was found between tIVT and trans-tricuspid E/E′ ($P < 0.0001$; 0.78 (95% CI: 0.715–0.831) while weaker between tIVT and E/A ($P = 0.001$; −0.283 95% CI: −0.413 to −0.143).

Conclusion: The normal values of RV tIVT increase with age and correlate significantly with Doppler diastolic parameters.

KEYWORDS

diastolic function, echocardiography, reference values, right ventricle, total isovolumic time

Boffi, Savioli, Greco and Pavesi are joint second author.

This manuscript presents results from a multicentric study performed at: Fondazione Policlinico San Matteo IRCCS, Intensive Care department, Cardiology Department Pavia and Centro Cardiologico Monzino IRCCS, Milano.

1 | INTRODUCTION

Our understanding of the right ventricle in health and disease has lagged behind the left ventricles for many years. In the last decades, many studies have focused on right ventricle (RV) pathophysiology in pulmonary hypertension, left ventricular cardiomyopathy, and ischemic heart disease.[1,2] Echocardiography is widely adopted as first imaging modality of choice for the assessment and monitoring of biventricular function. Despite considerable effort has been dedicated to validate reliable ways to assess the RV, it still remains challenging in the daily practice, especially in patients with suboptimal-to-poor acoustic window. Beside tricuspid annular plane systolic excursion (TAPSE) and pulsed-wave (PW) tissue Doppler to assess the RV systolic function are the most commonly used parameters to assess RV systolic function. Beside those, a number of additional parameters have been studied, including speckle tracking, myocardial acceleration during isovolumic contraction, and 3D echocardiography, but they may carry important limitations in certain patient populations, including the critically ill.[3,4]

The evaluation of cardiac time intervals, since the introduction of the phonocardiogram to the validation of echocardiographic Doppler techniques, has always played a role in the comprehension of the cardiovascular pathophysiology.[5-8]

Left-sided cardiac time intervals are strongly associated with pathophysiology of ischemic cardiac disease and heart failure.[9-12] The total isovolumic time (tIVT) is a sensitive indicator of myocardial ischemia and associated with limitation of cardiac output and VO_2 at peak stress during dobutamine administration in patients with dilated cardiomyopathy (DCM) and coronary artery disease (CAD).[11,13] tIVT is highly predictive of functional, symptomatic, and mortality endpoints in patients with advanced heart failure[14,15] and has a strong correlation with hemodynamic parameters in patients in cardiogenic shock receiving β-adrenergic agents and positive pressure ventilation regardless of volume status.[16]

In patients with congenital heart disease, the right-sided tIVT has been explored in one study showing an excellent correlation with QRS duration, peak oxygen consumption, and exercise capacity.[17,18] Despite being potentially an important parameter for RV evaluation, RV tIVT lacks normal reference values. Therefore, in this study we aimed to define the normal values of RV tIVT in healthy volunteers of different age groups.

2 | METHODS

A total of 181 healthy volunteers with no evidence of cardiac disease detected by echocardiography were evaluated with high-quality echocardiographic images according to a standardized protocol. The study protocol was approved by local hospital ethics committees (Department of Intensive Care and Department of Cardiology Fondazione Policlinico San Matteo, IRCCS Pavia, Italy; Echocardiography Laboratory Ospedale Monzino Milano, Italy). All the participants gave written informed consent.

2.1 | Study population

Subjects with no history of cardiovascular, respiratory, metabolic disease and with normal ECG and blood pressure were enrolled. For the analysis, the population was divided into four categories according to age (range 20–69 years old): A < 30 years; B 30–39 years; C 40–49 years; and C ≥ 50 years old.

2.2 | Echocardiography

Echocardiography was performed with the subject in the left lateral decubitus position using Vivid I and Vivid 7 (GE Healthcare) equipped with a dedicated phased array probe. The frame rate was maintained at 100 frames/s by using a single-focus, narrow imaging sector and appropriate depth. An electrocardiogram was displayed on the ultrasound system. At least three measurements were averaged for each parameter; all the variables measured were taken at end expiration. Left and right ventricular echocardiographic parameters were acquired in accordance with the most recent recommendations.[19,20]

2.2.1 | Total isovolumic time

Tricuspid inflow peak E and A velocities and E-wave deceleration time were measured using PW Doppler with the sample volume placed at the tip of the tricuspid leaflets in modified parasternal long-axis view and in the 4-chamber view. The best signal obtained was then analyzed. Ejection and filling periods were measured as the intervals, respectively, from onset of forward pulmonary flow to the pulmonary valve closure artifact in parasternal short-axis view and from the onset of the E-wave to the end of the A-wave (Figure 1A–B).[11,13] Total ejection time (tET) and total filling time (tFT) were derived as the product of the corresponding time interval and heart rate. For example, the tFT was measured as : ([60 000/RR interval] * FT)/1000.[11] The total isovolumic time (tIVT) was calculated as 60 – (tET + tFT); all the intervals were corrected for the heart rate and expressed as seconds/minute (s/min).[11]

2.3 | Statistical analysis

We used Stata 15 (StataCorp) for computation. A 2-sided *P*-value < 0.05 was considered statistically significant.

We described data with the mean and the standard deviation if continuous and with counts and percent if categorical. We checked normality of the distribution for continuous variables with the q-q plot. We compared echocardiographic measures between age groups and gender with a generalized linear regression model. We measured the association between continuous variables with the Pearson R and its 95% confidence interval (CI). We computed reference limits for RV tIVT according to the nonparametric method (2.5th–95th percentiles) together with their 90% CI. Also, we used fractional polynomials to compute and plot age-specific reference limits, with 95% CIs using the normal model.[21]

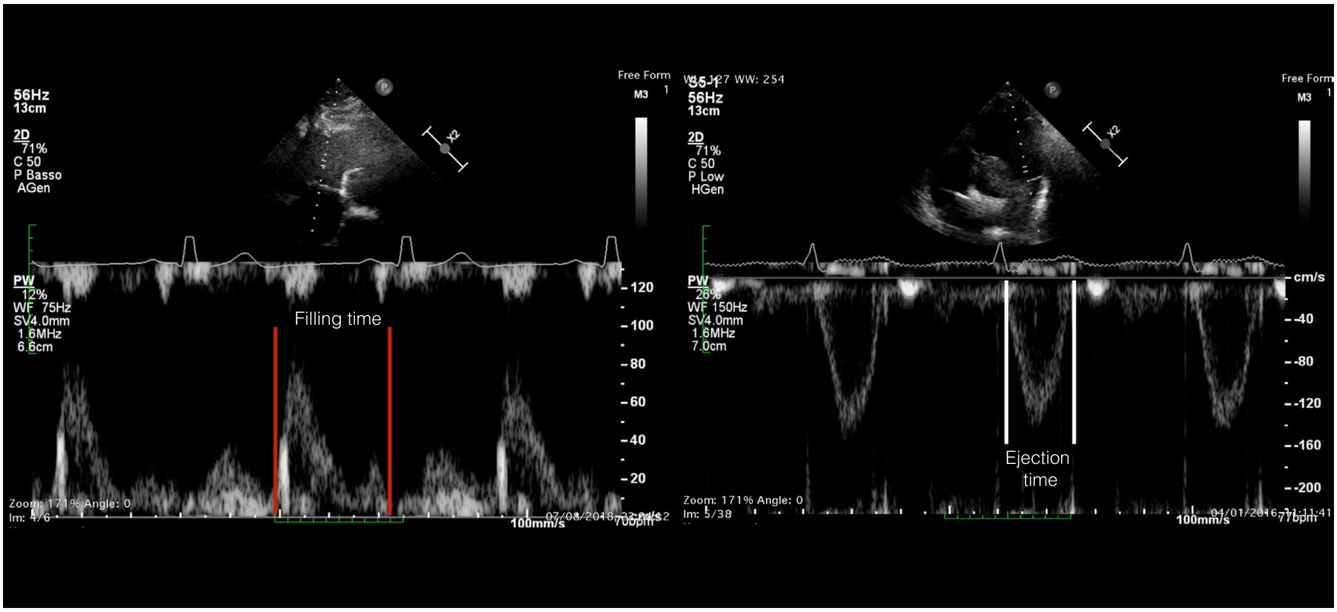

FIGURE 1 Right ventricular total isovolumic time measurement. Left panel: Tricuspid inflow sampled with pulsed-wave Doppler. Filling time (red lines) is measured from the onset of the E (proto-diastolic) and A (tele-diastolic—atrial contraction) waves, and then, the total filling time (tFT) is obtained, measuring the RR interval on the ECG trace, using the following formula: tFT = ([60 000/RR] * FT)/1000. Right panel: Ejection time (ET) is measured from the onset to the end of the pulmonary forward flow (white line). As for the tFT, the total ejection time (t ET) is obtained, measuring the RR interval on the ECG trace, using the following formula: t ET = ([60 000/RR] * ET)/1000. The total isovolumic time is calculated as tIVT (s/min) = 60 − (tFT + t ET)

We assessed the inter- and intra-observer variability with the intra-class correlation coefficient (ICC) using a one-way random-effects model.

3 | RESULTS

Two hundred subjects were initially included; 18 were excluded due to abnormal findings on initial echocardiography (15 valvular abnormalities and 3 rhythm disturbances). Adequate recordings were obtained in all the remaining subjects (100%). Table 1 shows echocardiographic measures of the selected population (51% male). For the parameters measured, the operator intra-observer correlation was, respectively, 0.98 (95% confidence interval of 0.978–0.989) and the inter-observer variability was 0.94 (95% confidence interval of 0.92–0.95).

3.1 | RV tIVT

The mean RV tIVT was 7 ± 1.1; s/min (Table 1) and increased significantly with increasing age, from a minimum of 3.4 s/min to a maximum of 9.7 s/min (r^2 = 0.86, 95% CI: 0.87–0.92, $P < 0.001$).

Parametric reference values are plotted in Figure 2, and age-specific reference limits are detailed in the Data S1 together, while non-parametric reference limits are summarized in Table 2, both overall and by age group.

A strong linear correlation was found between tIVT and trans-tricuspid E/E′ ($P < 0.0001$; R = 0.78 [95% CI: 0.715–0.831]) (Figure 3A), whereas weak but statistically significant correlations were found between tIVT and E/A (P = 0.001; R −0.283 95% CI: −0.413 to −0.143—Figure 3B).

No significance correlations have been evidenced between tIVT and QRS (P = 0.04; R = 0.153; 95% CI: 0.007–0.292) and with the parameters of RV size (EDA $P < 0.05$; ESA $P < 0.05$) and fractional area change ($P < 0.05$)—Figure 4.

The mean value of tFT and tET was, respectively, 32.6 s/min (±2.2 s/min) and 20.2 (±2.1) s/min. Significant differences were found for the tFT between age groups (Table 2), whereas no differences were noted between genders for both cardiac time intervals (Table 1Figure S1).

3.2 | Diastolic parameters and age

The mean RV E- and A-wave velocity was, respectively, 0.52 ms (±0.09 ms) and 0.33 ms (±0.07 ms); significant, but weak, differences were found between groups (Table 2), with older subjects showing lower values of E-wave peak velocity (Figure 5), in accordance with reference values recently published.[20] No differences were noted between male and females ($P > 0.5$). The mean E/A value was 1.64 (±0.32) and varied significantly with age (Table 2). The mean E-wave deceleration time was 207 ms (±48 ms), and significant differences were found with increasing age (Table 2) and between genders (P 0.001) Table 1. Mean E/E′ was 5.1 (±1.3), demonstrating a constant and significant increase with age (Table 2; Data S1—Figure 6).

TABLE 1 Table showing the echocardiographic parameters with the total mean and standard deviation for the entire population, the first and third quartile and the mean for the male and the female population with the *P* value for the difference

	Total (N 181)		Female (N 93)	Male (N 88)	
Parameters	Mean ± SD	1st–3rd quartile	Mean ± SD	Mean ± SD	*P* value
RV tIVT (s/min)	7 ± 1	6.2–7.8	7.1 ± 1	7 ± 1.1	0.59
RV tFT (s/min)	32.6 ± 2.2	31–34.0	32.3 ± 2.2	32.9 ± 2.2	0.06
RV tET (s/min)	20.2 ± 2.1	18.8–21.5	20.5 ± 2.0	19.9 ± 2.2	0.10
RV E (cm/s)	0.52 ± 0.09	0.46–0.59	0.53 ± 0.10	0.52 ± 0.09	0.58
RV A (cm/s)	0.33 ± 0.07	0.28–0.36	0.33 ± 0.07	0.32 ± 0.07	0.72
RV Dec Time (s)	207.5 ± 47.6	173.5–240	195.3 ± 41.4	218.9 ± 50.3[†]	0.001
RV E/A	1.6 ± 0.3	1.4–1.8	1.6 ± 0.3	1.6 ± 0.3	0.54
RV E/e′	5.1 ± 1.3	4–6.1	5.1 ± 1.2	5.1 ± 1.4	0.93
TAPSE (mm)	24.2 ± 3	22–26	24.2 ± 3.2	24.2 ± 2.9	0.91
RVEDA (cm^2)	17.8 ± 5.1	14.2–21	14.8 ± 3.3	20.7 ± 4.8	<0.001
RVFAC (%)	46.3 ± 9	41.4–52.5	48.6 ± 8	44.4 ± 9.4	<0.001
RV basal (mm)	30.7 ± 5.2	27–34	28.4 ± 4.8	32.8 ± 4.7	<0.001
MPI	0.34 ± 0.08	0.28–0.39	0.34 ± 0.08	0.34 ± 0.07	0.9
PV ACC time	154 ± 21	142–166	154 ± 20	155 ± 21	0.7

Abbreviations: A = peak PW Doppler A-wave; annular = basal right ventricle diameter in apical 4 chamber view; Dec time = deceleration time; E = peak E-wave; e′ = peak e′ wave; EDA = end-diastolic area; FAC = fractional area change; RV = right ventricle; TAPSE = tricuspid annular systolic excursion; tET = total ejection time; tFT = total filling time; tIVT = right ventricle total isovolumic time.

3.3 | Right ventricular systolic function and size

The mean TAPSE was 24.2 mm (±3) and did not vary significantly with age or gender. Fractional area was significantly different among gender and age (respectively, $P < 0.001$ and $P < 0.01$—Tables 1,2).

Right ventricle end-diastolic area and annular diameter were, respectively, 17.8 cm^2 (±5.12) and 30.7 mm (±5.2) and were significantly different between genders ($P < 0.001$—Table 1) and age ($P < 0.05$—Table 2).

Myocardial performance index (MPI) measured with pulse wave Doppler[22] did not show any difference between gender (*P* 0.9) and a weak difference among group age (*P* 0.004 r^2 0.06) – Table 1,2; Figure S2.

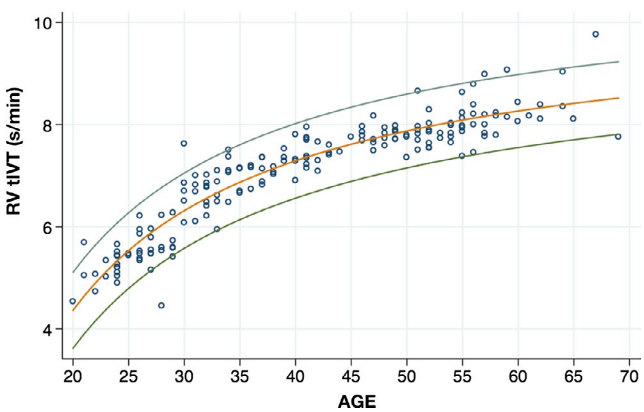

FIGURE 2 Right ventricular total isovolumic time values plotted with age. RVtVIT in s/min

4 | DISCUSSION

This is the first study providing systematic data regarding reference values for RV tIVT in a cohort of healthy volunteers, well distributed for age and gender, in addition to comprehensive RV Doppler parameters and chamber dimensions.

Total isovolumic time represents the time during which the ventricles neither eject nor fill. LV tIVT has been widely validated in different cohorts of patients, and a value > 14 s/min was defined as an index of dyssynchrony and reduced electromechanical efficiency.[11,13,15,23] Ventricular segments that are dyssynchronous between each other have a detrimental impact during both contraction and relaxation reducing the time available, respectively, for both ejection and filling.[17] It has been shown that a good correlation exists between reduction of the LV tIVT using cardiac resynchronization therapy and a significant improvement in cardiac output and symptoms in patients with heart failure and prolonged tIVT.[13,24]

Total isovolumic time normal values are significantly shorter in the right as compared with the left ventricle, reflecting differences in physiology between the two chambers. Unlike the LV, that has a trapezoidal pressure volume loop pattern with well-defined isovolumic periods, the normal RV has a completely different isovolumic pattern. Whereas the aortic dicrotic notch and the termination of ejection occur shortly after the onset of pressure decline, a continued ejection occurs from the RV during the phase of pressure fall, resulting in a very poorly defined phase of isovolumetric relaxation.[25] Moreover, the RV exhibits a very short phase of isovolumetric contraction as ejection into pulmonary arteries starts very early during pressure rise, reflecting low-impedance high compliance

TABLE 2 Echocardiographic measures by class of age with mean and standard deviation

Parameters	Age < 30 y (n°42) Mean ± SD	Age 30–39 (n°46) Mean ± SD	Age 40–49 (n°38) Mean ± SD	Age ≥ 50 (n°55) Mean ± SD	*P* value	r^2
RV tIVT	5.43 ± 0.4*	6.9 ± 0.3*	7.6 ± 0.2*	8 ± 0.4*	<0.001	0.86
RV tET	20.5 ± 2.5	20.6 ± 2.2	19.9 ± 2	19.8 ± 20.2	0.16	0.02
RV tFT	33.9 ± 2.4	32.4 ± 2.3†	32.4 ± 2†	32 ± 1.7*	<0.001	0.1
RV E (cm/s)	0.5 ± 0.06	0.55 ± 0.08	0.50 ± 0.1†	0.4 ± .1*	<0.001	0.13
RV A (cm/s)	0.3 ± 0.05	0.33 ± 0.07	0.34 ± 0.07	0.3 ± 0.07	<0.001	0.02
RV Dec Time (s)	209.1 ± 33.7	190.3 ± 37.9	178.6 ± 32.5*	241.2 ± 53*	<0.001	0.26
RV E/A	1.7 ± 0.2	1.7 ± 0.2	1.4 ± 0.3*	1.5 ± 0.3†	<0.001	0.12
RV E/e′	3.5 ± 0.4	4.6 ± 0.7*	5.7 ± 0.7*	6.3 ± 0.9*	<0.001	0.66
TAPSE (mm)	24.4 ± 3.2	24.3 ± 2.8	24.2 ± 3.4	24 ± 2.8	0.95	0.001
RVFAC (%)	41.4 ± 8.0	48.2 ± 7.5*	46 ± 8.5	48.9 ± 10.1	0.01	0.06
RVEDA (cm^2)	18.1 ± 3.8	16.3 ± 4.8	18 ± 6.5	18.8 ± 4.9	0.08	0.03
RV basal (mm)	34.4 ± 5.3	30.3 ± 4.5*	29 ± 5.3*	29.4 ± 4.4*	<0.001	0.15
MPI	0.31 ± 0.06†	0.34 ± 0.07	0.36 ± 0.09†	0.33 ± 0.08	0.004	0.06
PV Acc time	157 ± 16	156 ± 25	153 ± 20	154 ± 22	0.7	0.006

Notes: Table showing the echocardiographic measures by class of age with mean and standard deviation. In the last column, the *P* value and *r*-squared for linear regression.

Abbreviations: A = peak PW Doppler A-wave; annular = basal right ventricle diameter in apical 4 chamber view; Dec time = deceleration time; E = peak E-wave; e′ = peak e′ wave; EDA = end-diastolic area; FAC = fractional area change; RV = right ventricle; TAPSE = tricuspid annular systolic excursion; tET = total ejection time; tFT = total filling time; tIVT = total isovolumic time.

P value for the post hoc comparison between classes of age:†<0.05; *<0.001.

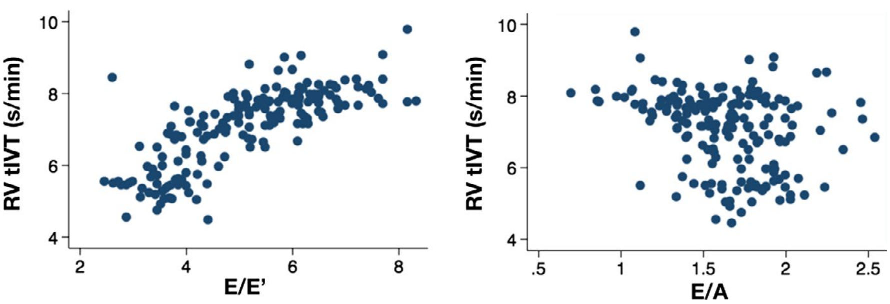

FIGURE 3 On the left scatter plot of right ventricle (RV) total isovolumic time (tIVT) (in seconds/minute) vs E/E′ showing a strong linear correlation (*R* = 0.78 *P* < 0001). On the right scatter plot of RV tIVT vs E/A showing a weak linear correlation (*R* = −0.283, *P* = 0.001)

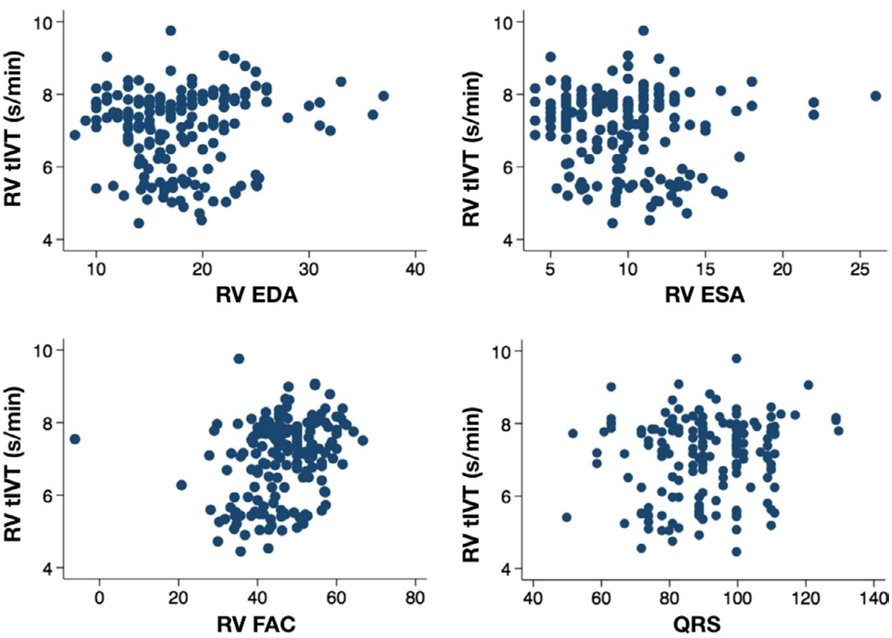

FIGURE 4 Scatter plot of right ventricle (RV) total isovolumic time (seconds/minute) vs RV end-diastolic area (RVEDarea in cm^2, top left; *P* = 0.09), RV end systolic area (RVESarea in cm^2, top right; *P* = 0.26), RV fractional area change (RVFAC in %, bottom left, *R* = 0.275 *P* < 0.001), and QRS duration (in seconds, bottom right, *R* = 0.15 *P* = 0.04)

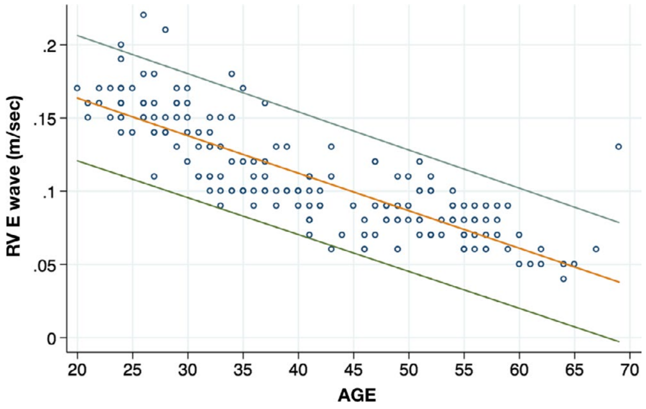

FIGURE 5 Linear regression normal model for right ventricle e′ (RVE in cm/s) showing constant decrease with age. The lines represent the 2.5th, 50th, and 97.5th percentiles

circulation (under normal conditions) and making the RV extremely sensitive to load conditions.[26] The prolongation of RV tIVT over decades may depend on the physiological age-associated pulmonary arterial remodeling, increasing blood vessel stiffness and modification in RV diastolic performance[27] Our knowledge on the right ventricular pathophysiology has increased mainly through the study of pulmonary hypertension. However, many functional and morphological changes occur before clinical hemodynamic alterations and before changes detectable with commonly used echocardiographic parameters (wall thickness, FAC, longitudinal function, RV EDA/LV EDA).[28,29] There is still a lack of reliable, reproducible, and noninvasive indices allowing the evaluation of right ventricular failure in the early phase. MPI has been published more than 20 years ago, and it has showed a good correlation with invasive parameters of RV function in patients with pulmonary hypertension.[30] However, a comparison study between tIVT and MPI found a higher sensitivity for tIVT in detecting abnormalities of ventricular activation in a variety of cardiac conditions.[31]

The relevance of RV function in pathology is becoming increasingly apparent. However, a comprehensive evaluation of its physiology and pathophysiology in all settings in which the RV plays a key

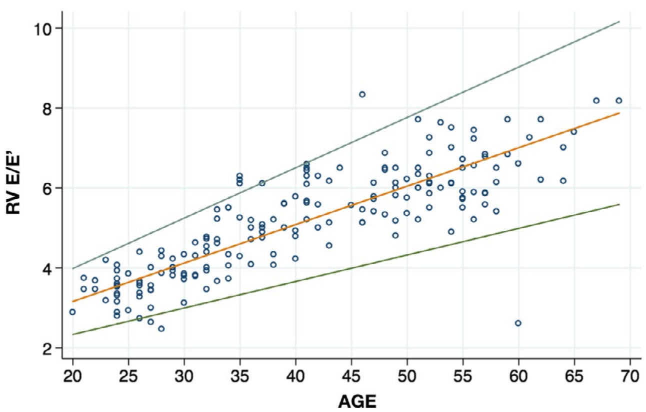

FIGURE 6 Linear regression normal model for E/e′ (EE) showing a constant increase with age. The lines represent the 2.5th, 50th, and 97.5th percentiles

role in the hemodynamic profile (PH, ARDS, sepsis, ischemia, etc.) remains extremely challenging. RV tIVT is a new index that varies with age potentially detecting subtle, but physiological, changes systo-diastolic performance. It may have important applications in evaluating the extent of RV systolic and diastolic dysfunction regardless of the underlying etiology.

4.1 | Limitations

The RIVITA study included only Caucasian subjects; thus, the results may not apply to other ethnic populations. Although all subjects were considered normal, we cannot exclude the possibility of subclinical coronary artery disease, which can influence the values of systolic and diastolic parameters.

5 | CONCLUSIONS

Despite the increased awareness of the role of RV function in many pathological conditions, reliable and accurate noninvasive indices to assess the complex right side cardiovascular in disease are lacking. In healthy volunteers, RV total isovolumic time varies significantly with age and was found to correlate with commonly used diastolic indices. Considering the established clinical utility of the left ventricular tIVT, the validation of RV tIVT as index of systolic-diastolic interaction, with potential clinical implications, appears warranted.

CONFLICT OF INTEREST

None.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Right ventricular total isovolumic time values plotted with age in female (left panel) and male (right panel). RVtVIT in s/min.

Figure S2. Myocardial performance index (MPI) values plotted with Age.

Data S1. Nonparametric reference limits for the right total isovolumic time in s/min, together with their 90% CI. Overall values and by age group in years.

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