Reference Ranges and Determinants of Tricuspid Regurgitation Velocity in Healthy Adults Assessed by Two-Dimensional Doppler-Echocardiography

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Keywords

Tricuspid regurgitation velocity · Healthy subjects · Doppler-Echocardiography · Reference ranges

Abstract

Background: Tricuspid regurgitation velocity (TRV) is the most widely used parameter by transthoracic echocardiography (TTE) in the evaluation of patients with suspected pulmonary hypertension (PH). **Objectives:** To explore the physiologic range of TRV in healthy adults and to investigate its clinical determinants. **Methods:** In the first part of the study, 614 healthy individuals (age 45.7 ± 14.7 years, 60.26% women) were prospectively assessed by TTE. In the second part, a pooled meta-analysis of 16 already published studies with TRV values in healthy subjects ($n = 981$) was performed. Sta-

tistical analysis included the calculation of 95% quantiles for defining reference ranges. **Results:** In the prospectively enrolled cohort, mean TRV was 2.01 ± 0.29 m/s (5–95% CI 1.987–2.033 m/s). It was significantly but weakly positively correlated with age, body mass index, systolic blood pressure, diastolic blood pressure, left atrial volume and negative with mitral inflow E/A ratio. No significant differences were found between males and females. The prospectively enrolled data revealed similar values to the literature-based datasets resulting in a mean TRV of 1.96 m/s (95% CI 1.91–2.02 m/s) and a 95% quantile of 2.55 m/s. **Conclusions:** To the best of our knowledge, this is the largest dataset to describe reference ranges of TRV and their clinical determinants in healthy adults years. The determined cut-off value of 2.55 m/s of this study has to be confirmed in specific pathologies such as patients at risk of PH.

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Introduction

Pulmonary hypertension (PH) occurs in many different diseases and is defined as an increase in mean pulmonary arterial pressure (PAPm) ≥ 25 mm Hg assessed by right heart catheterization (RHC) [1]. Recent data has shown that the normal PAPm at rest is 14 ± 3 mm Hg with an upper limit of normal of approximately 20 mm Hg [2]. In the new joined guidelines of the European societies for respiratory medicine and cardiology for the diagnosis and treatment of PH, transthoracic color-Doppler-echocardiography (TTE) plays a central role in diagnostic work-up [1, 3, 4]. It should be used to visualize the effects of PH on the heart and to estimate systolic pulmonary artery pressures through continuous wave Doppler measurements. The European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines recommend grading the probability of PH based on tricuspid regurgitation velocity (TRV) at rest as high (≥ 3.5 m/s), intermediate (2.9–3.4 m/s) or low (≤ 2.8 m/s), and on the presence of additional echocardiographic variables that suggest PH [1]. Based on these echocardiographic parameters and further clinical findings, a decision must be made about whether RHC is necessary.

Echocardiography should always be performed when PH is suspected or in PH patients in follow-up assessments [1, 3, 5, 6]. In this regard, TRV is a well-established and most widely used TTE parameter for non-invasive determination of pulmonary pressure [7]. However, the cut-off values proposed in the current ESC/ERS guidelines for establishing the probability of PH are more or less arbitrary and have not yet been scientifically evaluated or validated for PH [3, 4, 8]. Retrospective data from a large cohort of patients with high pre-test probability suggests that in experienced hands determining the systolic pulmonary artery pressure using the TRV and estimated right atrial pressure (RAP) correlated well with the invasively measured values ($r = 0.87$) and, when the suggested limit (36 mm Hg) was used, it has a specificity of 79% and a sensitivity of 87% to detect PH [9]. However, in routine clinical practice, large deviations can occur in individual cases, and only 90% of patients with PH had tricuspid regurgitation [10]. Furthermore, the physiologic spectrum of TRV in healthy subjects remains unclear. The aim of this study was to explore the full range of TRV in a large cohort of healthy adults and to perform a meta-analysis of all previously reported normal values, in order to define TRV cut-off values. Furthermore, we want to identify clinical determinants of TRV-values.

Methods

In the first part of this study, we prospectively assessed consecutive healthy volunteers or healthy subjects being referred for work ability assessment by clinical work-up as previously described [11–13]. Indeed the “Cava de’ Tirreni and Amalfi Coast” Hospital is responsible for the assessment of working eligibility for the local area. Examinations included a questionnaire on medical history, use of medications, cardiovascular risk factors and lifestyle habits (alcohol intake, smoking, physical activity). Physical examinations (height, weight, heart rate [HR] and blood pressure [BP]) and clinical assessments were conducted according to standardized protocols by trained and certified staff (F.F. and E.B.). Body surface area (BSA) was calculated according to the DuBois formula ($BSA = 0.20247 \times \text{height [m]}^{0.725} \times \text{weight [kg]}^{0.425}$). Exclusion criteria were coronary artery disease, systemic arterial hypertension, diabetes mellitus, significant (at least moderate) valvular heart disease, congenital heart disease, congestive heart failure, cardiomyopathies, sinus tachycardia, atrial fibrillation or flutter, use of illicit drugs, elite athletes and inadequate echocardiographic image quality [14]. Three BP measurements were obtained from the right arm by sphygmomanometer and the results were averaged to determine systolic and diastolic BP. Pulse pressure was calculated as the difference between brachial systolic and diastolic BP. None of the subjects had cardiovascular structural or functional abnormalities or received any medication.

In the second part of the study, a systematic literature search and pooled meta-analysis was performed. The study was approved by the institution’s ethics board and informed consent was obtained from the participants. The work has been carried out in accordance with the code of Ethics of the World Medical Association (Declaration of Helsinki).

TTE examinations were performed with commercially available equipment (Vivid 7 – GE Healthcare, Milwaukee, WI, USA) as previously described [15]. Specific views included the parasternal long- and short-axis views, apical 4, 2 and 3 chamber (CH) views and subcostal views including respiratory collapse of the inferior vena cava. Pulsed and continuous wave Doppler interrogation was performed on all 4 cardiac valves. Images were recorded digitally and later analysed by 2 independent observers (F.F. and L.C.) using off-line software (EchoPAC – Clinical Workstation Software – GE Healthcare, Milwaukee, WI, USA). All measurements were performed according to the recommendations for echocardiographic assessment of the left and right heart by the American Society of Echocardiography/European Association of Cardiovascular Imaging, available in the enrolment period (June 2007 to February 2014), as previously reported [12, 14, 16, 17].

Taking into account that TRV measurements are angle dependent, TRV was assessed from multiple views, searching for the best envelope and maximal velocity. Peak TRV was measured from the spectral profile of the tricuspid regurgitation jet in the right ventricular (RV) inflow projection of the parasternal long-axis view, the parasternal short-axis view, or the apical 4-chamber view. Care was taken in order to ensure the best alignment between regurgitant flow and the Doppler signal velocity. The highest trans-valvular velocity was used for calculation of TRV [14].

TRV is presented as mean $\pm$ SD. Normal distribution of the continuous values was assessed by the Kolmogorov-Smirnov test.

Table 1. Demographic characteristics of study population

	Overall (<i>n</i> = 614)			Women (<i>n</i> = 370)	Men (<i>n</i> = 244)	<i>p</i> value
	mean ± SD	median	range	mean ± SD	mean ± SD	women vs. men
Age, years	45.73±14.7	48.00	16.00–88.00	46.81±14.5	44.09±14.8	0.025
BMI, kg/m ²	24.59±2.96	24.61	17.71–31.56	24.11±2.98	25.34±2.76	0.0001
BSA, m ²	1.76±0.19	1.75	1.06–2.76	1.67±0.14	1.9±0.17	0.0001
Systolic BP, mm Hg	122.54±12.49	120.00	90.00–150.00	121.2±13.19	124.57±11.07	0.001
Diastolic BP, mm Hg	76.29±7.97	80.00	50.00–90.00	75.26±8.08	77.86±7.54	0.0001
Pulse pressure, mm Hg	46.25±10.06	45.00	20.00–80.00	45.94±10.16	46.71±9.9	0.358
HR, beats/min	73.02±11.18	71.00	45.00–100.00	74.73±10.67	70.41±11.45	0.0001

BMI, body mass index; BP, blood pressure; BSA, body surface area; HR, heart rate.

Variables were compared between men and women using the 2-sided unpaired *t* test. As upper cut-off values for normal TRV for women and men, we used the 95% quantile. Partial correlation (Pearson) was used to assess univariate relations. The variables were selected according to their clinical relevance and potential impact on TRV. TRV was also analysed according to age classes (<30, 31–50, 51–70, and >70 years) and BMI classes (<18, 18–25, 25–30, and >30 kg/m²) with ANOVA. Bland-Altman graphs were used to plot the difference between 2 observations versus the mean of the observations to look for overall bias as well as for systematic variation with increased measurement of TRV as described elsewhere [18]. The interobserver variability was examined using both paired *t* tests and intraclass correlation coefficients (ICCs) in 100 randomly selected cases. An ICC of >0.8 indicated good agreement. Analyses were performed by a biometrician (N.B.).

This study was designed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement [19]. A systematic literature search was performed using Medline, Scopus, ISI Web of Sciences and Cochrane Database for studies published between January 1985 and April 2017 reporting echocardiographic TRV-measurements in healthy subjects. Only records in English reporting absolute TRV values were included in the meta-analysis. Studies with unclear echocardiographic techniques or status of subjects were excluded. Studies were identified by the following headings: “right heart,” “right ventricle,” “tricuspid regurgitation velocity,” “systolic pulmonary arterial pressure,” “echocardiography,” “echocardiogram,” “echocardiograms,” “Doppler,” “ultrasounds” combined with “healthy,” “healthy individuals,” “healthy subjects,” “sane,” “control group,” “controls.” Because only aggregated data, namely, means, SD and sample sizes, are given in the literature, the pooled TRV mean and the pooled SD were used in order to estimate the 95% percentiles and respective 5–95% CIs. Mean, 5–95% CI and 95% were weighted according to sample size. To analyse the influence of single studies on the pooled estimate, a sensitivity analysis was performed by leaving out one study at a time, calculating the pooled estimates with the remaining studies [13]. All statistical analyses were performed with using SPSS, Version 21 (Chicago, IL, USA).

Results

Prospective Study

From June 2007 to March 2017, a sample of 675 healthy subjects was prospectively and consecutively studied by TTE at the Cardiology Division, “Cava de’ Tirreni-Amalfi Coast,” Heart Department, University Hospital of Salerno, Italy. Among these, 61 subjects (9%) were excluded due to TRV that was not assessable. The final study cohort consisted of 614 healthy individuals (mean age 45.73 ± 14.67 years, range 18–88 years; 370 [60.26%] women; Table 1). Compared with men, women were older, had lower body dimensions (BSA and BMI), lower systolic and diastolic BP and higher HRs (Table 1).

Males had higher right and left ventricular (LV) dimensions, as shown by higher values of LV end-diastolic and LV end-systolic volumes, LV mass, and RV diameters. On the other hand, no differences in LV ejection fraction, LV diastolic function and tricuspid annular plane systolic excursion were registered between men and women (Table 2).

TRV showed a normal distribution (2.00 ± 0.29 m/s, 5–95% CI 1.98–2.03 m/s, range 1.10–2.85 m/s; Fig. 1). No differences (*p* = 0.615) were found between males (2.01 ± 0.31 m/s) and females (2.00 ± 0.27 m/s). In the univariate analysis, TRV was significantly but weakly positively correlated with systolic BP (*r* = 0.151, *p* = 0.0001), diastolic BP (*r* = 0.095, *p* = 0.018) and LA volume (*r* = 0.097, *p* = 0.02). TRV correlated negatively and weakly with mitral inflow E/A ratio (*r* = −0.109, *p* = 0.007). TRV varied significantly according to age classes (*p* = 0.002; Fig. 2) and BMI (*p* = 0.001, data not shown). The Bland-Altman analysis (Fig. 3) gave a mean difference of 0.0106 m/s (5–95% CI −0.14 to 0.16 m/s). The interobserver variability

Table 2. Left and right heart dimension and function

	Overall (<i>n</i> = 614)			Women (<i>n</i> = 370)	Men (<i>n</i> = 270)	<i>p</i> value
	mean ± SD	median	range	mean ± SD	mean ± SD	women vs. men
LA volume/BSA, mL/m ²	18.31±4.01	17.85	8.92–32.77	18.41±3.84	18.17±4.24	0.473
LV-ED volume/BSA, mL/m ²	37.08±7.78	35.36	19.20–69.51	35.37±6.78	39.66±8.48	0.0001
LV-ES volume/BSA	13.16±3.43	12.21	7.24–28.73	12.66±3.11	13.92±3.76	0.0001
LV-EF, %	65.06±4.91	65.00	54.00–79.00	64.99±4.62	65.16±5.33	0.662
LV mass, g	136.5±33.87	132.00	62.00–242.00	121.58±26.84	159.13±30.76	0.0001
Mitral E/A inflow ratio, cm/s	1.25±0.41	1.24	0.53–2.79	1.25±0.41	1.26±0.39	0.39
E/e'ratio	6.62±1.69	6.31	3.61–14.72	6.73±1.69	6.44±1.67	0.36
MDT, ms	183.37±35.44	179.50	109.0–368.0	183.95±35.87	182.49±34.84	0.62
RV diameter base, mm	33.69±3.19	3.19	25.00–39.00	32.49±2.97	35.50±2.60	0.0001
RV diameter mid cavity, mm	26.88±3.45	3.48	20.00–39.00	25.59±2.93	28.83±3.24	0.0001
TAPSE, mm	22.63±2.28	22.00	17.00–29.00	22.60±2.27	22.69±2.31	0.645

TAPSE, tricuspid annular plane systolic excursion; RV, right ventricle; MDT, mitral deceleration time; LV, left ventricle; EF, ejection fraction; BSA, body surface area; ES, end-systolic; ED, end-diastolic; LA, left atrial.

analysis revealed ICCs of 0.959 for the single measure (5–95% CI 0.940–0.973) and 0.979 for the average of measures (5–95% CI 0.969–0.989).

Meta-Analysis of Previous Published Studies Pooled with the Prospectively Collected Data

Table 3 reports the description of the 16 studies found in medical literature reporting TRV values in healthy subjects. Out of 5,389 records detected by screening of the Medline and Cochrane database for TRV using the aforementioned keywords, 90 full-text papers were identified. Seventy-four papers were excluded for several reasons (mainly because the TRV values were not reported). A total number of 16 papers published between 1992 and 2016 was identified (Fig. 4) [10, 20–34]. The pooled analysis of the previously published studies and the current cohort included 1,595 subjects in total. Correlation analyses regarding age and BSA or analyses of differences between sex and training status were not possible because only mean values of TRV were given and no analysis for determinants had been reported in the literature. In all studies, subjects were classified as healthy and free of cardiovascular diseases. Most studies had performed chest X-ray, electrocardiograms and physical examinations to exclude any cardiovascular or respiratory disease. Overall, the assessed subjects were between 18 and 80 years old. The sample size ranged from 14 to 230 subjects per study. All studies, except one [21] included subjects of both sexes. Figure 5 shows the 95% quantiles and CIs of TRV of previously published studies and our prospective

Fig. 1. Distribution of tricuspid regurgitation velocity (TRV) in the prospectively enrolled cohort.

data. Pooled data resulted in a weighted mean TRV of 1.96 m/s (95% CI 1.90–2.01 m/s) and a 95% quantile of 2.55 m/s (95% CI 1.90–2.01 m/s).

The influence of each study was analyzed by leaving out one study at a time. If the data of the current study was excluded from the pooled analysis, the cut-off value would be slightly higher (95% quantile: 2.59 m/s; 95% CI 1.86–2.02 m/s). The leave-one-out estimates for the 95% quantiles varied between 2.53 and 2.68 m/s. Three out of

614 prospectively enrolled subjects had a TRV measurement higher than 2.8 m/s, which is the cut-off suggested by current guidelines. Similar results were obtained when excluding these patients (data not shown).

Discussion

To the best of our knowledge, the current report represents the largest dataset dealing with TRV in healthy individuals. The main finding is that the 95% quantile of TRV in a healthy population corresponds to 2.55 m/s, which is lower than the current cut-off of 2.8 m/s, suggested by the guidelines of PH [1].

TRV is widely used in daily clinical practice, given its linear positive correlation with sPAP in the absence of RV outflow tract obstruction and/or pulmonic valve stenosis, through the Bernoulli formula ($4 \times [\text{TRV}]^2 + \text{RAP}$) [3, 35, 36]. The accuracy and the precision of estimation of pulmonary pressures with TTE with regards to RCH measurements were investigated by D'Alto et al. [7] among 161 patients referred to an echo-lab for the suspicion of PH. According to D'Alto and colleagues, TTE allows accurate measurement of pulmonary pressures (bias and confidence intervals: ± 3 mm Hg, ± 5 mm Hg, for mPAP and LAP, respectively) but with moderate precision (lower limit mean $-SD$ /upper limit $+SD$: $+19$ and -18 mm Hg for mPAP respectively, and $+8$ and -12 mm Hg for LAP) leading to the conclusion that the estimation of pulmonary pressure by TTE is valid for population studies but might not be appropriate for the individual diagnosis of PH [7]. In light of all these aspects, current ESC/ERS joint guidelines on PH [1], as well as American Society of Echocardiography guidelines on right chambers assessment [16], suggest that a TTE be performed whenever a PH is clinically suspected, due to the utmost importance of an early PH diagnosis, regardless of its cause. Along with other echocardiographic indexes and clinical signs, guidelines recommend the use of the absolute value of TRV and not the estimated sPAP as main value to confer the echocardiographic probability of PH [1]. Indeed, they indicate that PH diagnosis can be excluded with a high likelihood for patients with a TRV less than 2.8 m/s [1]. Kovacs et al. [2] performed a comprehensive systematic review on 1,187 individuals from 47 studies in 13 countries in order to determine the normal values of pulmonary pressures assessed by RHC. In this study, an upper limit of normality of 29.6 mmHg was found for sPAP. According to Bernoulli formula and assuming a RAP of 5 mm Hg, the upper limit of normality suggested by our

Fig. 2. Tricuspid regurgitation velocity (TRV) according to different age classes.

current report (2.55 m/s) would lead to an estimated sPAP of 31.01 mm Hg, an upper limit very close to 29.6 mm Hg reported by Kovacs et al. [2]. Interestingly, our results are in line with the results of a previous prospective study from Grünig et al. [13] assessing 191 healthy controls [22] and identifying a TRV at rest of 1.96 ± 0.25 m/s, which was not correlated with gender [22]. McQuillan et al. [37] evaluated TRV retrospectively from a database not explicitly excluding patients with coronary artery disease and/or pulmonary diseases. In this study, 95% upper limit was equivalent to a TRV of 2.61 m/s. However, the higher values may be due to a different cohort as in-hospital patients were assessed.

In our prospectively enrolled cohort, TRV was very weakly positively correlated with age and BMI. The linear relation between cardiac output and BMI is well established, leading to the speculation that subjects with higher body mass have higher cardiac output and consequently slightly higher pulmonary pressures [38]. However, our data and a previous prospective study [22] do not support this assumption, given the low correlation between BMI and TRV that we found. Indeed, only 2.5% of the TRV data might be explained by age.

Other indices weakly correlating with TRV were arterial BP, LA volume and diastolic function. All these parameters are associated with a backward transmission of pressure from the left ventricle to the pulmonary circulation [39]. Although right heart dimensions in healthy adults vary in the 2 sexes [13, 15], with men having larger RV [13] and RA [15] than women, pulmonary pressure values are similar in men and women in physiologic states [2], albeit women are more prone to develop PH

Fig. 3. Bland Altman plot of tricuspid regurgitation velocity (TRV) assessment between the two operators. The red thick line represents mean difference and the red thin lines represent 95% of the confidence interval. The blue thin lines represent the limits of agreement (5–95% CI).

Table 3. Pooled studies reporting TRV values in healthy subjects

Author	Year	Country	Setting	Sample <i>n</i>	Females <i>n</i>	Age, years mean $\pm$ SD	TRV, m/s mean $\pm$ SD	TRV, m/s 95% CI	TRV, m/s 5–95% quantile
Jobic [14]	1992	France	Healthy volunteers	32	7	29.4 $\pm$ 7.9	2.13 $\pm$ 0.26	2.04–2.22	1.70–2.55
Bossone [15]	1999	USA	Control vs. Athletes	14	0	18.0 $\pm$ 0.9	1.70 $\pm$ 0.11	1.64–1.75	1.51–1.88
Aessopos [16]	2000	Greece	Healthy volunteers	53	34	38.9 $\pm$ 12.7	2.10 $\pm$ 0.23	2.03–2.16	1.72–2.47
Bossone [17]	2000	USA	Controls vs. PH	22	12	38.4 $\pm$ 8.3	2.30 $\pm$ 0.25	2.19–2.40	1.88–2.71
Aliyu [18]	2008	Nigeria	Controls vs. SCD	94	29	33.0 $\pm$ 12.0	1.80 $\pm$ 0.5	1.69–1.90	0.97–2.62
Van Dijk [19]	2008	The Netherlands	Controls vs. LBBB	15	7	61.0 $\pm$ 5.0	2.56 $\pm$ 0.31	2.40–2.71	2.05–3.07
Mahjoub [20]	2009	France	Healthy volunteers	70	36	48.0 $\pm$ 16.0	2.00 $\pm$ 0.20	1.95–2.04	1.67–2.32
Sahin [21]	2009	Turkey	Controls vs. HT	30	22	47.4 $\pm$ 10.5	2.05 $\pm$ 0.30	1.94–2.15	1.55–2.54
Grünig [22]	2009	Germany	Controls vs. relatives of IPAH and HPAH	191	78	37.0 $\pm$ 16.0	1.96 $\pm$ 0.25	1.92–1.99	1.54–2.37
Celik [23]	2011	Turkey	Controls vs. PTE	20	11	56.0 $\pm$ 7.0	1.70 $\pm$ 0.30	1.56–1.83	1.20–2.19
Grapsa [24]	2012	UK	Controls vs. PAH	30	22	nr $\pm$ nr	1.60 $\pm$ 0.30	1.49–1.70	1.10–2.09
D’Andrea [25]	2013	Italy	Controls vs. Athletes	230	90	27.5 $\pm$ 11.3	1.80 $\pm$ 0.70	1.71–1.89	0.64–2.95
D’Andrea [26]	2013	Italy	Controls vs. HTR	80	51	56.8 $\pm$ 5.2	1.90 $\pm$ 0.50	1.79–2.01	1.07–2.72
Zimbarra-Cabrita [27]	2013	UK	Controls vs. PAH	37	21	44.7 $\pm$ 16.4	2.30 $\pm$ 0.24	2.22–2.37	1.90–2.69
Vasconcelos [28]	2015	Brazil	Controls vs. SCD	20	11	27.5 $\pm$ 7.0	2.20 $\pm$ 0.20	2.11–2.28	1.87–2.52
Lin [29]	2016	China	Controls vs. CP	43	24	46.8 $\pm$ 14.5	2.13 $\pm$ 0.30	2.04–2.22	1.63–2.62
Current study	2017	Italy	Healthy volunteers	614	370	45.7 $\pm$ 14.7	2.01 $\pm$ 0.29	1.98–2.03	1.53–2.48
Pooled	–	–	–	1,595	825	–	1.96*	1.90–2.01*	1.37–2.55*

TRV, tricuspid regurgitation velocity; PH, pulmonary hypertension; SCD, sickle cells disease; LBBB, left bundle branch block; ex-PH, exercise pulmonary hypertension; HAT, hashimoto’s thyroiditis; IPAH, idiopathic pulmonary arterial hypertension; HPAH, heritable pulmonary arterial hypertension; PTE, pulmonary thromboembolism; PAH, pulmonary arterial hypertension; HTR, heart transplant recipients; CP, constrictive pericarditis; nr, not reported. * Weighted.

[40]. This might lead to the speculation that right heart chambers are more dependent from body size than TRV. Based on all these conclusions, we might assume that TRV is a stable index, being weakly influenced by other parameters and variables. This is also true taking into ac-

count the minimal intra-observer and inter-observer variability we recorded (Fig. 3). Our study owes few limitations.

First, correlations between TTE data and invasively assessed pulmonary pressures were not investigated. How-

Fig. 4. PRISMA 2009 flow diagram. TRV, tricuspid regurgitation velocity.

Fig. 5. Forest plot of pooled data regarding tricuspid regurgitation velocity (TRV) in healthy subjects. The forest plot presents the 95% quantile of the TRV and the range of 95% confidence intervals of our prospective data and previous publications selected for pooled analysis. The bigger value at the bottom of the graph shows the weighted pooled confidence interval for the 95% quantile of TRV (2.55 m/s).

ever, it would be unethical to perform such an invasive procedure in healthy individuals without a clinical indication. Second, our sample did not include severely obese individuals, with only 22 patients among 614 (3.6%) mildly obese, with a BMI $>30 \text{ kg/m}^2$ with a highest value

of BMI of 31.56 kg/m^2 . However, similar results would have been obtained, if these 22 subjects with a BMI above 30 kg/m^2 had been excluded from the analysis (mean TRV 1.95 m/s; 95% quantile 2.57 m/s). The 95% quantile was used as normal reference values because the largest

5% of values may indicate pathological processes. However, if a 97.5% percentile were used, the reference values would change only slightly (2.66 m/s).

In conclusion, the current report provides the resting upper physiologic limits of TRV and may serve as a further insight in understanding non-invasive assessment of pulmonary pressure under physiologic circumstances. The meaning of a cut-off of 2.55 m/s for the risk evaluation of PH should be further investigated, as it might help to identify more subjects who are prone to develop or al-

ready have a manifest PH. Moreover, according to our data, TRV is a robust and stable index, without any clinical meaningful influence from body size, age, sex and it is characterized by a strong reproducibility.

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

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