Experimental Study

Right Ventricular and Pulmonary Vascular Function are Influenced by Age and Volume Expansion in Healthy Humans

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ABSTRACT

Background: Patients with heart failure (HF) often show signs of right ventricular (RV) dysfunction. The RV function of coupled with the pulmonary circulation (tricuspid annular plane systolic excursion [TAPSE]/pulmonary arterial systolic pressure [PASP]) has been shown to divide HF patients into distinct prognostic strata, but less is known about which factors influence this prognostic marker, and whether those factors can be modified. We sought to obtain normative values and discern the individual effects of age, sex, and fluid overload on RV function.

Methods and Results: Sixty healthy subjects aged 20−80 years were enrolled in this prospective study. Right heart catheterization with hemodynamic measurements were performed at rest after a rapid saline solution infusion (10 mL/kg, 150 mL/min). Linear regression and Spearman correlation models were used to estimate associations between TAPSE/PASP and relevant variables. In healthy persons of all ages, the median (5th−95th percentiles) normative TASPE-PASP ratio was 1.25 (0.81−1.78) mm/mm Hg. The correlation between progressive age and declining TAPSE/PASP was significant ($r = -0.35$; $P = .006$). Sex did not influence TAPSE/PASP ($P = .30$). Rapid fluid expansion increased central venous pressure from 5 ± 2 mm Hg to 11 ± 4 mm Hg after fluid infusion ($P < .0001$). This resulted in a 32% decrease in the TAPSE-PASP ratio after fluid infusion, compared to baseline ($P < .0001$).

Conclusions: The TAPSE-PASP ratio was affected by age, but not sex. TAPSE/PASP is not only a reflection of intrinsic RV function and pulmonary vascular coupling, but fluid status also dynamically affects this index of RV function. Normative values with invasive measurements were obtained for future assessment of HF patients. (*J Cardiac Fail 2019;25:51−59*)

Key Words: Heart failure, TAPSE/PASP, right heart function, hemodynamics, fluid bolus, healthy, sex, age.

The majority of patients with heart failure (HF) with preserved ejection fraction (HFpEF) display increased left ventricular filling pressure.[1] In turn, this leads to postcapillary pulmonary hypertension followed by decreased right ventricular (RV) function and a higher right heart pressure-flow relationship (ie, mean pulmonary arterial pressure/cardiac output).[2−4] The presence and degree of these abnormalities are associated with mortality in HF patients,[2,5,6] and therefore may represent a target for future interventions.[7,8] Because RV function is closely linked to conditions with increased pulmonary vascular afterload,[5] incorporating RV function and pulmonary arterial pressure for risk stratification seems to be justified. The importance of these parameters in HF was highlighted in a recent position paper from the European Society of Cardiology (ESC).[3] In addition, the ratio of tricuspid annular plane systolic excursion to pulmonary arterial systolic pressure (TAPSE/PASP), a marker of the coupling of RV function to the pulmonary circulation, has been shown to divide HF patients across the left ventricular ejection fraction (LVEF) spectrum

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into distinct prognostic strata.[9,10] Older age, comorbidities, and certain medications (diuretics and beta-blockers) have each been associated with a lower TAPSE-PASP ratio—a marker of poor RV-pulmonary vascular coupling—and therefore worse prognosis.[10−12] Because the HF syndrome is primarily observed in elderly patients, the question remains of what proportion of an abnormal TAPSE-PASP ratio is attributable to HF and what is due to the physiologic aging of the cardiovascular system, concurring comorbidity, and intravascular fluid status. Currently normative data for TAPSE/PASP is lacking with the use of criterion-standard invasive measurements,[11,12] highlighting an unmet need if this metric is to be a valid biomarker of HF severity and prognosis.[3,13] Furthermore, the proportion of women and men who develop HF at a given age is not similar; therefore, understanding how age and sex influence the TAPSE-PASP ratio is another unmet need.[14,15]

We therefore sought to study the TAPSE-PASP ratio in healthy participants across a large age range, in both sexes, and in response to rapid fluid expansion to determine normative values for the TAPSE-PASP ratio, with the goal of increasing the utility of the TAPSE-PASP ratio in the clinical evaluation of HF patients. We prospectively recruited 60 healthy participants to avoid the influence of any comorbidities or significant medication use; the participants were distributed evenly across ages 20−80 years and between sexes. We used right heart catheterization and echocardiography, to evaluate the TAPSE/PASP relationship across ages and sex. Furthermore, in a subset of 50 patients, a rapid fluid bolus was administered to examine how fluid expansion affects the TAPSE-PASP relationship in the healthy heart.

Methods

Sixty-two healthy subjects aged 20−80 years were enrolled from the community using advertisements in this prospective two-center study, as reported previously.[16] Two subjects were excluded owing to inadequate echocardiographic acoustic windows to visualize the RV, leaving 60 subjects for this study. Subjects were recruited to evenly represent sex and age when stratified into 3 decadal groups (20−39 years [n = 19], 40−59 years [n = 21], and 60−80 years [n = 20]) with relatively equal numbers of men and women in each group). Healthy subjects were deemed to be eligible if: free from history of any acute or chronic cardiac or pulmonary disease or active smoking; echocardiography (performed 0−2 weeks before experimental day) showed no signs of chamber hypertrophy, reduced LVEF, or significant valvular disease; normal spirometry for their age; routine blood chemistry test with normal values (including estimated glomerular filtration rate, glycosylated hemoglobin, N-terminal pro−B-type natriuretic peptide, thyroid stimulating hormone, hemoglobin, C-reactive protein, white blood cell counts, and lipids); body mass index (BMI) 20−30 kg/m^2; and an exercise test with electrocardiography (ECG) with no pathologic findings. Any medication with cardiovascular effects was held 48 hours before the echocardiography and invasive tests.

A comprehensive description of the study design, including inclusion and exclusion criteria has been reported previously.[16] Participants provided oral and written informed consents before any testing. The protocol was approved by the regional Ethical Committee (Capital Region of Denmark; H-2-2013-072). The protocol was published on Clinicaltrials.gov (NCT01974557). The experimental protocol pertaining to the rapid saline solution infusion was ethically approved subsequent to the approval of the resting measurement protocol, which precluded 10 patients from being subjected to the saline solution infusion.

Echocardiography

Examinations were performed with the use of a Phillips iE33 (Phillips Healthcare, Best, Netherlands) or a Vivid 9 (General Electric, Horten, Norway) ultrasound system. Measurements were made according to EACVI/ASE guidelines.[17] Left ventricular volumes and LVEF were assessed by means of the Simpson modified biplane rule with the use of apical 2- and 4-chamber views. LV mass was measured by means of LV wall thickness and LV end-diastolic diameter, as described by Devereux et al.[18] Maximal left atrial volume was measured by means of biplane planimetry (area-length method). TAPSE was measured in a 4-chamber view with the use of M-mode recording at the junction of the tricuspid valve and right ventricular free wall.

Right Heart Catheterization

Right heart catheterization was performed with the use of a standard 7.5-F triple lumen Swan-Ganz catheter (Edwards Lifesciences, Irvine, California). With the use of the Seldinger technique and guided by ultrasound, the catheter was introduced under local anesthesia into the internal jugular vein and advanced to the pulmonary artery, with the position of the catheter verified by identifying the characteristic pressure curves. Central venous pressure (CVP), systolic, diastolic, mean pulmonary arterial pressures (PASP, PADP, and mPAP, respectively), and pulmonary capillary wedge pressure (PCWP) were measured. Cardiac output (CO) was measured by means of thermodilution as the average of 3 measurements with $<10\%$ variance and was indexed to body surface area as cardiac index (CI).

Calculations

Body surface area was estimated with the use of the Dubois formula. Pulmonary vascular resistance in Wood units was calculated as (mPAP − PCWP)/CO. Systemic vascular resistance was calculated as $80 \times$ (MAP − CVP)/CO. Stroke volume was calculated as CO/heart rate. TAPSE/PASP was calculated with the use of echocardiographic measurements of TAPSE divided by invasive measurements of PASP.

Protocol and Saline Solution Infusion

Participants were allowed to consume their normal diet; however, participants were asked to refrain from consuming products containing caffeine. After voiding, invasive and noninvasive equipment was placed on the patient (blood pressure monitor, pulse oximeter, ECG, Swan-Ganz catheter). After resting, simultaneous invasive and echocardiographic examinations were made in the supine position with the legs resting flat (rest). After the rest measurements, isotonic saline solution was administered via the internal jugular vein at an infusion rate of 150 mL/min, until a total volume of 10 mL/kg body weight of isotonic saline solution was infused. This protocol was used to increase CVP to values similar to those observed in HF patients.[7,19] After the saline solution infusion, simultaneous invasive and echocardiographic measurements were repeated.

Statistical Analyses

Baseline characteristics are summarized for 2 categories: participants with data available at rest (n = 60) and participants who also participated in the fluid infusion protocol (n = 50). Twenty-nine participants who underwent the saline solution infusion protocol had sufficient paired echocardiographic data (baseline + post-fluid) to assess the TAPSE-PASP relationship, whereas all 50 participants had invasive measurements available. All data were formally tested for normality with the use of Shapiro-Wilk tests, histograms, and normal probability plots. Data were normally distributed except TAPSE/PASP, which was right skewed. Normative values are summarized as median (5th−95th percentiles). Linear regression models and Pearson correlation were used to estimate the associations between listed variables. When analyzing changes from baseline to post-fluid, absolute Δ-values were used in the regression models. Unless otherwise noted, all associations listed are simple linear regression. Paired *t* tests were used to compare values before versus after infusion within individuals. Values are tabulated as mean ± SD, unless otherwise stated. All analyses were conducted with the use of Stata version 14 (College Station, Texas).

Results

Of 60 participants with satisfactory RV echocardiograhic measurements obtained for assessment of resting conditions, 50 patients (83%) were also subjected to a rapid saline solution load and had sufficient data for analysis. Baseline characteristics of both groups are summarized in Table 1.

Table 1. Characteristics of All Patients at Baseline and the Subset of Patients Who Also Underwent Fluid Infusion

Characteristic	Baseline (n = 60)	Fluid Infusion (n = 50)
Age (y)	50 ± 17	51 ± 17
Male/female	28/32	22/28
Weight (kg)	75 ± 11	74 ± 11
BMI (kg/m^2)	24 ± 3	24 ± 3
BSA (m^2)	1.9 ± 0.2	1.9 ± 0.2
HR (beats/min)	63 ± 10	64 ± 10
SBP (mm Hg)	132 ± 17	133 ± 17
DBP (mm Hg)	74 ± 12	74 ± 13
FEV_1 (L)	3.4 ± 0.8	3.4 ± 0.8
FVC (L)	4.4 ± 1.1	4.4 ± 1.1
VO_2 max (mL/min)	2627 ± 749	2578 ± 767
VO_2 max, indexed (mL·min^{-1}·kg^{-1})	35 ± 9	35 ± 9
Hemoglobin (mmol/L)	8.9 ± 0.7	8.9 ± 0.8
NT-proBNP (pmol/L)	7 (6−12)	7 (6−12)
Echocardiography		
LVEF (%)	62 ± 7	62 ± 7
LVEDD (cm)	4.6 ± 0.7	4.6 ± 0.7
LA volume (mL)	40 ± 12	40 ± 13
E/A	1.5 ± 0.7	1.4 ± 0.7
E/e′	8.2 ± 2.7	8.3 ± 2.9
TR (mm Hg)	18 ± 6	18 ± 6
TAPSE (mm)	26 ± 4	25 ± 4
Hemodynamics		
CVP (mm Hg)	5 ± 2	5 ± 2
PASP (mm Hg)	21 ± 5	21 ± 5
PADP (mm Hg)	11 ± 4	11 ± 3
mPAP (mm Hg)	15 ± 4	15 ± 4
PCWP (mm Hg)	9 ± 3	9 ± 3
CI (L·min^{-1}·m^{-2})	2.9 ± 0.5	2.9 ± 0.5
SVR (dyne/s·cm^5)	1187 ± 348	1138 ± 340
PVR (mm Hg·L^{-1}·min^{-1})	1.2 ± 0.5	1.2 ± 0.5

BMI, body mass index; BSA, body surface area; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; VO_2 max, maximal oxygen consumption; NT-proBNP, N-terminal pro−B-type natriuretic peptide; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LA, left atrial; TR, tricupid regurgitation pressure gradient; TAPSE, tricuspid annular plane systolic excursion; CVP, central venous pressure; PASP, systolic pulmonary artery pressure; PADP, diastolic pulmonary artery pressure; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; CI, cardiac index; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance. NT-proBNP values are presented as median (IQR), all other variables as mean ± SD.

Right Ventricular Function and Pulmonary Coupling—Effect of Age

The TAPSE-PASP ratio decreased with age (Fig. 1 and Table 2). The range of TAPSE/PASP among the participants was 0.71−2.67 mm/mm Hg. The correlation between progressive age and declining TAPSE/PASP was significant ($r = -0.35$; $P = .006$; Table 2). The regression coefficient was −0.0076 (95% confidence interval [CI] −0.013 to −0.002; $P = .006$). The variance in the TAPSE-PASP ratio explained by age was $r^2 = 12\%$. The changes leading to a lower TAPSE-PASP ratio with age was attributable to an increasing PASP with age (coefficient 0.11 [0.04 to 0.17]; $P = .002$), whereas TAPSE did not change with age (coefficient 0.02 [−0.04 to 0.08]; $P = .47$). Heart rate was not associated with TAPSE/PASP ($P = .52$). Regression statistics are summarized in Table 2.

To dissect whether physiologic components of aging were accountable for the association between PASP and age, a secondary analysis was performed with adjustments for systolic/diastolic blood pressure, heart rate, BMI, LVEF, and E/e′. This attenuated the effect of age on PASP ($P = .054$).

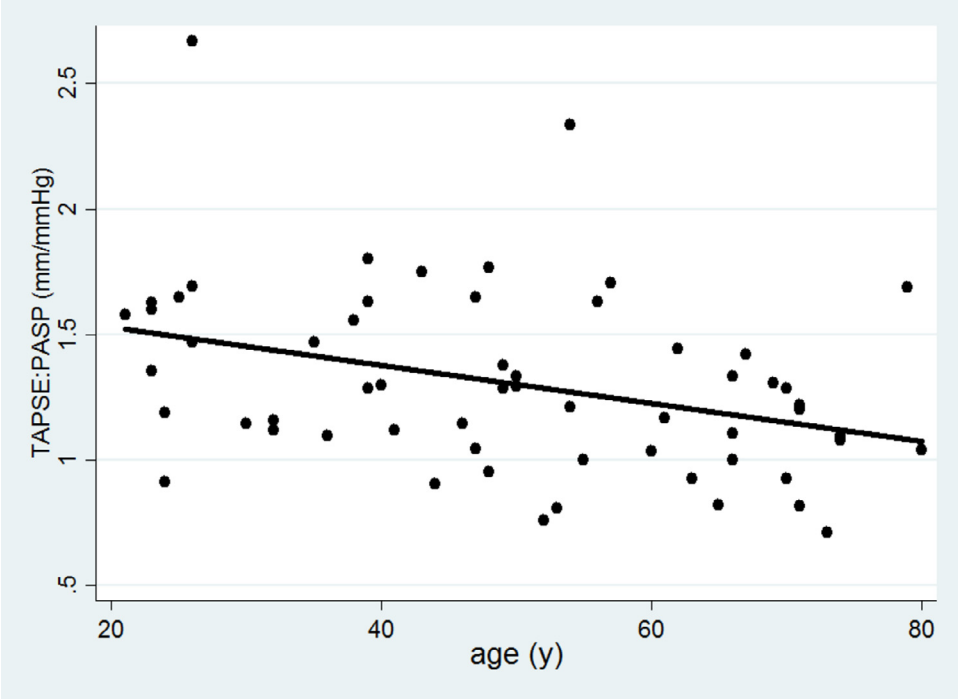

Fig. 1. Scatterplot of TAPSE/PASP and age in all participants (n = 60).

Right ventricular function and pulmonary coupling—effect of gender

As listed in Table 1, 32/60 participants (53%) were female. There was no significant effect of sex on TAPSE/PASP ($r = 0.14$ [95% CI −0.12 to 0.38]; $P = .30$; Table 2), nor was there any interaction between age and sex ($P = .47$) and TAPSE/PASP.

Right Ventricular Function and Pulmonary Coupling—Effect of Rapid Fluid Bolus

The mean amount of fluid infused was 744 mL (range 540−960 mL). The volume infused was independent from age ($P = .65$). There was an increase in CVP from 5 ± 2 mm Hg at baseline to 11 ± 4 mm Hg after fluid infusion ($P < .0001$). Both TAPSE and PASP increased, although PASP increased relatively more (PASP +6.8 mm Hg [$P < .0001$]; TAPSE +1.6 mm [$P = .01$]; Table 3). This resulted in a 32% decrease in the TAPSE-PASP ratio after fluid infusion compared with baseline ($P < .0001$; Fig. 2), with a ΔTAPSE/PASP range of 0.49−1.73 mm/mm Hg. After fluid infusion, 6 of 29 patients (21%) dropped below the lowest TAPSE/PASP value observed at baseline. The magnitude of decrease in TAPSE/PASP after fluid infusion was not different between sexes ($P = .90$) nor across ages ($P = .32$; Table 3). The TAPSE-PASP ratio was associated with CVP both at baseline (coefficient −0.06 [−0.11 to −0.01]; $r^2 = 19\%$; $P = .022$) and after fluid infusion (coefficient −0.03 [−0.05 to −0.01]; $r^2 = 38\%$; $P = .012$), whereas CVP was not associated with age, neither at rest ($P = .55$), nor after fluid infusion ($P = .06$). The normative baseline and post-fluid TAPSE-PASP ratios are summarized according to age groups in Table 4.

The right heart pressure-flow relationship—defined as mPAP/CI—was positively associated and correlated with age (coefficient 0.03 [0.01 to 0.04]; $P = .005$; see Table 2 for correlation coefficients). The variance in the mPAP-CI

Table 2. Correlations Between Hemodynamic Variables and Age/Sex at Baseline and After Fluid Infusion (Post-fluid)

Age/Sex	TAPSE		PASP		TAPSE/PASP		mPAP		CI		mPAP:CI	
	R	*P*	*R*	*P*	*R*	*P*	*R*	*P*	*R*	*P*	*R*	*P*
Baseline												
Age	0.09	.47	0.38	.002*	−0.35	.006*	0.25	.050*	−0.11	.37	0.35	.005*
Sex	0.01	.92	−0.08	.52	0.14	.30	−0.02	.85	0.05	.70	−0.05	.70
Post-fluid												
Age	0.01	.96	0.42	.003*	−0.22	.25	0.23	.11	−0.39	.005*	0.42	.002*
Sex	0.31	.10	−0.04	.76	0.21	.29	0.10	.50	0.16	.28	0.0	1.0

R, *R* value, correlation coefficient; *P*, *P* value; other abbreviations as in Table 1.
*$P < 0.05$.

Table 3. Hemodynamic Variables Before and After Rapid Saline Solution Infusion (Post-fluid) in Patients Who Underwent Both Measurements

Variable	Baseline (n = 50)	Post-fluid (n = 50)	*P* Value*	*P* Value†	
				Age	Sex
TAPSE (mm)	25 ± 4	27 ± 4‡	.01	.93	.10
PASP (mm Hg)	21 ± 5	28 ± 7	<.001	.08	.45
TAPSE/PASP (mm/mm Hg)	1.3 (0.8, 1.8)	1.0 (0.5, 1.5)‡	<.001	.32	.90
mPAP (mm Hg)	15 ± 4	22 ± 5	<.001	.82	.07
PCWP (mm Hg)	9 ± 3	15 ± 4	<.001	.74	.62
CI (L/min/m^2)	2.9 ± 0.5	3.9 ± 1.0	<.001	.012§	.28
mPAP/CI (mm Hg/[L·min^{-1}·m^{-2}])	5.3 ± 1.3	5.8 ± 1.7	0.07	.39	.79
SVR (dyne/s·cm^5)	1138 ± 340	804 ± 275	<.001	.63	.78
PVR (mm Hg·L^{-1}·min^{-1})	1.2 ± 0.5	1.0 ± 0.5	<.001	.67	.47
HR (beats/min)	65 ± 9	72 ± 11	<.001	.87	.81
MAP (mm Hg)	72 ± 11	80 ± 14	<.001	.92	.07

MAP, mean arterial pressure; other abbreviations as in Table 1. Interaction *P* values show whether age or sex influenced changes in hemodynamic variables from baseline to post-fluid. All variables are presented as mean ± SD, except TAPSE-PASP ratio, which is presented as median (5th−95th percentiles). All pressures and cardiac index were invasively measured.

*Paired *t* test (baseline vs post-fluid).

†*P* values of the main effect of age and sex when included as covariates.

‡n = 29.

§$P < 0.05$.

ratio explained by age was $r^2 = 12\%$. The ratio increased numerically after fluid infusion (baseline 5.3 ± 1.3 vs post-fluid 5.8 ± 1.7; Fig. 3), but this was not statistically significant (*P* = .07). The changes in mPAP/CI after saline solution load did not differ with age (*P* = .39) or between sexes (*P* = .79; Table 3).

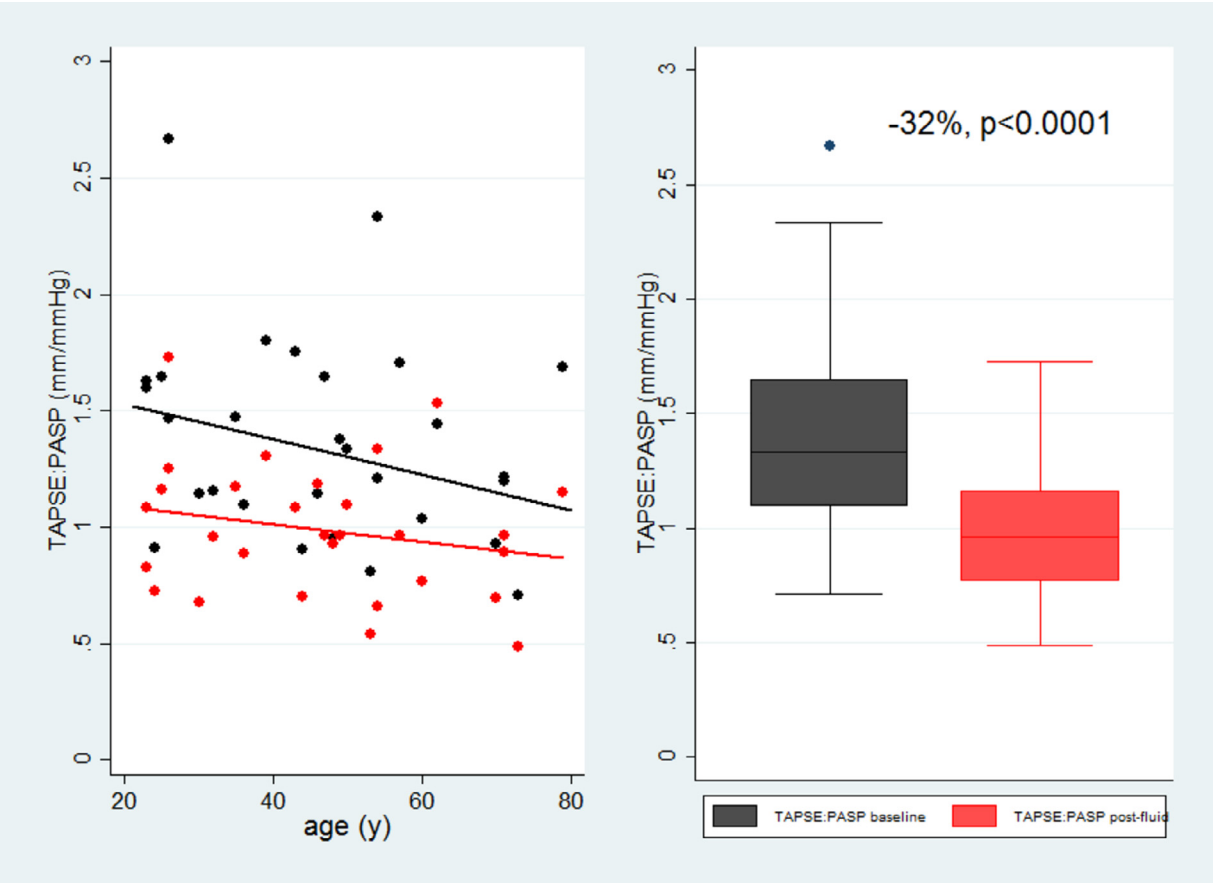

Fig. 2. Left: Scatterplot of TAPSE/PASP at baseline (*black*) and after fluid infusion (*red*) according to age (n = 29). Right: Boxplot of TAPSE/PASP at baseline and after fluid infusion (n = 29).

Table 4. The TAPSE-PASP Ratio at Baseline and After a Rapid Saline Solution Infusion (Post-fluid)

Measurement	All patients	20−39 y	40−59 y	60−80 y
Baseline (n = 60)	1.25 (0.81−1.78)	1.47 (0.91−2.67)	1.29 (0.81−1.76)	1.10 (0.76−1.57)
Post-fluid (n = 29)	0.96 (0.54−1.53)	1.08 (0.68−1.73)	0.96 (0.54−1.33)	0.89 (0.49−1.53)

Values are presented as median (5th−95th percentiles).

Right Ventricular Function and Pulmonary Coupling Assessment With the Use of Invasive Versus Sonographic Measures

The association between invasively measured PASP and estimated PASP (echocardiography) was significant ($r = 0.45$; $P = .0006$, Fig. 4). The echocardiographic estimates tended to overestimate the PASP. In effect, the TAPSE-PASP ratio was smaller if estimated PASP was used compared with the invasively measured PASP (baseline 1.19 vs 1.30 mm/mm Hg [$P = .016$]; post-fluid 0.98 vs 0.81 mm/mm Hg [$P = .0003$]).

Discussion

In this study, we prospectively enrolled healthy participants to propose normative values for TAPSE/PASP at rest and after saline solution infusion (to account for fluid loading) with the use of invasively measured PASP. In addition we show that aging—but not sex—affects this measure. The measure of TAPSE/PASP was not only a reflection of intrinsic right heart function and pulmonary vascular coupling, but it was also sensitive to acute changes in RV preload.

This information not only shows us how physiologic aging affects the cardiovascular system, but it also provides important information about the incremental pathophysiologic stress that diseases such as HFpEF have on the cardiovascular system, specifically that factors such as age and fluid status significantly affect this index of RV function.

Although the effect of physiologic aging on the cardiovascular system has received attention in recent years,[16,20,21] to our knowledge the relationship between aging and TAPSE-PASP ratio determined with the use of invasive measurements has not been described in healthy humans. A recent consensus paper from the European Society of Cardiology to list normative values stressed the importance of this measure in HF.[3] The metric of TAPSE/PASP has been described by several groups to have independent prognostic value in HF across the spectrum of LVEF and clinical severity.[9,22] This has fueled speculation of whether treatments that can alleviate right heart dysfunction could be a future avenue of exploration.[3,7,8] However, in this context, knowing the incremental impact of disease (eg, HF) on RV function as distinct from that of physiologic aging seems prudent, because the latter is nonmodifiable. In our healthy cohort, progressive age was strongly associated with an increased PASP, and therefore a lower TAPSE/PASP, which has been associated with worse outcomes in HF.[9,10] These findings are in accordance with previous studies using echocardiography to estimate pulmonary arterial

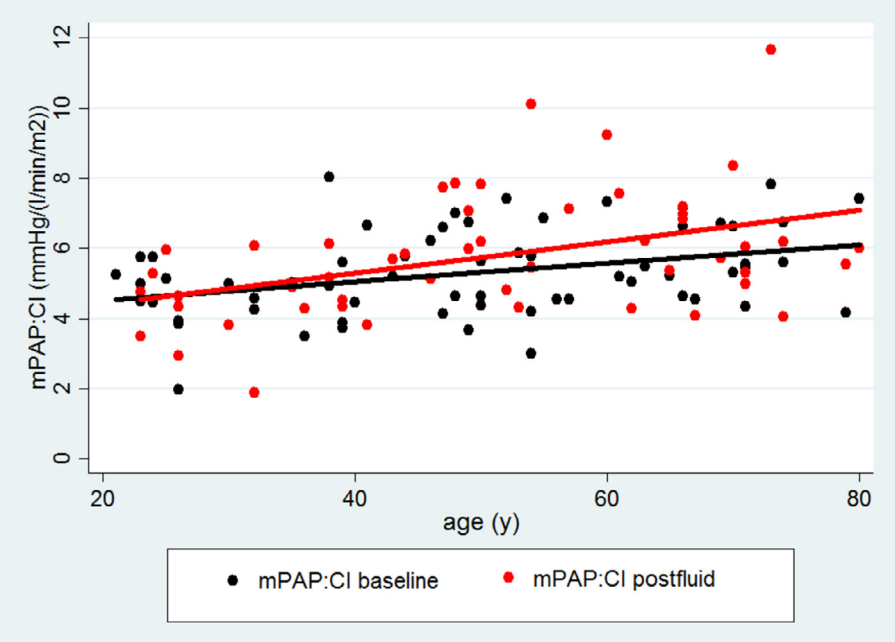

Fig. 3. Scatterplot of mPAP/CI and age at baseline (*black*; n = 50) and after fluid infusion (*red*; n = 50).

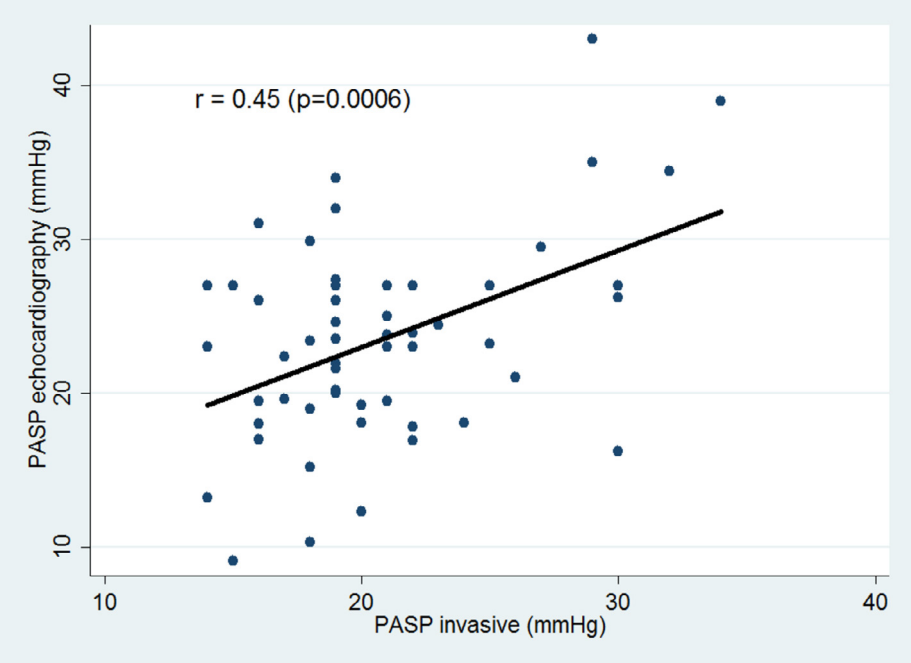

Fig. 4. Scatterplot of TAPSE/PASP with the use of either estimated PASP (echocardiography) or invasively measured PASP.

pressure.[11,12] Age modestly explained changes in TAPSE-PASP ratio ($r^2 = 12\%$), but it should be considered in any clinical evaluation or risk score pertaining to prognosis or treatment decision. Therefore, a low TAPSE-PASP ratio in a younger patient is likely indicative of more serious RV dysfunction compared with a similar ratio in an older patient.

Because age was significantly associated with PASP, we did further exploratory multivariable analyses adjusting age for blood pressure, heart rate, BMI, LVEF, and E/e′, because these variables have been shown to affect PASP.[23] This analysis suggested that the effect of age was attenuated after adjustment.

When comparing our TAPSE/PASP values with those observed in both HFpEF and HFrEF populations,[9,10] there was an overlap between our normative values and those observed in these patients, especially after fluid bolus. The variability in TAPSE/PASP was notable in our healthy population, which might make this metric difficult to use at an individual patient level for prognostication. However, we can not infer that the prognostic significance of TAPSE/PASP values are similar between HF and non-HF individuals, merely that TAPSE/PASP is influenced by aging and fluid status in healthy individuals, which may also be the case for HF patients. Further studies are needed to address these associations in HF patients.

Importantly, there was a downward shift in the TAPSE-PASP ratio if estimated PASP was used, because estimated PASP tended to be higher than the invasively measured PASP. This should be noted when using normative values in clinical assessment.

Because registries of HFpEF patients often show a predominance of women,[15] it was of interest to learn if the physiologic changes in TAPSE/PASP varied between sexes. No sex differences in TAPSE/PASP were found at any age or slope of change with age. Thus, our data do not suggest that healthy women are more prone to right heart dysfunction with age compared with their male peers.

We used a rapid fluid infusion to learn how fluid status may dynamically affect measures of right heart function. The infusion protocol has previously been shown to successfully unmask falsely low filling pressures induced by vigilant diuretic use in patients with pulmonary hypertension as well as in several mechanistic studies.[19,24,25] Our fluid intervention did change hemodynamics, with more than a doubling in CVP, from 5 to 11 mm Hg, making it comparable to the CVP measured in stable HFpEF patients (10 ± 4 mm Hg), as reported by Borlaug et al.[4] That group reported that the right heart pressure-flow relationship (ie, mean pulmonary arterial pressure/cardiac output) was impeded in HFpEF patients compared with healthy participants. However, the HFpEF group had more comorbidity, higher intake of vasoactive medications, and average age 9 years older than the control group. In addition, the HFpEF patients showed signs of fluid overload compared with the control group (CVP 10 vs 4 mm Hg, respectively). Therefore, some of these differences in pressure-flow relationship ascribed to HFpEF could be due to age, fluid status, and comorbidity rather than intrinsic cardiac dysfunction. In our healthy participants, we were able to discern the effects of age and fluid status on the right heart pressure-flow relationship in participants without comorbidities. We found that the mPAP-CI ratio was age dependent. However, the magnitude of increase in mPAP/CI after saline solution infusion was not associated with age, as others have also reported.[19] In participants aged 60−80 years, there was an increase of

9% in mPAP/CI after fluid challenge, averaging a ratio of 6.4. In comparison, HFpEF patients have a ratio of ~10 at rest,[4,26] suggesting that HF induces RV dysfunction beyond that of fluid overload and aging.

Our data suggest that age and fluid status not only influence the RV hemodynamic phenotype of HFpEF, but that a component of the prognostic information contained in the TAPSE/PASP may be attributable to congestion and age. These data help our understanding of the HF syndrome, not only HFpEF.

Our findings of no sex differences both at rest and after fluid bolus do not give leverage to the belief that the female cardiovascular system is more physiologically prone to diastolic dysfunction compared with the male. The predominance of women in HFpEF registries might be caused by longevity differences between sexes, although conflicting data on this issue exist.[14,27,28]

Study Limitations

Our main limitation lies in the low number of patients enrolled, especially those with echocardiographic measurements in the fluid infusion protocol. Of note, prospective studies in healthy individuals are limited in size historically owing to the invasive nature of the study and the ethical considerations in this context. The present study is one of the largest with healthy individuals,[25,26,29,30] and with even representation of participants aged 20−80 years and sexes. The limitation in size may have introduced less robust estimates and possibly type II statistical errors. We used an acute saline solution bolus, which may not induce the same hemodynamic changes as that of chronic fluid overload, despite similar CVP.

It should be noted that our population was white, which might limit the generalizability of our results and normative values to other races or ethnicities. Furthermore, because we used invasively determined PASP, our normative data should be assessed in that context, especially if only echocardiographic estimates of PASP are available.

Conclusion

This is the first invasive study to quantify the impact of age and fluid on RV function coupled with pulmonary circulation without the influence of comorbidity, vasoactive medications, and possible fluid overload. In addition, we provide normative invasive values for future reference of the TAPSE-PASP ratio in the clinical evaluation of HF patients.

We found that age and fluid status were significant drivers of metrics describing RV function. With advancing age, RV function coupled with pulmonary circulation showed signs of decreasing function with no sex difference, accentuated by using a rapid intravascular volume expansion. These data may serve to discern factors that influence metrics describing RV and pulmonary circulation, and provide insight into the mechanisms behind the prognostic value of these metrics and hence future targets of intervention.

Disclosures

None.

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