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

Wolsk, Emil; Bakkestrøm, Rine; Kristensen, Charlotte Burup; Aagaard Myhr, Katrine; Thomsen, Jakob H.; Balling, Louise; Andersen, Mads J.; Dahl, Jordi S.; Shah, Sanjiv J.; Gustafsson, Finn; Hassager, Christian; Møller, Jacob E.

Published in:
Journal of Cardiac Failure

DOI:
10.1016/j.cardfail.2018.11.013

Publication date:
2019

Document version
Accepted manuscript

Document license
CC BY-NC-ND

Citation for published version (APA):

Terms of use
This work is brought to you by the University of Southern Denmark through the SDU Research Portal. Unless otherwise specified it has been shared according to the terms for self-archiving. If no other license is stated, these terms apply:

• You may download this work for personal use only.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying this open access version

If you believe that this document breaches copyright please contact us providing details and we will investigate your claim. Please direct all enquiries to puresupport@bib.sdu.dk

Download date: 22. Feb. 2021
Right ventricular and pulmonary vascular function are influenced by age and volume expansion in healthy humans

Emil Wolsk MD PhD, Rine Bakkestrøm MD, Charlotte Burup Kristensen MD, Katrine Aagaard Myhr MD, Jakob H. Thomsen MD PhD, Louise Balling MD PhD, Mads J. Andersen MD PhD, Jordi S. Dahl MD PhD, Sanjiv J. Shah MD, Finn Gustafsson MD DMSc, Christian Hassager MD DMSc, Jacob E. Møller MD DMSc

PII: S1071-9164(18)31267-3
DOI: https://doi.org/10.1016/j.cardfail.2018.11.013
Reference: YJCAF 4240

To appear in: Journal of Cardiac Failure

Received date: 11 March 2018
Revised date: 1 November 2018
Accepted date: 19 November 2018

Please cite this article as: Emil Wolsk MD PhD, Rine Bakkestrøm MD, Charlotte Burup Kristensen MD, Katrine Aagaard Myhr MD, Jakob H. Thomsen MD PhD, Louise Balling MD PhD, Mads J. Andersen MD PhD, Jordi S. Dahl MD PhD, Sanjiv J. Shah MD, Finn Gustafsson MD DMSc, Christian Hassager MD DMSc, Jacob E. Møller MD DMSc, Right ventricular and pulmonary vascular function are influenced by age and volume expansion in healthy humans, Journal of Cardiac Failure (2018), doi: https://doi.org/10.1016/j.cardfail.2018.11.013

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
Right ventricular and pulmonary vascular function are influenced by age and volume expansion in healthy humans

Emil Wolsk, MD PhD¹, Rine Bakkestrøm MD², Charlotte Burup Kristensen MD¹, Katrine Aagaard Myhr MD¹, Jakob H. Thomsen MD PhD¹, Louise Balling MD PhD¹, Mads J. Andersen MD PhD¹, Jordi S. Dahl MD PhD², Sanjiv J. Shah MD³, Finn Gustafsson MD DMSc¹, Christian Hassager MD DMSc¹, Jacob E. Møller MD DMSc².

Affiliation:
1. Dept. of Cardiology, Rigshospitalet, University Hospital of Copenhagen, Copenhagen, Denmark.
2. Dept. of Cardiology, Odense University Hospital, Odense, Denmark
3. Division of Cardiology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA.

Corresponding author:
Emil Wolsk MD PhD
Department of Cardiology
Rigshospitalet
Copenhagen, Denmark
E-mail: wolsk@dadlnet.dk
Phone: +45 35453545

Background

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

Methods

Sixty healthy subjects aged 20-80 years were enrolled in this prospective study. Right heart catheterization with hemodynamic measurements were performed at rest and following a rapid saline infusion (10 ml/kg, 150 ml/min). Linear regression and Spearman correlation models were used to estimate associations between TAPSE:PASP and relevant variables.

Results

In healthy persons of all ages, the normative TAPSE:PASP ratio was median (5th-95th percentile) 1.25 (0.81-1.78) mm/mmHg. The correlation between progressive age and declining TAPSE:PASP was significant (r: -0.35, p=0.006). Gender did not influence TAPSE:PASP (p=0.30). Rapid fluid expansion increased central venous pressure from 5 ± 2 mmHg to 11 ± 4 mmHg after fluid infusion (p<0.0001). This resulted in a 32% decrease in the TAPSE:PASP ratio after fluid infusion, compared to baseline (p<0.0001).

Conclusions

The TAPSE:PASP ratio was affected by age, but not gender. TAPSE:PASP is not only a reflection of intrinsic RV function and pulmonary vascular coupling, but fluid status dynamically affects this index of RV function. Normative values with invasive measurements were obtained for future assessment of HF patients.

Key words

Heart failure, TAPSE:PASP, Right heart function, hemodynamics, fluid bolus, healthy, gender, age
Abbreviations used in manuscript

BMI – body mass index
BSA – body surface area
CI – cardiac index
CVP – central venous pressure
LV - left ventricular
MAP – mean arterial pressure
PASP – pulmonary artery systolic pressure
PCWP – pulmonary capillary wedge pressure
PVR – pulmonary vascular resistance
RV – right ventricular
SVR – systemic vascular resistance
TAPSE - tricuspid annular plane systolic excursion
VO2-max – maximal volume of oxygen uptake (whole body)
Introduction

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 (i.e. mean pulmonary artery pressure:cardiac output)(2–4). The presence and degree of these abnormalities are associated with mortality in HF patients(2, 5, 6), and hence may represent a target for future interventions(7, 8). As RV function is closely linked to conditions with increased pulmonary vascular afterload(5), incorporating RV function and pulmonary artery pressure for risk stratification seems 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 artery 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 LVEF spectrum into distinct prognostic strata(9, 10). Older age, comorbidities, and certain medications (diuretics and beta-blockers) have each been associated with a lower ratio of TAPSE:PASP—a marker of poor RV-pulmonary vascular coupling—and hence worse prognosis(10–12). Since the HF syndrome is primarily observed in elderly patients, the question remains what proportion of an abnormal TAPSE:PASP ratio is attributable to HF and what is due to the physiological aging of the cardiovascular system, concurring comorbidity, and intravascular fluid status. Currently normative data for TAPSE:PASP is lacking using gold-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 gender influences the TAPSE:PASP ratio is also an unmet need(14, 15).
We therefore sought to study the TAPSE:PASP ratio in healthy participants across a large age range, in both genders, 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 genders. We used right heart catheterization and echocardiography, to evaluate the TAPSE:PASP relationship across ages and gender. 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 due to inadequate echocardiographic acoustic windows to visualize the RV, leaving 60 subjects for this study. Subjects were recruited to evenly represent gender and age when stratified into 3 decadal groups (20-39 years, n=19, 40-59 years, n=21, 60-80 years, n=20, with relatively equal numbers of males and females in each group). Healthy subjects were deemed eligible if free from history of any acute or chronic cardiac or pulmonary disease, or active smoking; echocardiography without signs of chamber hypertrophy, reduced left ventricular (LV) ejection fraction or significant valvular disease (performed 0-2 weeks before experimental day); normal spirometry for their age; routine blood chemistry test with normal values (including estimated glomerular filtration rate (eGFR), glycosylated hemoglobin (HbA1c), N-terminal pro-brain natriuretic peptide (NT-proBNP), thyroid stimulating hormone (TSH), hemoglobin (Hgb), C-reactive protein (CRP), white blood cell counts, and lipids); BMI 20-30 kg/m²; and an exercise test
with ECG without any pathological findings. Any medication with cardiovascular effects was held 48 hours prior to 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 consent prior to 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 infusion was ethically approved subsequent to the approval of the resting measurement protocol, which precluded 10 patients from being subjected to the saline infusion.

**Echocardiography**

Examinations were performed using 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 LV ejection fraction (LVEF) were assessed with the Simpson modified biplane rule using apical 2- and 4-chamber views. LV mass was measured using LV wall thickness and LV end-diastolic diameter, as described by Devereux et al.(18). Maximal left atrial volume was measured using biplane planimetry (area-length method). TAPSE was measured in a 4-chamber view using M-mode recording at the junction of the tricuspid valve and right ventricular free wall.

**Right heart catheterization**

Right heart catheterization was performed using a standard 7.5-F triple lumen Swan-Ganz catheter (Edwards Lifesciences, Irvine, CA). Using 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 artery pressures (PASP, PADP, mPAP, respectively), and pulmonary capillary wedge pressure (PCWP) were measured. Cardiac output (CO) was measured using 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 (BSA) was estimated using the Dubois formula. Pulmonary vascular resistance (PVR) in Wood units was calculated as (mPAP - PCWP)/CO. Systemic vascular resistance (SVR) was calculated as 80 x (MAP – CVP)/CO. Stroke volume was calculated as CO/heart rate (HR). TAPSE:PASP was calculated using echocardiographic measurements of TAPSE divided by invasive measurements of PASP.

Protocol and Saline 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, 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 was administered via the internal jugular vein at an infusion rate of 150 ml/min, until a total volume of 10 ml/kg bodyweight of isotonic saline was infused. This protocol was used to increase CVP comparable to values observed in HF patients(4, 19). Following saline 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 infusion protocol, had sufficient paired echocardiographic data (baseline + post-fluid) to assess the TAPSE:PASP relationship, whereas all 50 participants had invasive measurements obtained. All data were formally tested for normality using Shapiro-Wilk tests, histograms, and normal probability plots. Data was normally distributed, except TAPSE:PASP which was right skewed. Normative values are summarized as median (5th-95th percentile). Linear regression models and Pearson correlation were used to estimate the associations between listed variables. When analysing 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 pre- vs. post-infusion within individuals. Values are tabulated as mean (±standard deviation), unless otherwise stated. All analyses were conducted using STATA version 14 (College Station, TX).

Results

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

Right ventricular function and pulmonary coupling – effect of age

The TAPSE:PASP ratio decreased with age (Figure 1 and Table 2). The range of TAPSE:PASP among the participants was 0.71-2.67 mm/mmHg. The correlation between progressive age and declining TAPSE:PASP was significant (r: -0.35, p=0.006, Table 2). The regression coefficient was -0.0076 (95% confidence interval [95% CI] -0.013, -0.002), p=0.006. 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, 0.17], p=0.002), whereas TAPSE did not change with age (coefficient: 0.02 [-0.04, 0.08], p=0.47). Heart rate was not associated with TAPSE:PASP (p=0.52). Regression statistics are summarized in Table 2.

To dissect whether physiological 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=0.054).

**Right ventricular function and pulmonary coupling – effect of gender**

As listed in Table 1, 32/60 (53%) participants were female. There was no significant effect of gender on TAPSE:PASP (r: 0.14 [95% CI] -0.12, 0.38, p=0.30, Table 2), nor was there any interaction between age and gender (p=0.47) and TAPSE:PASP.

**Right ventricular function and pulmonary coupling – effect of rapid fluid bolus**

The fluid infused was mean (range) 744 ml (540-960 ml). The volume infused was independent of age (p=0.65). There was an increase in CVP from 5 ± 2 mmHg at baseline to 11 ± 4 mmHg after fluid infusion (p<0.0001). Both TAPSE and PASP increased, however PASP increased relatively more (PASP: +6.8 mmHg, p<0.0001; TAPSE: +1.6 mm, p=0.01, Table 3). This resulted in a 32% decrease in the TAPSE:PASP ratio after fluid infusion, compared to baseline (p<0.0001, Figure 2), with a ΔTAPSE:PASP range 0.49-1.73 mm/mmHg. Following 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 genders (p=0.90), nor
tolerance across ages (p=0.32), Table 3. The TAPSE:PASP was associated with CVP both at baseline (coefficient -0.06 [-0.11, -0.01], $r^2$: 19%, p=0.022) and after fluid infusion (coefficient -0.03 [-0.05, -0.01], $r^2$: 38%, p=0.012), whereas CVP was not associated with age, neither at rest (p=0.55), nor after fluid infusion (p=0.06). The normative baseline and post-fluid TAPSE:PASP ratio’s 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, 0.04], p=0.005, see Table 2 for correlation coefficients). The variance in the mPAP:CI 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), but this was not statistically significant (p=0.07). The changes in mPAP:CI after saline load did not differ with age (p=0.39), or between genders (p=0.79), Table 3.

Right ventricular function and pulmonary coupling assessment using invasive vs. sonographic measures

The association between invasively measured PASP and estimated PASP (echocardiography) was significant (r: 0.45, p=0.0006, Figure 4). The echocardiographic estimates tended to overestimate the PASP compared to invasively measured values: $PASP_{inv} = 0.33 \times PASP_{echo} + 13$. In effect, the TAPSE:PASP ratio was smaller if estimated PASP was used compared to the invasively measured PASP (baseline: 1.19 vs. 1.30 mm/mmHg, p=0.016. Post-fluid: 0.98 vs 0.81 mm/mmHg, p=0.0003)

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

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

Although the effect of physiological aging on the cardiovascular system has received attention in recent years(16, 20, 21), the relationship between aging and TAPSE:PASP ratio using invasive measurements has not been described in healthy humans to our knowledge. This precluded a recent consensus paper from ESC to list normative values, but rather stress 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 heart failure 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 (e.g. HF) on RV function from that of physiological aging seems prudent, as the latter is non-modifiable. In our healthy cohort progressive age was strongly associated with an increasing PASP, and hence 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 artery pressure(11, 12). Age modestly explained changes in TASPE:PASP ratio ($r^2 = 0.12$), but should be considered in any clinical evaluation or risk score pertaining to prognosis or
treatment decision. Hence, a low TASPE:PASP ratio in a younger patient is likely indicative of a more serious RV dysfunction, compared to a similar ratio in an older patient.

As age was significantly associated with PASP, we did further exploratory multivariable analyses adjusting age for blood pressure, heart rate, BMI, LVEF and $E/e'$, as 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 to 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 index was notable in our healthy population, which might make this metric difficult to use at an individual patient level for prognostication. However, we cannot 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, as estimated PASP tended to be higher than the invasively measured PASP. This should be noted when using normative values in clinical assessment.

As registries of HFpEF patients often show a predominance of women(15), it was of interest to learn if the physiological changes in TAPSE:PASP varied between genders. No gender differences in TAPSE:PASP were found at any age or slope of change with age. Hence, our data do not suggest that healthy women are more prone to right heart dysfunction with age, compared to 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 mmHg, making it comparable to the CVP measured in stable HFpEF patients (10 ± 4 mmHg), as reported by Borlaug et al (4). This group reported that the right heart pressure:flow relationship (i.e. mean pulmonary artery pressure:cardiac output) was impeded in HFpEF patients compared to healthy participant. However, the HFpEF group had more comorbidity, higher intake of vasoactive medications, and patients were on average 9 years older than the control group. In addition, the HFpEF patients showed signs of fluid overload compared to healthy (CVP 10 vs. 4 mmHg, respectively). Hence, some of these differences in pressure:flow relationship ascribed 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 void of comorbidity. We found that the mPAP:CI ratio was age-dependent. However, the magnitude of increase in mPAP:CI following saline infusion was not associated with age, as others have also reported (19). In participants between 60-80 years, there was an increase of 9% in PAPm:CI after fluid challenge, averaging a ratio of 6.4. In comparison, HFpEF patients have a ratio of approximately 10 at rest (4, 26), suggesting HF induced RV dysfunction beyond that of fluid overload and aging.

Our data suggests that age and fluid status not only influences 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 least HFpEF.

Our findings of no gender differences both at rest and following fluid bolus, does not give leverage to the belief that the female cardiovascular system is more physiologically prone to diastolic dysfunction compared to their male peers. Hence, the predominance of women in HFpEF registries
might be caused by longevity differences between genders, albeit conflicting data on this issue exists (14, 27, 28).

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 due to the invasive nature of the study and the ethical considerations in this context. This makes this study one of the largest studies with healthy individuals (25, 26, 29, 30), not least 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 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 Caucasian, which might limit the generalizability of our results and normative values to other races and ethnicities. Furthermore, as we used invasively determined PASP, our normative data should be assessed in this context, especially if only echocardiographic estimates of PASP are available.

In conclusion, this is the first invasive study to quantitate 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 gender 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 gain insight into the mechanisms behind the prognostic value of these metrics, and hence future targets of intervention.


Figure legends
Figure 1. Scatterplot of TAPSE:PASP and age in all participants (n=60).
Figure 2. Left pane: Scatterplot of TAPSE:PASP at baseline (black circles) and after fluid infusion (red circles) according to age (n=29).

Right pane: Boxplot of TAPSE:PASP at baseline and after fluid infusion (n=29).
Figure 3. Scatterplot of mPAP:CI and age at baseline (black circles, n=50) and after fluid infusion (red circles=50).
Figure 4. Scatterplot of TAPSE:PASP using either estimated PASP (echocardiography) or invasively measured PASP.
Table 1. Patient characteristics of all patients at baseline (Baseline, n=60), and the subset of patients who also underwent fluid infusion (n=50).

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n=60)</th>
<th>Fluid infusion (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>50 ± 17</td>
<td>51 ± 17</td>
</tr>
<tr>
<td>Male / Female</td>
<td>28 / 32</td>
<td>22 / 28</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75 ± 11</td>
<td>74 ± 11</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24 ± 3</td>
<td>24 ± 3</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.9 ± 0.2</td>
<td>1.9 ± 0.2</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>63 ± 10</td>
<td>64 ± 10</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>132 ± 17</td>
<td>133 ± 17</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>74 ± 12</td>
<td>74 ± 13</td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td>3.4 ± 0.8</td>
<td>3.4 ± 0.8</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>4.4 ± 1.1</td>
<td>4.4 ± 1.1</td>
</tr>
<tr>
<td>VO2 max (ml/min)</td>
<td>2627 ± 749</td>
<td>2578 ± 767</td>
</tr>
<tr>
<td>VO2 max – indexed (ml/min/kg)</td>
<td>35 ± 9</td>
<td>35 ± 9</td>
</tr>
<tr>
<td>Hemoglobin (mmol/l)</td>
<td>8.9 ± 0.7</td>
<td>8.9 ± 0.8</td>
</tr>
<tr>
<td>NT-proBNP (pmol/l)</td>
<td>7 [6; 12]</td>
<td>7 [6; 12]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n=60)</th>
<th>Fluid infusion (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF (%)</td>
<td>62 ± 7</td>
<td>62 ± 7</td>
</tr>
<tr>
<td>LVEDD (cm)</td>
<td>4.6 ± 0.7</td>
<td>4.6 ± 0.7</td>
</tr>
<tr>
<td>LA volume (ml)</td>
<td>40 ± 12</td>
<td>40 ± 13</td>
</tr>
<tr>
<td>E/A</td>
<td>1.5 ± 0.7</td>
<td>1.4 ± 0.7</td>
</tr>
<tr>
<td>E/e'</td>
<td>8.2 ± 2.7</td>
<td>8.3 ± 2.9</td>
</tr>
<tr>
<td>TR (mmHg)</td>
<td>18 ± 6</td>
<td>18 ± 6</td>
</tr>
<tr>
<td>TAPSE (mm)</td>
<td>26 ± 4</td>
<td>25 ± 4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n=60)</th>
<th>Fluid infusion (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVP (mmHg)</td>
<td>5 ± 2</td>
<td>5 ± 2</td>
</tr>
<tr>
<td>PASP (mmHg)</td>
<td>21 ± 5</td>
<td>21 ± 5</td>
</tr>
<tr>
<td>PADP (mmHg)</td>
<td>11 ± 4</td>
<td>11 ± 3</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>15 ± 4</td>
<td>15 ± 4</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>9 ± 3</td>
<td>9 ± 3</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>2.9 ± 0.5</td>
<td>2.9 ± 0.5</td>
</tr>
<tr>
<td>SVR (dynes/s·cm⁵)</td>
<td>1187 ± 348</td>
<td>1138 ± 340</td>
</tr>
<tr>
<td>PVR (mmHg/l/min)</td>
<td>1.2 ± 0.5</td>
<td>1.2 ± 0.5</td>
</tr>
</tbody>
</table>

BMI – body mass index. BSA – body surface area. HR – heart rate. SBP – systolic blood pressure. DBP – diastolic blood pressure. FEV1 – forced expiratory volume in 1 second. FVC – forced vital capacity. VO2 max – maximal oxygen consumption. LVEF – left ventricular ejection fraction. LVEDD – left ventricular end-diastolic diameter. LA – left atrial. TR – tricuspid 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 was summarized as median[IQR], all other variables as mean±SD.
Table 2. Correlations between hemodynamic variables and age/gender at baseline and after fluid infusion (Post-fluid).

<table>
<thead>
<tr>
<th></th>
<th>TAPSE</th>
<th>PASP</th>
<th>TAPSE:PASP</th>
<th>mPAP</th>
<th>CI</th>
<th>mPAP:CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$R$</td>
<td>$P$</td>
<td>$R$</td>
<td>$P$</td>
<td>$R$</td>
<td>$P$</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.09</td>
<td>0.47</td>
<td>0.38</td>
<td>0.002</td>
<td>-0.35</td>
<td>0.006</td>
</tr>
<tr>
<td>Gender</td>
<td>0.01</td>
<td>0.92</td>
<td>-0.08</td>
<td>0.52</td>
<td>0.14</td>
<td>0.30</td>
</tr>
<tr>
<td>Post-fluid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.01</td>
<td>0.96</td>
<td>0.42</td>
<td>0.003</td>
<td>-0.22</td>
<td>0.25</td>
</tr>
<tr>
<td>Gender</td>
<td>0.31</td>
<td>0.10</td>
<td>-0.04</td>
<td>0.76</td>
<td>0.21</td>
<td>0.29</td>
</tr>
</tbody>
</table>

$R=$-value, correlation coefficient; $P=$p-value

Table 3. Hemodynamic variables before and after rapid saline infusion (Post-fluid) in patients who underwent both measurements.

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n=50)</th>
<th>Post-fluid (n=50)</th>
<th>P-value*</th>
<th>P-values#</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAPSE (mm)</td>
<td>25±4</td>
<td>27±4*</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>PASP (mmHg)</td>
<td>21 ± 5</td>
<td>28 ± 7</td>
<td>&lt;0.001</td>
<td>0.08</td>
</tr>
<tr>
<td>TAPSE:PASP (mm/mmHg)</td>
<td>1.3 (0.8-1.8)</td>
<td>1.0 (0.5-1.5)*</td>
<td>&lt;0.001</td>
<td>0.32</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>15 ± 4</td>
<td>22 ± 5</td>
<td>&lt;0.001</td>
<td>0.82</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>9 ± 3</td>
<td>15 ± 4</td>
<td>&lt;0.001</td>
<td>0.74</td>
</tr>
<tr>
<td>CI (L/min/m$^2$)</td>
<td>2.9 ± 0.5</td>
<td>3.9 ± 1.0</td>
<td>&lt;0.001</td>
<td>0.012</td>
</tr>
<tr>
<td>mPAP:CI (mmHg/[L/min/m$^2$])</td>
<td>5.3 ± 1.3</td>
<td>5.8 ± 1.7</td>
<td>0.07</td>
<td>0.39</td>
</tr>
<tr>
<td>SVR (dynes/s·cm5)</td>
<td>1138 ± 340</td>
<td>804 ± 275</td>
<td>&lt;0.001</td>
<td>0.63</td>
</tr>
<tr>
<td>PVR (mmHg/l/min)</td>
<td>1.2 ± 0.5</td>
<td>1.0 ± 0.5</td>
<td>&lt;0.001</td>
<td>0.67</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>65 ± 9</td>
<td>72 ± 11</td>
<td>&lt;0.001</td>
<td>0.87</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>72 ± 11</td>
<td>80 ± 14</td>
<td>&lt;0.001</td>
<td>0.92</td>
</tr>
</tbody>
</table>

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. HR – heart rate. MAP – mean arterial pressure. *Paired t-test (baseline vs. post-fluid). Interaction P-values show whether age or gender influenced changes in hemodynamic variables from baseline to post-fluid. All variables are summarized as mean±SD, except TAPSE:PASP ratio, median (5th-95th percentile). All pressures and cardiac index were invasively measured. *n=29. # P-values of the main effect of age and gender when included as covariates.
Table 4. The TAPSE:PASP ratio at baseline and after a rapid saline infusion (Post-fluid).

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>20-39 years</th>
<th>40-59 years</th>
<th>60-80 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline (n=60)</strong></td>
<td>1.25 (0.81-1.78)</td>
<td>1.47 (0.91-1.67)</td>
<td>1.29 (0.81-1.76)</td>
<td>1.10 (0.76-1.57)</td>
</tr>
<tr>
<td><strong>Post-fluid (n=29)</strong></td>
<td>0.96 (0.54-1.53)</td>
<td>1.08 (0.68-1.73)</td>
<td>0.96 (0.54-1.33)</td>
<td>0.89 (0.49-1.53)</td>
</tr>
</tbody>
</table>

Values are median (5th-95th percentile).