Clinical Correlates and Reference Intervals for Pulmonary Artery Systolic Pressure Among Echocardiographically Normal Subjects

Brendan M. McQuillan, MBBS, FRACP; Michael H. Picard, MD; Marcia Leavitt, BS; Arthur E. Weyman, MD

Background—Data in normal human subjects on the factors affecting pulmonary artery systolic pressure (PASP) are limited. We determined the correlates of and established a reference range for PASP as determined by Doppler transthoracic echocardiography (TTE) from a clinical echocardiographic database of 102,818 patients, of whom 15,596 (15%) had a normal Doppler TTE study.

Methods and Results—A normal TTE was based on normal cardiac structure and function during complete Doppler TTE studies. The PASP was calculated by use of the modified Bernoulli equation, with right atrial pressure assumed to be 10 mm Hg. Among TTE normal subjects, 3790 subjects (2432 women, 1358 men) from 1 to 89 years old had a measured PASP. The mean PASP was 28.3 ± 4.9 mm Hg (range 15 to 57 mm Hg). PASP was independently associated with age, body mass index (BMI), male sex, left ventricular posterior wall thickness, and left ventricular ejection fraction (P < 0.001). The estimated upper 95% limit for PASP among lower-risk subjects was 37.2 mm Hg. A PASP > 40 mm Hg was found in 6% of those > 50 years old and 5% of those with a BMI > 30 kg/m².

Conclusions—Among 3790 echocardiographically normal subjects, PASP was associated with age, BMI, sex, wall thickness, and ejection fraction. Of these subjects, 28% had a PASP < 30 mm Hg, and the expected upper limit of PASP may include 40 mm Hg in older or obese subjects. These findings support the use of age- and BMI-corrected values in establishing the expected normal range for PASP. (Circulation. 2001;104:2797-2802.)

Key Words: hypertension, pulmonary obesity aging sex echocardiography

Data in humans on the factors affecting pulmonary artery systolic pressure (PASP) in otherwise normal subjects are limited. Small studies have reported associations with age,1–3 obesity,4 and systolic blood pressure.2 Recent reports of potential adverse effects of anorexigens on the pulmonary vasculature5,6 have increased awareness of pulmonary hypertension and raised questions about the appropriate normal values for pulmonary artery (PA) pressures for large populations of varying age and body habitus.

Transthoracic echocardiography (TTE) has been validated for the noninvasive assessment of cardiac structure and function in clinical and population studies.7 In individual subjects, estimation of right ventricular systolic pressure (RVSP) by Doppler TTE assessment of tricuspid valve regurgitation (TR) jet peak velocity accurately predicts the PASP observed by invasive measurement.8–10 It has been suggested, however, that Doppler TTE methods may overestimate PASP in population studies, because TR is more common and more easily recorded in patients with higher PASP.9

To evaluate the factors influencing observed PASP, we studied the clinical and echocardiographic correlates and range of PASP in echocardiographically normal subjects (“echocardiographic normals”) derived from a large clinical database. We examined trends in the detection of TR and the measurement of PASP and assessed their impact on observed PASP.

Methods

Subject Selection and Echocardiography

From a clinical echocardiography database of 102,818 reports recorded at the Massachusetts General Hospital between January 1, 1990, and December 31, 1999, we collected subjects with normal TTE studies. Normality was defined by (1) normal left (LV) and right (RV) ventricular function and dimensions, (2) normal left (LA) and right (RA) atrial dimensions, (3) absence of valvular stenosis, (4) absence of significant valvular insufficiency (absence of aortic regurgitation, mitral regurgitation less than mild, TR and pulmonic regurgitation less than moderate), (5) absence of aortic root dilatation, and (6) absence of pericardial disease.11 To reduce the influence of body size, height-adjusted values were considered for normal cardiac dimensions, and we adjusted for height in all regression analyses.12

TR was graded as none, trace, mild, moderate, or severe by assessment of the color-flow jet in relation to the RA area in multiple
TABLE 1. Clinical Indication for Doppler Transthoracic Echo Study

<table>
<thead>
<tr>
<th>Clinical Indication/Question</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murmur</td>
<td>5301 (34.0)</td>
</tr>
<tr>
<td>Palpitations/arrhythmia</td>
<td>3041 (19.5)</td>
</tr>
<tr>
<td>Assess LV function</td>
<td>2069 (13.3)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>753 (4.8)</td>
</tr>
<tr>
<td>Central source of embolus</td>
<td>743 (4.8)</td>
</tr>
<tr>
<td>Sepsis/infective endocarditis</td>
<td>679 (4.4)</td>
</tr>
<tr>
<td>Dyspnea/fungal disease</td>
<td>578 (3.7)</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>537 (3.4)</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>381 (2.4)</td>
</tr>
<tr>
<td>Pulmonary hypertension/pulmonary embolus/RV function</td>
<td>282 (1.8)</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>226 (1.4)</td>
</tr>
<tr>
<td>Pericarditis/myocarditis</td>
<td>219 (1.4)</td>
</tr>
<tr>
<td>Organ transplant recipient</td>
<td>171 (1.1)</td>
</tr>
<tr>
<td>Aortic disease</td>
<td>143 (0.9)</td>
</tr>
<tr>
<td>Anorexigen exposure</td>
<td>129 (0.8)</td>
</tr>
<tr>
<td>Family history of disease</td>
<td>115 (0.7)</td>
</tr>
<tr>
<td>Other</td>
<td>229 (1.5)</td>
</tr>
<tr>
<td>Total</td>
<td>15596 (100)</td>
</tr>
</tbody>
</table>

orthogonal views. Only subjects with less than moderate TR were considered for this analysis. With continuous-wave Doppler, the maximum peak TR velocity (V) recorded from any view was used to determine the RVSP with the simplified Bernoulli equation \( RVSP = 4V^2 + RAP \), with RA pressure (RAP) assumed to be 10 mm Hg. PASP was assumed to equate the RVSP in the absence of pulmonic stenosis and RV outflow tract obstruction. Reports were not excluded on the basis of the PASP values recorded unless criteria for normality were not met. All studies were interpreted by a clinical staff member experienced in TTE (level III, American Society of Echocardiography).

Demographic data and the indication for the TTE study were collected. Reports for subjects <1 year old were excluded because of the variability of PA pressures during early infancy. The indications for the TTE study are shown in Table 1. These indications were determined from the clinical echocardiography request forms and represent the question raised to initiate referral for Doppler TTE. It is important to note that many of the suspected conditions were excluded by a normal TTE (eg, a subject referred with the question “assess murmur” who had a normal Doppler echo study can be considered normal).

TABLE 2. Subject Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Normal Subjects (n=15596)</th>
<th>Tricuspid Regurgitation Present (n=10719)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absent (n=4877)</td>
<td>Present (n=10719)</td>
</tr>
<tr>
<td>Age, y</td>
<td>34.1±19.7</td>
<td>32.0±17.3</td>
</tr>
<tr>
<td>Women, %</td>
<td>54</td>
<td>59</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.56±0.19</td>
<td>1.61±2.8</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>61.1±20.7</td>
<td>67.5±27.2</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.4±7.0</td>
<td>24.1±5.6</td>
</tr>
<tr>
<td>Echo dimensions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aorta, mm</td>
<td>27.7±5.7</td>
<td>27.8±5.1</td>
</tr>
<tr>
<td>LA, mm</td>
<td>30.4±5.5</td>
<td>30.8±4.8</td>
</tr>
<tr>
<td>LV end-diastolic diameter, mm</td>
<td>43.8±6.6</td>
<td>44.8±5.8</td>
</tr>
<tr>
<td>Interventricular septum, mm</td>
<td>8.5±1.8</td>
<td>8.3±1.6</td>
</tr>
<tr>
<td>Posterior wall, mm</td>
<td>8.4±1.8</td>
<td>8.3±1.5</td>
</tr>
<tr>
<td>EF, %</td>
<td>69.5±6.3</td>
<td>69.2±5.9</td>
</tr>
</tbody>
</table>

Values are mean±SD. Measurements were performed at sea level.

Results

Subject Characteristics

Of 102,818 reports in the echo database entered between January 1, 1990, and December 31, 1999, 15,596 (15% of total; 8914 women, 6682 men) met the inclusion criteria for analysis in this study. The characteristics of subjects according to the presence of less than moderate TR and (among
those with TR) PASP recording are shown in Table 2. Subjects with less than moderate TR were slightly younger and had a lower body mass index (BMI), and a higher proportion were female, than those without TR. They also had marginally larger LA and LV end-diastolic diameters and a lower ejection fraction (EF) but thinner LV walls. Among those with TR, subjects with a recorded PASP (n = 3790) had similar echocardiographic dimensions and BMI but were more likely to be men and were older than those in whom a PASP was not obtained (Table 2). Among the 3790 subjects with a recorded peak TR velocity, the mean RV-to-RA gradient was 18.3 ± 4.9 mm Hg (range, 5 to 47 mm Hg), equivalent to a mean PASP of 28.3 ± 4.9 mm Hg.

Detection of TR and PASP Recording
Overall, less than moderate TR was detected in 69% (n = 10 719) of those with a normal TTE. Detection of less than moderate TR increased progressively from 48% (631/1303) of subjects with a normal TTE in 1990 to 80% (1573/1965) of normals in 1999 (P < 0.001). Similarly, PASP recording increasing progressively from 9% (57/631) of those with trace or mild TR in 1990 to 59% (926/1573) in 1999 (P < 0.001). Despite this increased sensitivity for the detection of TR and the recording of a PASP, the annual mean PASP remained relatively constant (range of means, 27.1 to 29.0 mm Hg). The mean absolute difference in PASP between years was 0.5 mm Hg (range, 0 to 1.9 mm Hg). After adjustment for age and sex, there was no difference in the annual mean PASP over the last 5 years of observation.

Correlates of PASP and Predictors of Elevated PASP
On bivariate analyses, PASP was associated with age (Spearman ρ [r] = 0.25), BMI (r = 0.19), interventricular septal...
After adjustment for age and BMI, men had higher PASP than women (adjusted mean PASP, 28.8 versus 28.0 mm Hg, respectively; \( P < 0.001 \)). The Figure demonstrates the mean PASP across age (A) and BMI (B) groups for each sex.

On multiple linear regression analyses, age, BMI, male sex, EF, posterior wall thickness, and clinical referral category composed the best predictive model for PASP (model \( R^2 = 0.12 \), \( P < 0.001 \)). Similar factors composed the best-fit models for PASP among analyses restricted to women (excluding sex as a variable) (\( R^2 = 0.17 \), \( P < 0.001 \)), subjects >20 years old (\( R^2 = 0.14 \), \( P < 0.001 \)), and those at lower risk of pulmonary hypertension (\( R^2 = 0.12 \), \( P < 0.001 \)).

The mean PASPs for each referral category, adjusted for age, sex, and BMI, are shown in Table 3. General linear model analysis indicated a significant overall association between referral category and mean PASP (\( P < 0.001 \)). The highest observed mean PASP was among subjects with a history of suspected or known pulmonary hypertension, pulmonary embolism, or RV dysfunction (30.6±6.8 mm Hg). With reference to the index category (“assess murmur”), the 4 highest PASP categories were found to have higher mean PASPs (Table 3).

Among 3790 subjects with a recorded PASP, 1060 (28%) had a PASP >30 mm Hg. We used multiple logistic regression to determine the predictors of a PASP >30 mm Hg. We found age (>50 years) (OR 2.69; 95% CI 2.24, 3.23), BMI (>30 kg/m²) (OR 1.67; 95% CI 1.34, 2.07), LV posterior wall thickness (>9 mm) (OR 1.54; 95% CI 1.30, 1.82), and male sex (OR 1.27; 95% CI 1.09, 1.48) to be independent predictors of a higher PASP (all \( P < 0.01 \)).

### PASS Reference Range
Among all subjects with a recorded PASP (\( n = 3790 \)), the mean PASP was 28.3±4.9 mm Hg (95% CI 18.7, 37.9 mm Hg). This 95% upper limit is equivalent to a peak TR velocity of 2.64 m/s. After exclusion of subjects referred for TTE because of the suspicion of clinical conditions that may be associated with pulmonary hypertension (\( n = 578 \); see Table 3), the mean PASP in the remaining subjects (\( n = 3212 \)) was 28.0±4.7 mm Hg (95% CI 18.8, 37.2 mm Hg; peak TR velocity 2.61 m/s). Among these lower-risk subjects, we also defined age- and BMI-specific 95% reference ranges for PASP in women and men (Table 4).

### Discussion
In this study of 15 596 echocardiographic normals studied over a decade, we observed an almost linear increase in the sensitivity of echo Doppler techniques for the recording of less than moderate TR and measurable RV-to-RA pressure gradients. Despite this increased recording sensitivity for TR, we observed consistency in the mean population PA pressures for each year. Among these echocardiographic normals, there was a clear stratification of PASP based on referral category. There were also significant associations between PASP and the demographic variables age, sex, and BMI and the echocardiographic measures of LV wall thickness and LV EF.

### Detection of TR and Recording of PASP
The estimation of PASP by Doppler techniques requires a detectable TR jet. Early Doppler TTE studies suggested that the proportion of patients with recordable TR increased with increasing PA pressure and that TR was difficult to record in normals. Because of this tendency to undersample regurgi-
tant lesions in patients with lower PA pressures, it has been suggested that Doppler TTE tends to systematically overestimate PA pressures in population studies. In our study, the percentage of echocardiographic normals in whom less than moderate TR could be detected increased from 48% in 1990 to 80% in 1999. Because it is unlikely that the actual prevalence of trace or mild TR has increased, we attribute this change to improvements in instrumentation and recording techniques. Interestingly, the mean PASP has not changed significantly from the beginning to the end of our study, despite the increase in the percentage of “normals” in whom these values were recorded. If there had been a systematic bias in favor of higher PA pressures, one would have expected the mean PASP to decrease each year as the percentage of recordable trivial and mild TR increased, which was not the case. Formal assessment of the reproducibility for measurements of peak TR velocity in our database was not undertaken. A lower reproducibility may be expected for clinical studies compared with research trials, which would be expected to increase the range of observed PASP values.

Referral Categories and PASP

Attempts to define normal values for PA pressure have proven difficult, and many strategies have been used. Studies of selected normals or control groups for other echocardiographic studies are generally small and nonrandomized and therefore suffer from potential selection bias and fail to provide the power to reveal many of the associations demonstrated in this article. The commonly used reference values for PA pressure are derived from catheterization normals. Although similar in concept to the use of echocardiographic normals as a reference group, patients referred for catheterization are likely to be more selected than those referred for echocardiography.

Our reference normal group (assess murmur; n=1414; 37% of the total) is consistent with the populations represented in most studies of echocardiographic normals in which patients with suspected confounding diseases are excluded a priori. The mean PASP for this group was 28.1 mm Hg. The grand mean for all subjects (28.3 mm Hg) and the mean after exclusion of groups with PASP values significantly higher than the reference group (27.9 mm Hg) differ from the reference mean by only 0.2 mm Hg, which is well below the accuracy of clinical measurement.

Similar values for PASP have been observed in previous studies based on echocardiographic normals. In a study of 53 subjects 14 to 55 years old who were screened for cardiac and pulmonary disease, Aessopos et al reported a mean RV-to-RA gradient of 19.3 mm Hg (equivalent to a PASP of 29.3 mm Hg if RA pressure is assumed to be 10 mm Hg). Dib et al found a mean PASP of 26.6 mm Hg among 134 subjects 20 to 85 years old. In young, highly conditioned athletes, an average peak TR velocity of 2.25 m/s (equivalent to a PASP of 30.2 mm Hg) has been reported. Thus, our mean values approximate the midpoint of other smaller studies. Because our subjects were not formally screened for the presence of conditions known to be associated with elevated PA pressure, the inclusion of subjects with such conditions would tend to increase the observed mean PASP, and the present study should be interpreted in this context.

Correlates of PASP

This study has demonstrated an independent association of age, male sex, and BMI with PASP among echocardiographic normals. Age was the strongest predictor of PASP, with an average increase in PASP of 0.8 mm Hg per decade over the wide age range studied. Previous studies in small groups of patients have also reported an association between age and PASP. Although there is variability between studies, there is an increase in PASP of $\approx 1$ mm Hg per decade of age among echocardiographic normals. This has been attributed to an increase in pulmonary vascular resistance and decreased LV compliance with aging.

We also noted that after adjustment for age, PASPs were significantly higher in men than in women. This finding differs from most previous reports and may relate to the large numbers in our study and the fact that we have corrected these values for differences in age between the sex groups. Of the echocardiographic parameters, LV posterior wall and interventricular septal thickness were independently associated with PASP even within the normal range of wall thickness considered in this study, a relationship not previously appreciated. LV wall thickness may relate to PASP through diastolic dysfunction and the effects of decreased LV compliance and increased LV end-diastolic pressure with aging and in such conditions as systemic hypertension.

Although LV dysfunction is associated with pulmonary hypertension in a variety of cardiac diseases, we observed a positive association between LV EF and PASP within the normal range of EF (ie, as the EF increased, the PASP increased). LV EF also correlated directly with LA size and LV end-diastolic internal diameter but remained predictive of PASP independent of these dimensions. The correlation of LVEF with LA and ventricular diameters suggests that the increase in EF may be mediated by the Frank-Starling mechanism. Increased EF and cardiac output (with higher pulmonary blood flow) may result in an increased PA pressure unless there is an accompanying decrease in pulmonary vascular resistance. Obesity is associated with an increased cardiac output, which may explain the association between BMI and PASP in this and other studies.

Noninvasive Estimation of PASP

Doppler TTE has become the noninvasive method of choice in the estimation of PASP. A number of studies have found close correlation between Doppler-determined estimates by use of the peak TR jet velocity and simultaneous catheter-derived measures To convert the RV-to-RA gradient to an absolute pressure, some estimate of RA pressure is required. Most commonly, a constant of 10 mm Hg is used, which has been shown to result in the most accurate prediction of PASP across the whole range of pressures encountered clinically. The constant 10 mm Hg, however, may overestimate RA pressure in patients with lower PA pressures and underestimate RA pressures in those with significantly elevated PA pressures. Other approaches, such as the use of a constant value of 5 mm Hg, reporting the transvalvular gradients...
instead of an absolute value for PASP,\textsuperscript{14} or the estimation of RA pressure from changes in inferior vena cavaal diameter during inspiration,\textsuperscript{17} have been used as alternatives. Because the 10 mm Hg value for RA pressure used in this study is a constant, individuals preferring to use other approaches may substitute different values for RA pressure without changing associations.

### Comparison With Invasive Hemodynamic Data
The most widely used normal values for PA pressures are derived from catheterization studies.\textsuperscript{18} The upper limits for PA pressure in this and other studies of echocardiographic normals are often higher than those given from hemodynamic studies. This difference most likely relates to the constant used to estimate RA pressure and differences in the selection of subjects. Although values for normal PA pressure from catheterization studies are presented in standard textbooks of cardiology,\textsuperscript{11,18,19} these values are often not referenced, so analysis of the groups from which they are derived is difficult.

Data on the risks of systemic arterial hypertension and the benefits of blood pressure treatment are based predominantly on noninvasive measurement of arterial blood pressure. There are, however, sparse data on the potential risks associated with increasing PASP. PA pressure has been identified as a predictor of mortality in patients with primary pulmonary hypertension\textsuperscript{20} and subjects undergoing cardiac catheterization who had significant comorbid disease\textsuperscript{21} or dilated cardiomyopathy.\textsuperscript{22} These studies are of limited value to the assessment of morbidity and mortality associated with PA pressure in the general population. The widespread application of noninvasive Doppler TTE techniques for the assessment of PASP provides more meaningful data in less selected subjects and can ethically be applied to prospective community-based studies to determine whether there is an independent relationship between PA pressure and disease. From these studies, it may then be possible to establish whether there is a threshold of PA pressure above which adverse events are more likely or whether there is a graded risk of disease across the range of pressures encountered clinically. Pending such data, it seems reasonable to establish independent echo Doppler TTE reference ranges for PASP, because such values are likely to be the standard for future population studies.

### Conclusions
This study represents the largest reported assessment of the clinical correlates of PASP. Detection of trivial or mild TR and measurement of PASP progressively improved during the past decade without an apparent impact on the observed mean PASP among echocardiographic normals. The ages and BMIs of subjects should be considered in the interpretation of their PASPs. We observed higher PASP in men than in women, independent of age and BMI. PASP correlated with LV wall thickness and EF, even within the normal range for these values. Among subjects with a normal Doppler TTE, 28% had a PASP $>30$ mm Hg. The expected upper limit of PASP is dependent on age, sex, and BMI and may include 40 mm Hg in some older or obese subjects.

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### References
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