Pulmonary arterial pulse pressure and mortality in pulmonary arterial hypertension

Kevin G. Blyth, Raheel Syyeda, James Chalmers, John E. Foster, Tarek Saba, Robert Naeije, Christian Melot, Andrew J. Peacock

Scottish Pulmonary Vascular Unit, Western Infirmary, Dumbarton Road, G11 6NT Glasgow, UK
University Libre de Bruxelles, Brussels, Belgium

Received 26 March 2007; accepted 5 July 2007
Available online 24 August 2007

KEYWORDS
Pulmonary arterial hypertension; Pulse pressure; Mortality; Survival

Summary
In the Framingham studies, systemic arterial pulse pressure correlated linearly with morbidity and mortality. Right ventricular (RV) systolic dysfunction and pulmonary circulation stiffening result in abnormalities of pulmonary arterial (PA) pulse pressure in PA hypertension (PAH). We investigated the prognostic potential of PA pulse pressure in 67 patients with PAH diagnosed between January 1996 and March 2004 (33 idiopathic PAH, 34 PAH-connective tissue disease). The population was arbitrarily divided into tertiles of PA pulse pressure (systolic/diastolic PA pressure) and 5-year mortality was assessed using the Kaplan–Meier method. The extent of RV systolic dysfunction and pulmonary circulation stiffening within each tertile was assessed by comparing the mean cardiac index and \( \alpha \) (a recently described measure of pulmonary circulation distensibility) in each. Independent predictors of mortality were identified by Cox regression.

Five-year mortality rates in patients with low, intermediate and high pulse pressures were 40%, 91% and 54%, respectively. Pulse pressure did not independently predict mortality, but cardiac index, 6-min walk test distance and mixed venous oxygen saturation did. Pulse pressure correlated with circulation stiffening (\( \alpha \)) but did not correlate with cardiac index which tended to be lower in patients with intermediate pulse pressure and high mortality. PA pulse pressure correlated with pulmonary circulation stiffening but did not predict mortality in this study. RV dysfunction provided better prognostic information and probably explains the higher mortality seen in patients with intermediate pulse pressure.

© 2007 Elsevier Ltd. All rights reserved.

Introduction
Pulmonary arterial hypertension (PAH) is a characterised by proliferative vascular remodelling within the small resistance
vessels of the lung, a reduction in the recruitability and
distensibility of the pulmonary vascular bed and subsequent
stiffening of the proximal, elastic, pulmonary vasculature in
response to elevated transmural pulmonary arterial pressure
(PAP).

Although elevated mean PAP is essential in the diagnosis
of PAH the prognostic influence of mean PAP at diagnosis has
proven inconsistent. Several previous studies found no
association between mean PAP and survival,\(^1\)\(^-\)\(^3\) while others
suggested that a high mean PAP at presentation conferred a
greater risk of early death.\(^4\) A single study identified an
apparently paradoxical association between low baseline
mean PAP and early mortality.\(^5\) Novel haemodynamic
variables that provided information on survival in PAH
would, therefore, be useful.

Survival in PAH is known to be largely dependent on right
ventricular (RV) function. The pressure loading conditions of
the RV in PAH are dictated by two individual pressure
components; one constant and one pulsatile. Mean PAP
describes the constant component and reflects steady flow
conditions within the distal resistance vessels of the lung.
The pulsatile component, in contrast, reflects the combined
effects of RV dysfunction and reduced pulmonary circulation
distensibility,\(^6\)\(^-\)\(^8\) or stiffening, and can be simply described
by pulmonary arterial pulse pressure (PA pulse pressure).
From animal models of PAH we know that pulmonary
vascular remodelling results in the early return of “reflec-
ted” pressure waves generated during RV contraction. If
these waves return early enough they will be transmitted to
the still ejecting RV before pulmonary valve closure. The
resulting increase in RV afterload adversely affects RV
systolic function.\(^7\) PA pulse pressure, therefore, tends to
increase as PAH progresses. Since recent evidence, including
the Framingham studies have demonstrated a linear
correlation between systemic arterial pulse pressure and
cardiovascular morbidity and mortality\(^9\)\(^-\)\(^14\) we hypothesised
that increasing PA pulse pressure would predict mortality in
patients diagnosed with PAH. The following study was
performed to test this hypothesis.

Methods

Study population

In March 2005 the Scottish Pulmonary Vascular Unit (SPVU)
database was reviewed retrospectively. Sixty-seven pa-
tients, diagnosed with PAH between January 1996 and
February 2004, were identified. Patients with pulmonary
hypertension due to other causes were excluded. Thirty-
three patients had idiopathic PAH (IPH); the remainder had
PAH associated with connective tissue disease (PAH-CTD).
Demographic and haemodynamic data for the study popula-
tion are summarised in Table 1. Of the 67 patients studied 3
were NYHA class I, 21 were NYHA class II, 28 were NYHA class
III and 15 were NYHA class IV. All patients underwent right
heart catheterisation\(^15\)\(^,\)\(^16\) and 6-min walk testing\(^17\) using
established techniques and standard diagnostic algorithms
were used to assess all patients.\(^19\)

Right heart catheterisation was performed using a 7F balloon
tipped, triple lumen thermodilution catheter (Edwards Life

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>50:17</th>
<th>56 (14)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (♀:♂)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical data</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic PA(^+) pressure (mmHg)</td>
<td>78 (22)</td>
<td></td>
</tr>
<tr>
<td>Diastolic PA pressure (mmHg)</td>
<td>28 (11)</td>
<td></td>
</tr>
<tr>
<td>Mean PA pressure (mmHg)</td>
<td>48 (14)</td>
<td></td>
</tr>
<tr>
<td>PVR(^1) (mmHg/l/min)</td>
<td>12 (6)</td>
<td></td>
</tr>
<tr>
<td>Cardiac index (l/min/m(^2))</td>
<td>2.2 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Mean right atrial pressure (mmHg)</td>
<td>7 (5)</td>
<td></td>
</tr>
<tr>
<td>PA occlusion pressure (mmHg)</td>
<td>9 (4)</td>
<td></td>
</tr>
<tr>
<td>PA pulse pressure (mmHg)</td>
<td>50 (15)</td>
<td></td>
</tr>
<tr>
<td>Mixed venous oxygen saturation (%)</td>
<td>63 (9)</td>
<td></td>
</tr>
<tr>
<td>Six-minute walk test distance (m)</td>
<td>275 (117)</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean(±1 SD).
\(^*\)PA: Pulmonary artery.
\(^1\)PVR: Pulmonary vascular resistance.

Data collection

The following variables were recorded for each patient from
these baseline tests: mean pulmonary artery pressure (PAP),
systolic PAP, diastolic PAP, mean right atrial pressure, mixed
venous oxygen saturation, pulmonary artery occlusion
pressure (PAOP), total pulmonary resistance (TPR) and
distance completed at 6-min walk test. PA pulse pressure
was determined in all subjects as systolic PAP–diastolic PAP.
For all subjects alive at the time of the study, survival was
recorded in months from the date of baseline right heart
catheterisation. For those patients who had died, survival
was recorded from date of catheterisation until death.

Statistics

For all variables a normal distribution was verified using
histograms and Kolmogorov–Smirnov tests. Normally distri-
uted variables were summarised by mean±one standard
deviation (±SD), non-normally distributed variables were
summarised by median (interquartile range). Correlations
were tested by Pearson’s method (after logarithmic trans-
formation for non-normally distributed variables). Patients
were stratified into tertiles of PA pulse pressure (low
\((<43\text{ mmHg}, n=22)\), intermediate \((44–54\text{ mmHg}, n=23)\)
and high \((\geq 55\text{ mmHg}, n=22)\)). Kaplan–Meier mortality
curves were generated for these tertiles and any inequality
in mortality rate was assessed by log rank testing. Differences
in the risk of death between tertiles were quantified by hazard
ratios (95% confidence interval). The extent of RV systolic
dysfunction and pulmonary circulation stiffening within each
tertile was assessed by comparing the
mean cardiac index and mean $\alpha$ (a recently described measure of pulmonary circulation distensibility, see below) of each. Differences in cardiac index and $\alpha$ were quantified by a one-way ANOVA (equal variances not assumed), utilising Tukey’s HSD test.

Independent predictors of mortality were identified by multivariable Cox regression after univariable regression analysis was performed for each recorded variable. Multivariable models were constructed using variables within the univariable regression analysis with $p$-values $\leq 0.2$ or those variables that we were particularly interested in studying, e.g., PA pulse pressure. The most efficient model for survival was identified using likelihood ratio testing. A backward elimination method was employed to eradicate any suppressor effect. All variables in the multivariable analyses were entered as continuous variables and met the assumptions of proportional hazards. Co-variables with a correlation coefficient $\geq 0.8$ were tested within separate regression models to avoid the effects of collinearity. The influence of individual predictor variables within survival models was determined by examining $\exp(\beta)$ (95% confidence interval), interpreted as hazard ratio for death per unit of the predictor variable. A $p$-value of $<0.05$ was considered statistically significant in all tests. All analyses were performed using SPSS for Windows 11.5 (Chicago, USA).

**Determination of $\alpha$**

The pulmonary circulation $\alpha$ coefficient, $\alpha$, can be used to describe pulmonary circulation distensibility in PAH. $\alpha$ can be determined from a distensible vessel model summarised below. This model has been described in detail elsewhere.\(^{18}\)

Mean $\text{PAP} = \frac{[(1 + \alpha \text{PAWP})^5 + 5\alpha \text{TPL.CO}]}{\alpha}$. Preliminary in vitro experiments have shown that the distensibility of isolated human pulmonary vessels, when described by $\alpha$, appears (a) a consistent characteristic of all of component vessels within the pulmonary circulation of a given individual and (b) independent, within that individual, of vessel diameter.\(^{19}\)

Subsequent authors have demonstrated diminished $\alpha$ in normal exercising humans under conditions of chronic, but not acute hypoxia and lower $\alpha$ in elderly subjects compared with young adults.\(^{18}\) These results are in keeping with the pulmonary vascular remodelling known to occur in chronic,\(^{20}\) but not acute hypoxia and age-related pulmonary vascular stiffening.\(^{21}\)

We utilised a mathematical equation solver within the MATLAB software package (MathWorks Inc., MA, USA) to determine $\alpha$ values for patients in our study, using the method of successive iterations. The values necessary for the computation of $\alpha$ were available in 61/67 patients (in six patients PA OPs were unavailable or technically unsatisfactory).

**Results**

During the study period 29/67 (43%) patients died (19/29 were female). The survival of patients with IPH and PAH-CTD was similar; median survival, for example, was 44 months in both groups (log rank $p = 0.213$). 12/29 patients who died had IPH. In all of the patients who died, the cause of death was felt to be related to PAH. The mean follow-up period for the study population was 26 ($\pm$ 20) months. The proportion of patients within each tertile of PA pressure that received individual therapies for PAH are summarised in Table 2.

PA pulse pressure was normally distributed in the study population. Mean PA pulse pressure was 49 ($\pm$ 16) mmHg. $\alpha$ was non-normally distributed. Median $\alpha$ was 0.036 (0.029–0.044). After logarithmic transformation mean log $\alpha$ was $-1.434$ (0.132).

Five-year mortality rate was highest in patients with intermediate pulse pressure (log rank statistic 10.25, $p = 0.006$, see Figure 1). Estimated 5-year mortality rates were 40%, 91% and 54% in patients with low, intermediate and high pulse pressures, respectively. The hazard ratio

<table>
<thead>
<tr>
<th>Low PAPP (%)</th>
<th>Intermediate PAPP (%)</th>
<th>High PAPP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>91</td>
<td>87</td>
</tr>
<tr>
<td>IV Epoprostenol</td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td>SC Treprostinil</td>
<td>14</td>
<td>22</td>
</tr>
<tr>
<td>Inhaled Iloprost</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td>Bosentan</td>
<td>27</td>
<td>30</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>9</td>
<td>26</td>
</tr>
<tr>
<td>CCBs*</td>
<td>27</td>
<td>43</td>
</tr>
</tbody>
</table>

Note that cumulative percentages will exceed 100 as multiple therapies were prescribed in most patients.

*CCBs: Calcium channel blockers.

Figure 1 Kaplan–Meier mortality curves were generated for tertiles of pulmonary artery pulse pressure determined in 67 patients with pulmonary arterial hypertension. The highest mortality was seen in patients with intermediate pulse pressure (log rank statistic 10.25, $p = 0.006$).

\(^{1}a\)
for death in patients with intermediate pulse pressure (44–54 mmHg) was over four times that seen in patients with low pulse pressure (≤ 43 mmHg) (HR 4.4 (1.5–12.2), p = 0.004). Although 5-year mortality rate appeared higher in patients with high (54%) vs. low (40%) pulse pressures, the hazard ratio for death was not significantly different between these groups.

PA pulse pressure correlated linearly with pulmonary circulation stiffening, indicated by a powerful inverse correlation with pulse pressure and log \( x \) (\( r = -0.838, p < 0.001 \), see Figure 2). \( x \) decreased significantly as pulse pressure rose through the three pulse pressure groups (0.048 (0.039–0.062) in the low group, 0.037 (0.032–0.041) in the intermediate group and 0.028 (0.027–0.03) in the high group) (see Figure 2(a)).

We found no correlation, in contrast, between pulse pressure and cardiac index (\( r = -0.148, p = 0.24 \)). Mean cardiac index tended to be lower in patients with intermediate pulse pressure (mean CI 2.0 (0.6) l/min) than it was in the high (mean CI 2.2 (0.6) l/min) or low (mean CI 2.4 (0.7) l/min) pulse pressure groups (see Figure 2(b)). These differences were replicated when mixed venous oxygen saturation was substituted for cardiac index as an alternative correlate of RV function (see Figure 2(c)), but in neither case did the differences reach statistical significance.

**Independent predictors of mortality**

Results of the initial univariable analyses are shown in Table 3. In a multivariable Cox regression model, summarised in Table 4, cardiac index, mixed venous oxygen saturation and 6-min walk test distance provided the best prognostic information. PA pulse pressure did not add prognostic information (Exp (\( \beta \)) (95% CI) = 0.999 (0.97–1.028), \( p = 0.93 \)).

---

**Figure 2** Pulmonary arterial pulse pressure and \( x \) were computed and correlated against each other in 67 patients with Pulmonary arterial hypertension (\( r = -0.838, p < 0.001 \)).

**Figure 3** Mean (±SD) log \( x \), cardiac index and mixed venous oxygen saturation were determined for each tertile of pulmonary arterial pulse pressure (PA pulse pressure) measured in 67 patients with pulmonary arterial hypertension. (a) Pulmonary circulation distensibility, as described by log \( x \), decreased progressively with each tertile of increasing PA pulse pressure. (b) There was a trend towards lower cardiac index in patients with intermediate PA pulse pressure. This difference did not achieve statistical significance. (c) There was a similar trend towards lower mixed venous oxygen saturation in patients with intermediate PA pulse pressure. This difference did not achieve statistical significance.
Discussion

In our study, PA pulse pressure correlated linearly with the degree of pulmonary circulation stiffening (see Figures 2 and 3(a)); however, this was not translated directly into an increase in mortality. Pulse pressure correlated poorly with cardiac index and did not predict survival when tested as an independent value. This poor prognostic performance is consistent with that of mean PAP in previous studies of patients with PAH.1-5 Our results reiterate the importance of cardiac index, mixed venous oxygen saturation and 6-min walk test distance, which are direct correlates of RV function and as such, proved the most reliable predictors of prognosis in our patients as has been shown before.1,3,4,22

In our study, mortality was highest in patients with intermediate pulse pressure (91%) in whom the risk of death was over four times that seen in patients with low pulse pressures. The poor independent prognostic performance of pulse pressure dictates that prognostic significance should not be attributed to intermediate levels of pulse pressure per se and can probably be understood by examining the relationship between pulse pressure and RV function. In our study we found a trend towards more significant RV dysfunction in the intermediate pulse pressure group, as defined by cardiac index and mixed venous oxygen saturation in Figures 3(b) and (c). We believe that this RV dysfunction, which determined survival in our study, is likely to explain the excessive mortality in these patients, although our results cannot definitively prove this.

A precedent for this concept that ventricular function can modify the potential prognostic impact of circulatory stiffening has recently been reported in patients with renal failure on haemodialysis23 and type-2 diabetes mellitus.24 In these groups, left ventricular dysfunction has been shown to be responsible for unexpectedly high mortality rates in patients with low systemic pulse pressures and, therefore, minimal arterial stiffening. Similar findings have also been reported in patients with PAH in whom low mean PAP has been associated with early mortality and attributed to RV dysfunction in an earlier study.2

We considered the possibility that the higher mortality of patients with intermediate pulse pressure might have reflected differences in the treatments given to the groups. Although there was some variation in the proportions of patients in each tertile treated with individual therapies, as shown in Table 2, we believe that any potential confounding effect of therapy should not be overstated. Only intravenous Epoprostenol has been shown, in a randomised controlled trial,25 to improve survival after diagnosis in patients with PAH, although Warfarin26 and Bosentan27 have been shown to influence survival in retrospective survival analyses. All patients in the current study were treated according to standardised treatment guidelines based on disease severity; however, the drugs available for treatment did change.

### Table 3
Results of univariable linear regression analysis of clinical & haemodynamic variables against survival in 67 patients with pulmonary arterial hypertension.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio</th>
<th>Low 95%CI</th>
<th>High 95%CI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic PAP* (mmHg)</td>
<td>1.006</td>
<td>0.990</td>
<td>1.022</td>
<td>0.469</td>
</tr>
<tr>
<td>Diastolic PAP* (mmHg)</td>
<td>1.008</td>
<td>0.978</td>
<td>1.039</td>
<td>0.592</td>
</tr>
<tr>
<td>Mean PAP* (mmHg)</td>
<td>1.008</td>
<td>0.984</td>
<td>1.033</td>
<td>0.513</td>
</tr>
<tr>
<td>PVR (mmHg/L/min)†</td>
<td>1.059</td>
<td>1.010</td>
<td>1.110</td>
<td>0.017</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>0.251</td>
<td>0.110</td>
<td>0.573</td>
<td>0.001</td>
</tr>
<tr>
<td>RAP† (mmHg)</td>
<td>1.053</td>
<td>0.969</td>
<td>1.144</td>
<td>0.223</td>
</tr>
<tr>
<td>PAOP† (mmHg)</td>
<td>1.036</td>
<td>0.943</td>
<td>1.138</td>
<td>0.459</td>
</tr>
<tr>
<td>PA pulse pressure (mmHg)</td>
<td>1.008</td>
<td>0.985</td>
<td>1.031</td>
<td>0.502</td>
</tr>
<tr>
<td>MV O2 saturation (%)</td>
<td>0.938</td>
<td>0.900</td>
<td>0.976</td>
<td>0.002</td>
</tr>
<tr>
<td>6MWT** distance (m)</td>
<td>0.996</td>
<td>0.992</td>
<td>0.999</td>
<td>0.01</td>
</tr>
</tbody>
</table>


### Table 4
Multivariable Cox regression analysis in 67 patients with pulmonary arterial hypertension.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Exp (β)</th>
<th>Low 95% CI</th>
<th>High 95% CI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>0.279</td>
<td>0.102</td>
<td>0.760</td>
<td>0.013</td>
</tr>
<tr>
<td>MV O2 saturation (%)</td>
<td>0.954</td>
<td>0.913</td>
<td>0.997</td>
<td>0.038</td>
</tr>
<tr>
<td>6MWT† distance (m)</td>
<td>0.996</td>
<td>0.993</td>
<td>0.999</td>
<td>0.048</td>
</tr>
</tbody>
</table>

*MV O2: Mixed venous oxygen saturation.†6MWT: Six-minute walk test.
during the study period with the development of novel oral agents such as Bosentan and Sildenafil for use in NYHA class II and III patients. All NYHA class IV patients would have been treated with IV Epoprostenol throughout the study period.

Patients with PAH-CTD are known to have a worse prognosis than those with IPAH, however, there were equal numbers of each in the intermediate pulse pressure cohort and median survival was, in our study, identical for patients with PAH-CTD and IPH (44 months in each). We have therefore concluded that this factor cannot explain the mortality of the intermediate group either.

Conclusion

PA pulse pressure proved a poor independent predictor of mortality in PAH. We do not, therefore, propose its use in this way. Instead, our findings emphasise the complicated nature of the relationship between PAP components, RV function and mortality encountered by previous authors of studies in PAH.1–3 Measurements that integrate information on pulmonary circulation distensibility and RV function, such as pulmonary arteriolar capacitance which has recently been described by Mahapatra and colleagues,28 may provide better prognostic information in future studies.

Acknowledgement

Kirsty Menzies is acknowledged for her assistance with data collection.

Conflict of Interest Statement

None

Funding

Dr. Blyth’s salary was provided by the National Services Division of the Scottish Executive. No other funding sources or sponsors.

Ethics

This was a retrospective study of data routinely acquired in the diagnosis of patients with PAH. Forty-three percent of the patients had died by the time of the data collection. No ethical permission was felt necessary or sought.

References

PA pulse pressure and mortality in PAH


