In Rotterdam, size really does matter: implications of pulmonary artery enlargement on mortality

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For quite some time, we have known that pulmonary hypertension (PH) is associated with an increased risk of death in chronic obstructive pulmonary disease (COPD) [1, 2]. The occurrence of PH in the context of chronic lung diseases is often the result of hypoxic pulmonary hypertension and is classified as Group III PH by the World Health Organization (WHO) [3]. The diagnosis of PH requires a high index of suspicion, as symptoms are often vague and nonspecific, particularly among individuals with pre-existing respiratory disease. PH is defined by hemodynamic measurement during right-sided heart catheterisation (RHC), even though RHC is not routinely performed in COPD, because of the invasive nature of the procedure and the lack of efficacious treatments [4–6]. Comorbid PH independently accounts for worsening dyspnoea, fatigue, impaired exercise tolerance and poor quality of life in COPD [7, 8], and is associated with increased risk of hospitalisation and higher mortality [2, 3, 9].

With advances in imaging technologies, many studies have evaluated the utility of various noninvasive surrogate markers for PH. These include echocardiography [10, 11], cardiac magnetic resonance imaging (MRI) [12] and computed tomography (CT) [9, 13–17]. Recently, there has been significant interest in the use of CT in COPD, with several studies evaluating the utility of the ratio of the pulmonary artery to ascending aortic diameter (PA:A ratio) and pulmonary arterial enlargement [15–19]. The PA:A has been calculated in several cohorts of healthy patients and those with different chronic respiratory conditions, and correlates with PA pressures as measured by RHC [9, 15–17, 20–22] and worsening clinical outcomes [15, 17, 18, 20, 21, 23–25]. In a cohort of very severe COPD patients, the PA:A correlated with invasive haemodynamics, and a PA:A >1 independently predicted PH defined as a mean PA pressure >25 mmHg at right heart catheterisation with a sensitivity of 73% and a specificity of 84% [16]. Moreover, its presence was independently associated with an increased risk of severe COPD exacerbations [17] and an increased risk of cardiac injury and in-hospital mortality in individuals hospitalised with COPD exacerbations [18]. The PA:A ratio also predicts increased mortality in patients with advanced lung disease; a PA:A>1 was significantly associated with an increased risk of mortality in patients with very severe COPD who were undergoing evaluation for lung transplantation [15]. Similar findings were reiterated in a similar study on idiopathic pulmonary fibrosis (IPF) [20]. The associations between the PA:A and clinical outcomes in

TABLE 1 Associations between the ratio of the pulmonary artery to ascending aortic diameter (PA:A ratio) and clinical outcomes

Study	Population	PA:A value	Outcome	Results
Wells et al. [17] (2012)	3464 patients with COPD	PA:A >1	Severe AECOPD	OR 3.44 (2.78–4.25)*
			Any AECOPD	OR 1.86 (1.54–2.24)*
	2005 patients with COPD	PA:A >1	Severe AECOPD in 1 year	OR 2.8 (2.11–3.71)*
			Any AECOPD in 1 year	OR 2.17 (1.71–2.74)*
			Severe AECOPD in 3 years	OR 3.81 (3.04–4.78)*
			Any AECOPD in 3 years	OR 6.68 (4.47–9.96)*
Nakanishi et al. [23] (2013)	1326 healthy patients	PA:A >0.9	Mortality	HR 3.2 (1.6–6.6)*
Baptista et al. [24] (2013)	39 patients with acute PE	PA:A	Mortality	NS
Shin et al. [15] (2014)	65 patients with advanced COPD	PA:A >1	Transplant-free survival	HR 5.05 (1.63–15.6)*
Karakus et al. [25] (2015)	159 patients with HFpEF	PA:A	Cardiovascular events	OR 1.068 (1.035–1.103)*
Wells et al. [18] (2016)	134 patients hospitalised for AECOPD	PA:A >1	Cardiac injury (troponin >0.01)	2-fold elevation in troponin
			ICU admission, respiratory failure, or death	2- to 3-fold increased incidence
Wells et al. [21] (2016)	74 patients with CF	PA:A >1	Acute exacerbation of CF in 1 year	OR 3·49 (1.18–10.3)*
	190 patients with CF	PA:A >1	Acute exacerbation of CF in 2 years	OR 2·41 (1.06–5.52)*
Shin et al. [20] (2016)	98 patients with IPF	PA:A >1	Transplant-free survival	HR 3.35 (1.54–7.26)*

COPD: chronic obstructive pulmonary disease; AECOPD: acute exacerbation of chronic obstructive pulmonary disease; PE: pulmonary embolism; NS: nonsignificant; HFpEF: heart failure with preserved ejection fraction; ICU: intensive care unit; CF: cystic fibrosis; IPF: idiopathic pulmonary fibrosis. *: p<0.05.

COPD and other diseases are shown in table 1. These studies however, have all been conducted in well-defined research populations or highly selected subgroups. Thus, little is known about the utility of the PA:A in a general population.

In the current issue of *The European Respiratory Journal*, Terzikhan *et al.* [26] explored the association of the PA:A ratio and all-cause mortality in a Dutch general population. This study was conducted using the well-described Rotterdam cohort, a large prospective population-based cohort. It included 2197 participants, of which 222 (10.1%) had COPD. Participants were followed for a median of 8.8 years, with 423 (19.3%) deaths being reported. The mortality rate in the COPD subgroup was two-fold higher than that in the entire population, with cardiovascular events accounting for most of these deaths. The PA diameter in the general population was 26±3.7 mm, whereas the PA:A was 0.71±0.10. These findings are consistent with those from the Framingham Heart Study, in which a PA diameter of 29 mm was observed in men and 27 mm in women, and a PA:A ratio of 0.9 was established as normal [19]. The COPD cohort had a mean PA:A of 0.72±0.10, similar to the general population. PA enlargement defined as a PA:A>1 was only present in 17 subjects (0.77%); thus, the authors evaluated the PA:A as a continuous measure. The authors found an association between an elevated PA:A and increased risk of mortality in patients with COPD, but not in the general population. This association was primarily driven by findings in severe COPD. Moreover, in patients with moderate to severe COPD, there was a significantly increased risk of mortality at higher quartiles of the PA:A values, with those at the highest PA:A quartile exhibiting a three-fold risk of mortality compared to those in the lowest quartile. Furthermore, Terzikhan *et al.* found a significant association between the PA:A and PH, defined as a pulmonary artery systolic pressure (PASP) >40 mmHg on echocardiography in both non-COPD and COPD groups.

The increased risk of all-cause mortality observed in individuals with PA enlargement and COPD does not come as much of a surprise. Epidemiological studies focused on idiopathic pulmonary arterial hypertension have reported a low prevalence of the disease in the general population, estimated to be around 5.9 cases per million adults [27]. Therefore, the prevalence of PA abnormalities is also expected to be low. In contrast, the prevalence of PH in COPD is thought to be anywhere between 10%–85%, depending on the severity of the disease and the methods used for its diagnosis [16]. In addition, 20%–37% of patients with COPD have PA abnormalities, with a PA:A >1 [9, 16]. PH occurs more commonly in severe COPD and the development of elevated pulmonary artery pressures is often associated with hypoxia-mediated vascular changes [28]. Although the study by Terzikhan *et al.* confirmed the associations between the PA:A and metrics suggestive of PH on echocardiography, it is noteworthy that

the PA:A ratio and PA enlargement are not absolutely indicative of PH. Mechanisms other than PH, including inflammation, airway remodelling [29] and hyperinflation also contribute to PA:A abnormalities [9]. Likewise, other comorbid conditions, including heart failure, morbid obesity, sleep apnoea, PA aneurysms and pulmonary embolism can affect the PA:A [30].

The study has many strengths, including the large cohort size, the prospective design and the generalisability achieved by including a large population of both healthy and sick individuals in the outpatient clinic setting. This is the first study to examine the PA:A ratio in a general population, rather than a carefully selected cohort such as those undergoing lung transplant evaluation or critically ill patients. However, it does also have several important limitations. First, PH was defined using echocardiographic measurements of PA systolic pressure, which have been shown to lack diagnostic accuracy in patients with hyperinflation and advanced obstructive lung disease [10]. The use of measurements from RHC might have revealed a greater number of patients with elevated pulmonary artery pressures, especially those with mild to moderate COPD. Second, the COPD group only comprised 10% of the study cohort and among this group, only 10.6% (n=22) had severe airflow obstruction. Increases in the risk of mortality were only observed in this small subset of the study cohort. These findings are consistent with those reported by SHIN et al. [15] and suggest that the PA:A might have the greatest prognostic utility for mortality in severe COPD. Third, the study did not report acute exacerbations of COPD in the cohort. Exacerbations are an important confounder to consider, given the associations between these events and the PA:A with mortality. Future studies should evaluate effect modifications due to exacerbations and the resulting associations between the PA:A and mortality. Finally, although this cohort is representative of the larger population, one cannot help but notice the relative absence of other comorbid conditions that are associated with PH.

Overall, the study by TERZIKHAN et al. [26] demonstrates the utility of the PA:A in a cohort of patients with COPD, sampled from a general population. However, it also raises additional questions about our understanding of the PA:A. Would the prevalence of PA enlargement increase if a greater number of patients with conditions associated with PH were included in the cohort? How do exacerbations influence the associations between PA:A and mortality? Does the PA:A change over time, and if so, do changes influence the risk of mortality? This study reveals just how much we still have to learn about the utility of the PA:A ratio in COPD. Given the enormous public health burden that COPD presents, there is a need to better understand the implications of imaging-based biomarkers like the PA:A for future studies and for clinical practice. This study is an important first step in this process.

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