

The authors also demonstrated sex differences in effects, which could be attributed to variations in personal exposures and, consequently, different degrees of exposure misclassification between men and women. This limitation is common in environmental studies lacking detailed information about cohort lifestyles and behavioral patterns, and it warrants more attention to these issues.

It is essential to note that none of the previous studies assessed the relationship between UFP and lung cancer by histologic subtype but that several studies on the larger particulate matter fractions have also found associations with specific subtypes. The authors' identification of an association with adenocarcinoma underscores the importance of considering etiologic heterogeneity across lung cancer histologic subtypes. There is evidence indicating that environmental risk factors are a primary driver for the steady increase in adenocarcinoma cases among lung cancer cases in recent years.

So, do we now know more about UFP and health? This paper certainly adds another piece to the large puzzle by presenting suggestive evidence for a role of UFP in the development of lung cancer. It supports prior studies on air pollution and adenocarcinoma of the lung and presents plausible biological pathways. Even more importantly, it is an example of a creative and thoughtful way to combine available current and historical information in the effort to assess (unmeasured) historical exposures. More studies like this are needed to finish the puzzle. ■

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Barbara Hoffmann, M.D., M.P.H.  
Katherine Ogurtsova, Ph.D.  
Medical Faculty  
Heinrich Heine University Düsseldorf  
Düsseldorf, Germany

ORCID IDs: 0000-0002-8435-5575 (B.H.); 0000-0002-3002-1916 (K.O.).

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## Ⓒ Pulmonary Artery Wedge Pressure in the Diagnosis of Pulmonary Arterial Hypertension

The diagnosis of pulmonary arterial hypertension (PAH) incorporates a pulmonary artery wedge pressure (PAWP)  $\leq$  15 mm Hg to exclude pulmonary hypertension (PH) due to left heart diseases (PH-LHD) (1). In this issue of the *Journal* (pp. 316–324), Harder and colleagues report data suggesting that the PAWP cutoff of 15 mm Hg may need to be reduced (2).

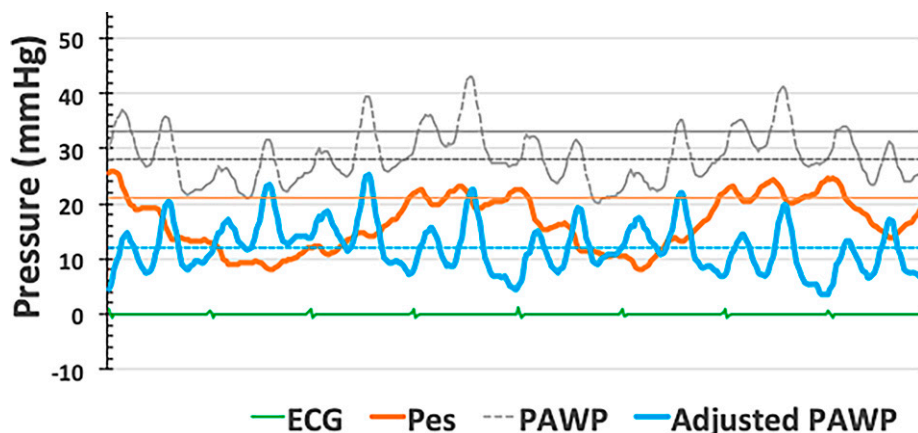
Harder and colleagues performed a longitudinal cluster analysis in 301 patients with PAH that revealed two distinct patterns of

PAWP progression: in one group the PAWP remained  $<$  15 mm Hg (76% of the patients), and in another group the PAWP increased to  $>$  15 mm Hg (24% of the patients). Baseline PAWP was around 9 and 12 mm Hg for the former and latter groups, respectively. A baseline PAWP  $>$  12 mm Hg predicted a higher PAWP during follow-up, which was associated with a greater number of heart failure with preserved ejection fraction risk factors and reduced transplant-free survival. Thus, patients with PAH with a baseline PAWP  $\geq$  12 mm Hg show characteristics of PH-LHD during follow-up (2).

A recent report by Gerges and colleagues in 593 patients with chronic thromboembolic PH found that a PAWP  $>$  15 mm Hg or  $>$  11 mm Hg was present in 11% and 37% of the patients, respectively (3). A PAWP above either cutoff was associated with a greater number of cardiovascular risk factors and worse long-term survival,

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**Figure 1.** Pulmonary artery wedge pressure (PAWP) and esophageal pressure (Pes) measurements in a patient with obesity and obstructed airways. Pressure tracings show large respiratory swings, with end-expiratory pressures being the highest. Pes is positive during the entire respiratory cycle in relation to the mechanical effects of morbid obesity in the supine position. Adjusting for Pes reduces PAWP from 33 mmHg at end-expiration (gray solid line) or 27 mmHg mean (gray dashed line) to 12 mmHg (blue solid line).

further supporting that a PAWP cutoff value  $\leq 15$  mm Hg fails to exclude a substantial proportion of patients with PH-LHD.

The PAWP cutoff to define postcapillary PH has evolved over time. It was initially set at 10–11 mm Hg, up to 12 mm Hg at the first World Symposium on Pulmonary Hypertension in 1973 (4, 5). In fact, a PAWP  $< 12$  mm Hg was one of the inclusion criteria required to enroll patients with idiopathic PAH (at that time called “primary PH”) in the National Institute of Health registry in the 1980s (6). However, the PAWP cutoff increased to 15 mm Hg in PH guidelines in the 2000s. Why? The main argument was not to preclude patients with PAH with concomitant LHD from receiving the newly developed PAH-specific therapies.

The heart and pulmonary circulation are exposed to subatmospheric pressure generated by the opposing elastic recoil of the lungs and chest wall. Intrathoracic pressure further decreases during inspiration; nevertheless, pressure changes are generally small (around 1–2 mm Hg in resting supine healthy subjects) because of the high compliance of the respiratory system. Hyperventilation is associated with more negative inspiratory and more positive expiratory pressures and may result in dynamic hyperinflation, with a disproportionate increase in the magnitude and duration of end-expiratory pulmonary pressures. Dynamic hyperinflation may occur in healthy subjects during moderate to strenuous exercise, but it may also be observed in patients with airway obstruction or obesity during low-intensity exercise or even at rest (7–9). In severe obesity, altered abdominal and chest wall mechanics may result in positive intrathoracic pressure throughout the respiratory cycle (9). In these circumstances, PAWP and left ventricular end-diastolic pressure (LVEDP) measured at end-expiration increasingly reflect the contribution of a higher intrathoracic pressure (10, 11). Figure 1 shows PAWP and esophageal pressure (a reflection of the intrathoracic pressure) in an obese patient with airway obstruction.

For the interpretation of PAWP, a correction for esophageal pressure as shown in Figure 1 would be ideal, but this is not practical. A generally acceptable compromise, except in morbid obesity, is to measure PAWP throughout the respiratory cycle (10, 11). End-expiratory and respiratory cycle-averaged PAWP most often differ by an average of 3 to 4 mm Hg, but with pronounced individual

differences in patients with cardiorespiratory conditions (7–9). It is difficult to speculate by how much PAWP would have increased at end-expiration in the studies by Harder and colleagues (2) or Gerges and colleagues (3)

Would LVEDP determination overcome the PAWP limitations? The answer is no. The Pascal principle applies; therefore, PAWP and LVEDP have to be equal, based on the stop-flow phenomenon downstream to a wedged pulmonary artery catheter (10). As a matter of fact, Gerges and colleagues demonstrated no significant bias in Bland-Altman analysis when PAWP and LVEDP determinations were compared (3). However, this similarity is only present when PAWP is measured at end-diastole, at the “pre-c wave” nadir, as was actually done by Gerges and colleagues (12). In cases in which “a or c waves” are not clearly identifiable, the measure may be timed with the QRS (10, 13). Electronic PAWP averaging, including “v waves,” slightly underestimates LVEDP but overestimates LVEDP in the presence of significant mitral valve disease and/or heart failure (10). Harder and colleagues measured the PAWP as an electronic mean (2), excluding patients with valvular heart disease or heart failure; hence, the difference between averaged and end-diastolic PAWP was probably negligible.

So, where do we go from here? Mounting evidence supports the revision of the current end-expiration PAWP cutoff of  $\leq 15$  mm Hg to exclude PH-LHD in the diagnostic workup of patients with PAH. Recent PH guidelines use the upper limit of normal for mean pulmonary artery pressure and pulmonary vascular resistance but not PAWP (1). The upper limit of normal of PAWP is 12 mm Hg. The PAWP measurement should be averaged over several respiratory cycles and strictly taken at end-diastole. When the PAWP determination is not consistent with the clinical scenario, which may be related to technical factors and/or inherent physiological variability (14), it is advised to repeat the PAWP measurement during exercise or after a fluid challenge (1). Qaiser and colleagues showed that PAWP measurements around the upper limit of normal often disclose occult PH-LHD after a fluid challenge (15). In general, one should be wary of clinical decisions based in a single number and carefully consider the applicability in a specific patient of guideline cutoffs derived from population studies.

Harder and colleagues (2) are to be commended for revitalizing the debate about PAWP measurement methodology and the upper limit of normal. Their study convincingly shows that current guidelines do not sufficiently exclude patients with heart failure who benefit less from PAH-specific therapies. ■

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Robert Naeije, M.D., Ph.D.  
Free University of Brussels  
Brussels, Belgium

Adriano R. Tonelli, M.D., M.Sc.  
Cleveland Clinic  
Cleveland, Ohio

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