Original Article

Wedge Pressure vs Left Ventricular End-Diastolic Pressure for Pulmonary Hypertension Classification and Prognostication in Severe Aortic Stenosis

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ABSTRACT

Background: Differentiation between precapillary and postcapillary pulmonary hypertension (PH) classically relies on mean pulmonary artery wedge pressure (mPAWP). The left ventricular end-diastolic pressure (LVEDP) is proposed as an equivalent alternative. However, mPAWP and LVEDP may differ substantially. We compared the impact of the choice of using the mPAWP vs the LVEDP on PH classification and mortality prediction in patients with severe aortic stenosis (AS) undergoing valve replacement.

Methods: In 335 patients with severe AS, both mPAWP and LVEDP were measured. A mean pulmonary artery pressure \( \geq 25 \text{ mm Hg} \) was defined as postcapillary PH, whereas \( \leq 15 \text{ mm Hg} \) was considered precapillary PH.

Results: In patients with pulmonary hypertension (PH), differentiating between precapillary and postcapillary forms is crucial because this has major impact on the further diagnostic and therapeutic approach. There is, however, an ongoing controversy about the best measure of "left-sided filling pressure" to use for this purpose. According to the 2015 guidelines and the 2018 World Symposium on Pulmonary Hypertension proposal, a mean pulmonary artery wedge pressure (mPAWP) \( > 15 \text{ mm Hg} \) vs \( \leq 15 \text{ mm Hg} \) differentiates postcapillary from precapillary PH. However, guidelines also emphasize that measurement of mPAWP can be challenging, and that when in doubt, left heart catheterization with measurement of the left ventricular end-diastolic pressure (LVEDP) should be performed.

However, mPAWP and LVEDP are pressures measured at different sites and at different time points, and they therefore reflect different pathophysiological aspects. There is increasing evidence that mPAWP and LVEDP are not interchangeable but may differ substantially and that this may be clinically relevant. The LVEDP provides information on the properties of the left ventricle, including active relaxation and passive stiffness, whereas the mPAWP reflects not only left ventricular performance but also left atrial hemodynamics, mitral valve disease, and the properties of the pulmonary veins.

The relationship between mPAWP and LVEDP may depend on the cardiac rhythm, and at least in certain settings, the prognostic value of mPAWP and LVEDP also differs substantially.

Accordingly, the PH classification may be significantly affected by the choice of mPAWP or LVEDP to be used to differentiate between postcapillary and precapillary PH. In patients with severe aortic stenosis (AS), PH is common, and prognosis depends on the presence and hemodynamic classification of PH. In the present study, we measured both mPAWP and LVEDP in a sizeable cohort of patients with severe AS undergoing aortic valve replacement (AVR). The aim of the study was to compare the PH classification using the standard mPAWP-based approach vs a previously
used to define PH, and either mPAWP or LVEDP was used to differentitate between precapillary and postcapillary PH ($< 15$ vs $> 15$ mm Hg). Mortality after a median follow-up of 1484 days after aortic valve replacement was assessed.

**Results:** Overall, mPAWP was lower than LVEDP ($16.8 \pm 8$ mm Hg vs $21.8 \pm 8$ mm Hg; $P < 0.001$). Among 140 patients (42%) with PH, the PAWP-based classification revealed 76 (54%) of those with PH) with isolated postcapillary PH, 48 (34%) with combined pre- and postcapillary PH, and 16 (12%) with precapillary PH. When the LVEDP was used, 59 patients (42%) were differently classified. These patients had higher mortality than those who were not differently classified [hazard ratio 2.79 (95% confidence interval, 1.17-6.65); $P = 0.02$]. Higher mPAWP was associated with increased mortality [hazard ratio 1.07 (95% confidence interval, 1.03-1.11) per 1 mm Hg; $P = 0.001$], whereas higher LVEDP was not.

**Conclusions:** Use of LVEDP rather than mPAWP results in a divergent PH classification in nearly every second patient with severe AS. These patients have higher mortality after aortic valve replacement. The mPAWP, but not the LVEDP, predicts mortality.

Published LVEDP-based approach and their prognostic implications, and to assess the prognostic role of mPAWP and LVEDP as single parameters. We hypothesized that an mPAWP-based approach vs an LVEDP-based approach would result in a substantially divergent PH classification, and that the mPAWP is a better prognostic predictor than the LVEDP in this setting.

### Materials and Methods

#### Study population

This is a subgroup analysis of prospectively collected data from a cohort of consecutive patients with severe AS undergoing cardiac catheterization prior to AVR in a single center between January 2011 and January 2016 (entire cohort: $n = 503$). For the present analysis, we included all patients in whom—apart from complete right heart catheterization—left heart catheterization with retrograde passage through the aortic valve into the left ventricle was performed, and LVEDP and mPAWP were measured in a near simultaneous manner—that is, within a few minutes. For inclusion into this analysis, patients were required to have complete data on systolic pulmonary artery pressure (sPAP), diastolic PAP (dPAP), and mean PAP (mPAP), mPAWP, LVEDP, and cardiac output (CO), so that an mPAWP-based and LVEDP-based PH classification was feasible. Patients with relevant mitral stenosis were excluded. The study protocol was approved by the local ethics committee (ethics committee of Eastern Switzerland, project number 2016-02113). We have previously reported on other hemodynamic factors in this population.

### Cardiac catheterization and hemodynamic definitions

Procedures were generally (> 95%) performed in the morning in the fasting state and after withholding loop diuretics and renin—angiotensin system inhibitors. Patients underwent coronary angiography using 5 or 6 F catheters via the femoral or radial artery, and right heart catheterization was feasible. Pa-
The hemodynamic parameters were calculated as follows:

\[ PVR = \frac{(mPAP - mPAWP)}{CO} \]

stroke volume = CO / heart rate

pulmonary capacitance = stroke volume / (sPAP - dPAP)

standard diastolic pressure gradient (DPG) = dPAP - mPAWP

\[ LVEDP-based DPG (DPG_{LVEDP}) = dPAP - LVEDP \]

\[ \Delta_{mPAWP-LVEDP} = mPAWP - LVEDP. \]

For the mPAWP-based PH classification, \(^1\) the standard DPG was used. For the LVEDP-based PH classification, a DPG\(_{LVEDP}\) was calculated as defined above. \(^17\) This method of DPG\(_{LVEDP}\) calculation has been used previously in one of the key papers on PH in patients with AS. \(^17\) This is not strictly according to current guidelines, but it is a way to get an idea of the pulmonary vascular component of PH when using a purely LVEDP-based PH classification. We also calculated \(\Delta_{mPAWP-LVEDP}\) as defined above as a simple measure of the relationship between mPAWP and LVEDP, although this is not a true physiological parameter. \(^8\) This parameter has recently been used in a study comparing mPAWP and LVEDP in patients with heart failure with preserved ejection fraction. \(^7\)

### PH definitions based on mPAWP vs LVEDP

For this study, we used the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) PH guidelines because: (i) all available invasive studies on PH in AS are based on this definition (recently summarized by Maeder et al. \(^11\)); and (ii) there is a published LVEDP-based PH definition that also relies on the 2015 definition. \(^17\) Any PH was defined as mPAP \(\geq 25\) mm Hg. \(^1\) The mPAWP- and LVEDP-based PH definitions are shown in Figure 1. According to the original 2015 ESC/ERS guidelines, \(^1\) PH is defined as mPAP \(\geq 25\) mm Hg; isolated postcapillary PH (IpcPH) is defined as mPAP \(\geq 25\) mm Hg, mPAWP > 15 mm Hg, PVR \(< 3\) WU, and/or DPG \(< 7\) mm Hg; combined pre- and postcapillary PH (CpcPH) is defined as mPAP \(\geq 25\) mm Hg, mPAWP > 15 mm Hg, PVR > 3 WU, and/or DPG \(\geq 7\) mm Hg, and precapillary PH is defined as mPAP \(\geq 25\) mm Hg and mPAWP \(\leq 15\) mm Hg. However, by this definition, there are unclassifiable patients (ie, those with discordant PVR and DPG: PVR \(\leq 3\) WU but DPG \(\geq 7\) mm Hg, or PVR > 3 WU but DPG < 7 mm Hg). \(^18\) Therefore, for the PAWP-based definition, IpcPH was defined as mPAP \(\geq 25\) mm Hg, mPAWP > 15 mm Hg, PVR \(\leq 3\) WU, and/or DPG \(< 7\) mm Hg; CpcPH was defined as mPAP \(\geq 25\) mm Hg, mPAWP > 15 mm Hg, and PVR > 3 WU and/or DPG \(\geq 7\) mm Hg (Fig. 1A). This approach is supported by the recent observation that among patients with PH in the context of left heart disease, those with PVR > 3 WU and/or DPG \(\geq 7\) mm Hg had a similar prognosis as those with PVR > 3 WU and DPG \(\geq 7\) mm Hg, whereas both groups had worse survival than those with PVR \(\leq 3\) WU and DPG < 7 mm Hg. \(^19\) For the LVEDP-based classification, IpcPH was defined as mPAP \(\geq 25\) mm Hg, LVEDP > 15 mm Hg, and DPG\(_{LVEDP}\) \(< 7\) mm Hg; CpcPH was defined as mPAP \(\geq 25\) mm Hg, LVEDP \(> 15\) mm Hg, and DPG\(_{LVEDP}\) \(\geq 7\) mm Hg; and precapillary PH was defined as mPAP \(\geq 25\) mm Hg and LVEDP \(\leq 15\) mm Hg (Fig. 1B). \(^17\)

### Echocardiography

All patients had an echocardiogram prior to cardiac catheterization, as a basis for the referral. Echocardiograms were performed by an experienced cardiologist according to contemporary guidelines but not according to a specified protocol. The data were retrospectively obtained from the reports. Right ventricular function was assessed by the tricuspid annular plane systolic excursion (TAPSE). To describe right ventricular to pulmonary artery coupling, we calculated the ratio TAPSE/sPAP \(^20\) (sPAP measured by right heart catheterization). Given the prognostic importance of right ventricular function, \(^21\) and right ventricular to pulmonary artery coupling, \(^22\) respectively, in AS patients, we assessed their relationship with mPAWP and LVEDP to better understand the differential pathophysiological importance of these 2 hemodynamic parameters.
Follow-up

Information on long-term follow-up was obtained from patients, general practitioners, and hospital or practice cardiologists. The clinical endpoint was all-cause mortality.

Statistical analysis

Categorical data are presented as numbers and percentages, and continuous data are reported as mean ± standard deviation or median (interquartile range), as appropriate. A Bland–Altman plot was constructed to visualize bias and limits of agreement between mPAWP and LVEDP. Correlations between mPAWP and LVEDP and other parameters of interest were described by Pearson correlation coefficients (ln-transformation of parameters with a skewed distribution) to highlight possible differences in mPAWP and LVEDP regarding the pathophysiology of PH. Meng’s test was used to determine whether there was a significant difference in the strength of univariate correlations.25 Patients were divided into quartiles based on mPAWP, LVEDP, and ΔmPAWP-LVEDP, to illustrate clinical and hemodynamic differences and detect possible gradients of risk. Patients in different quartiles for mPAWP, LVEDP, and ΔmPAWP-LVEDP were compared using χ² tests, analysis of variance, or Kruskal–Wallis tests, as appropriate. Survival of patients in different quartiles for mPAWP, LVEDP, and ΔmPAWP-LVEDP was compared using Kaplan–Meier plots and log–rank tests. Cox regression was used to describe the association between variables of interest and mortality. For a more intuitive demonstration of differences in the prognostic impact, we constructed receiver operator characteristic curves to assess the area under the curve for mPAWP, LVEDP, and ΔmPAWP-LVEDP, to predict mortality after AVR. A P-value < 0.05 was considered statistically significant. Analyses were performed using SPSS statistical package version 20.0 (SPSS Inc., Chicago, IL) and “R” version 4.0.2. (R Core Team, Vienna, Austria).

Results

Study population

We studied 335 patients with a mean age of 74 ± 10 years, and 61% were males. The mean indexed aortic valve area was 0.44 ± 0.13 cm²/m², and the mean left ventricular ejection fraction was 57% ± 12%. Detailed clinical characteristics, echocardiographic findings, and invasive hemodynamics of the entire study population are presented in Tables 1 and 2. Patients underwent surgical (74%) or transcatheter (26%) AVR after a median interval of 21 (12-35) days after cardiac catheterization. After a median follow-up of 1484 (1064-1944) days post-AVR, there were 30 deaths. Causes of death were perioperative/periprocedural within the first 30 days (n = 12), cancer (n = 2), infection (n = 1), clearly cardiovascular (n = 2), and unknown (n = 13).

mPAWP vs LVEDP

The overall group-average mPAP was 25 ± 10 mm Hg. Overall, mPAWP was lower than LVEDP (16 ± 8 mm Hg vs 21 ± 8 mm Hg; P < 0.001; mean ΔmPAWP-LVEDP := −5 ± 7 mm Hg). In 88 patients, mPAWP was higher than or equal to LVEDP, whereas in 247 patients, mPAWP was lower than LVEDP. The correlation between mPAWP and LVEDP was statistically significant but only moderate (r = 0.54; P < 0.001). Apart from the systematic bias (ΔmPAWP-LVEDP), the Bland–Altman plot revealed large limits of agreement between mPAWP and LVEDP (Supplemental Fig. S1). There were very close correlations between mPAP and mPAWP (r = 0.91; P < 0.001) and between mPAP and the PAWP v wave (r = 0.85; P < 0.001), whereas the correlation between mPAP and LVEDP (r = 0.48; P < 0.001) was only moderate (P < 0.001 by Meng’s z-test for the comparison of the strength of the correlations).

PH classification according to mPAWP vs LVEDP

There were 140 of 335 patients (42%) with PH. The mPAWP-based classification revealed 76 of 140 (54%) of those with PH patients with IpcPH, 48 of 140 (34%) with CpcPH, and 16 of 140 (12%) with precapillary PH. According to the LVEDP-based classification, 114 of 140 patients (82%) had IpcPH, 16 of 140 (11%) had CpcPH, and 10 of 140 (7%) had precapillary PH. Among the 140 patients with PH, 59 (42%) were differently classified when using the LVEDP-based rather than the standard mPAWP-based classification: 14 were reclassified from precapillary PH to IpcPH, 2 from CpcPH to precapillary PH, 6 from IpcPH to precapillary PH, 35 from CpcPH to IpcPH, and 2 from IpcPH to CpcPH (Fig. 2A). Among the 140 patients with PH, reclassified patients (divergent PH classification based on mPAWP or LVEDP) had significantly higher mortality than those who were not reclassified (discordant PH classification based on mPAWP and LVEDP; Fig. 2B; hazard ratio 2.79 [95% confidence interval [CI],1.17-6.65]; P = 0.02). The higher mortality of the reclassified patients was driven by patients who were reclassified from CpcPH to IpcPH when using the mPAWP-based rather than the LVEDP-based classification (hazard ratio 4.26 [95% CI, 1.74-10.44]; P = 0.002; referent: non reclassified PH patients).

Categorization according to mPAWP, LVEDP, and ΔmPAWP-LVEDP quartiles

Patients in the highest mPAWP quartile had the highest prevalence of atrial fibrillation, the highest B-type natriuretic peptide plasma concentration, the most severe symptoms, the most severe AS, the lowest left ventricular ejection fraction, the largest left atrial size, the most severe mitral regurgitation, and the worst right ventricular function. These patients also had the highest right atrial pressure, mPAP, LVEDP, and PVR, and the lowest pulmonary artery capacitance and stroke volume index (Tables 1 and 2). Clinical characteristics, echocardiographic findings, and invasive hemodynamics of patients categorized according to LVEDP and ΔmPAWP-LVEDP quartiles are shown in Supplemental Tables S1-S4.

The inverse correlation with TAPSE was strongest for mPAWP (mPAWP: r = −0.39; LVEDP: r = −0.18; ΔmPAWP-LVEDP: r = −0.27). The inverse correlation with the TAPSE/mPAP ratio was also strongest for mPAWP (mPAWP: r = −0.73; LVEDP: r = −0.43; ΔmPAWP-LVEDP: r = −0.41). The strength of these correlations was significantly greater for mPAWP than it was for LVEDP (P < 0.01 by Meng’s z-test).
Table 1. Clinical characteristics of the entire study population and according to mean pulmonary artery wedge pressure (mPAWP) quartiles

| Characteristic | All patients (n = 335) | Q1 (n = 98) mPAWP ≤ 10 mm Hg | Q2 (n = 72) mPAWP: 11–14 mm Hg | Q3 (n = 80) mPAWP: 15–19 mm Hg | Q4 (n = 85) mPAWP ≥ 20 mm Hg | P |
|----------------|------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|---|
| Age, y         | 74 ± 10                | 72 ± 10                       | 73 ± 10                       | 74 ± 10                       | 75 ± 10                       | 0.22 |
| Gender (male)  | 206 (61)              | 52 (53)                       | 49 (68)                       | 51 (64)                       | 54 (64)                       | 0.21 |
| Body mass index, kg/m² | 27.9 ± 4.9          | 27.2 ± 4.5                    | 27.9 ± 4.9                    | 28.0 ± 4.9                    | 28.6 ± 5.2                    | 0.29 |
| Hemoglobin, g/L | 136 ± 17              | 137 ± 16                      | 138 ± 16                      | 135 ± 18                      | 134 ± 20                      | 0.32 |
| Diabetes       | 68 (20)                | 17 (17)                       | 9 (13)                        | 23 (29)                       | 19 (22)                       | 0.07 |
| Stroke         | 25 (7)                 | 9 (9)                         | 2 (3)                         | 5 (6)                         | 9 (11)                        | 0.25 |
| Chronic obstructive lung disease | 46 (14) | 11 (11) | 13 (18) | 11 (14) | 11 (23) | 0.64 |
| FEV1 (% predicted) | 86 ± 21               | 93 ± 23                       | 84 ± 22                       | 84 ± 18                       | 79 ± 19                       | <0.001 |
| Heart rhythm   | 294 (88)               | 93 (95)                       | 65 (90)                       | 72 (90)                       | 64 (75)                       | 0.01 |
| Atrial fibrillation | 32 (9)               | 2 (2)                         | 5 (7)                         | 5 (6)                         | 20 (24)                       | 0.24 |
| Pacemaker      | 9 (3)                  | 3 (3)                         | 2 (3)                         | 3 (3)                         | 1 (1)                         | 0.02 |
| Heart rate, bpm | 69 ± 12                | 66 ± 10                       | 67 ± 11                       | 67 ± 12                       | 75 ± 13                       | <0.001 |
| Medication     |                        |                               |                               |                               |                               |     |
| Oral anticoagulation | 66 (20)               | 9 (9)                         | 14 (19)                       | 19 (24)                       | 24 (28)                       | 0.009 |
| Aspirin        | 217 (65)               | 73 (75)                       | 41 (57)                       | 50 (63)                       | 53 (62)                       | 0.09 |
| Loop diuretics | 165 (49)               | 35 (36)                       | 30 (42)                       | 42 (53)                       | 58 (68)                       | <0.001 |
| ß-blocker      | 163 (49)               | 41 (42)                       | 33 (46)                       | 40 (50)                       | 49 (58)                       | 0.18 |
| ACEI/ARB       | 197 (59)               | 62 (63)                       | 41 (57)                       | 48 (60)                       | 46 (54)                       | 0.59 |
| Spironolactone | 21 (6)                 | 3 (3)                         | 2 (3)                         | 5 (6)                         | 11 (13)                       | 0.02 |
| B-type natriuretic peptide, ng/L | 169 (79–393) | 87 (39–151) | 113 (53–250) | 206 (140–367) | 566 (283–1142) | <0.001 |
| Symptoms       |                        |                               |                               |                               |                               |     |
| Dyspnea NYHA class | 63 (19)               | 33 (34)                       | 12 (17)                       | 12 (15)                       | 6 (7)                         | <0.001 |
| I              | 174 (52)               | 50 (51)                       | 39 (54)                       | 45 (56)                       | 40 (47)                       | 0.009 |
| II             | 87 (26)                | 13 (14)                       | 18 (25)                       | 22 (28)                       | 33 (39)                       |     |
| III            | 11 (3)                 | 1 (1)                         | 3 (4)                         | 1 (1)                         | 6 (7)                         |     |
| IV             |                        |                               |                               |                               |                               |     |
| Mode of AVR    |                        |                               |                               |                               |                               |     |
| Surgical       | 249 (74)               | 83 (85)                       | 59 (82)                       | 57 (71)                       | 50 (59)                       | <0.001 |
| Transcatheter  | 86 (26)                | 15 (15)                       | 13 (18)                       | 23 (29)                       | 35 (30)                       |     |

Data are given as n (%), mean ± standard deviation, or median (interquartile range), unless otherwise indicated.

*ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; AVR, aortic valve replacement; bpm, beats per minute; eGFR, estimated glomerular filtration rate; FEV1, forced expiratory volume within the first second; NYHA, New York Heart Association.

mPAWP, LVEDP, and ΔmPAWP–LVEDP and prognosis

Patients in the highest mPAWP quartile had the highest mortality (Fig. 3A). Every increase in mPAWP by 1 mm Hg was associated with a 7% higher risk of death (hazard ratio 1.07 [95% CI, 1.03–1.11] per 1 mm Hg increase; P = 0.001). In contrast, mortality did not differ between patients in different LVEDP quartiles (Fig. 3B). When used as a continuous variable, LVEDP was not associated with mortality either (hazard ratio 1.00 [95% CI, 0.95–1.05] per 1 mm Hg increase; P = 0.94). As shown in Figure 4A, patients in the highest ΔmPAWP–LVEDP quartiles had a more than 7-fold higher mortality than those in the first quartile (hazard ratio 7.16 [95% CI, 1.65–31.17]; P = 0.009). Every increase in ΔmPAWP–LVEDP by 1 mm Hg was associated with a 10% higher risk of death (hazard ratio 1.10 [95% CI, 1.05–1.15] per 1 mm Hg increase; P < 0.001). The area under the receiver operating characteristic curve for the prediction of death was numerically larger for ΔmPAWP–LVEDP than for mPAWP (0.71 vs 0.68; Fig. 4B). Apart from higher mPAWP and lower LVEDP (by definition), the presence of atrial fibrillation (r = 0.29), larger left atrial size expressed as left atrial area in the apical 4-chamber view (r = 0.26), and the severity of mitral regurgitation (r = 0.25; P < 0.05 for all) were most strongly associated with higher ΔmPAWP–LVEDP.

Discussion

In this first detailed analysis of the impact of the choice of mPAWP vs LVEDP for the hemodynamic characterization of severe AS patients, we found the following. First, overall mPAWP was lower than LVEDP (mean difference of 5 mm Hg). Second, the use of an LVEDP-/DPG–LVEDP-based classification, instead of the classical (guideline-based) mPAWP–and PVR/DPG-based PH classification, resulted in a different classification of 42% of patients with PH. Also, reclassified patients had significantly higher mortality compared to those who were not reclassified. Third, mPAWP, but not LVEDP, was a predictor of mortality after AVR. Fourth, the ΔmPAWP–LVEDP as a marker of the relationship between mPAWP and LVEDP reflected an unfavorable hemodynamic profile and a particularly poor prognosis.

The LVEDP is regarded as the invasive gold standard for the characterization of LV preload and diastolic operating compliance.2 Guidelines highlight that LVEDP should be measured as a basis for PH classification if there is any doubt.
Table 2. Data from echocardiography and cardiac catheterization of the entire study population and according to mean pulmonary artery wedge pressure (mPAWP) quartiles (Q).

| Measure                                      | All patients (n = 335) | Q1 (n = 98) mPAWP \leq 10 mm Hg | Q2 (n = 72) mPAWP: 11–14 mm Hg | Q3 (n = 80) mPAWP: 15–19 mm Hg | Q4 (n = 85) mPAWP \geq 20 mm Hg | P    |
|----------------------------------------------|------------------------|----------------------------------|--------------------------------|--------------------------------|--------------------------------|------|
| E/e†                                         | 16.4 ± 8.6             | 13.6 ± 5.2                       | 15.7 ± 7.1                     | 15.2 ± 6.5                    | 21.9 ± 12.3                    | <0.001|
| Left atrial area, cm²                        | 25 ± 7                 | 22 ± 5                           | 23 ± 5                         | 26 ± 5                        | 30 ± 9                        | <0.001|
| TAPSE, mm                                     | 22 ± 5                 | 23 ± 5                           | 23 ± 4                         | 21 ± 5                        | 19 ± 5                        | 0.003 |
| Estimated dpAP                                | 39 ± 13                | 31 ± 9                           | 34 ± 7                         | 39 ± 9                        | 47 ± 15                        | <0.001|
| Mean aortic valve gradient                   | 44 ± 16                | 43 ± 13                          | 45 ± 16                        | 46 ± 18                       | 43 ± 17                        | 0.47  |
| Aortic valve area, cm²                       | 0.82 ± 0.25            | 0.88 ± 0.26                      | 0.87 ± 0.26                    | 0.79 ± 0.22                   | 0.74 ± 0.23                    | 0.001 |
| Indexed aortic valve area, cm²/m²             | 0.44 ± 0.13            | 0.48 ± 0.14                      | 0.45 ± 0.13                    | 0.42 ± 0.10                   | 0.39 ± 0.12                    | <0.001|
| Aortic regurgitation                          | 28 (8)                 | 5 (5)                            | 6 (9)                          | 6 (8)                         | 11 (13)                       | 0.33  |
| Mitral regurgitation (at least moderate)      |                       |                                  |                                |                               |                               | <0.001|
| Coronary artery disease                      |                       |                                  |                                |                               |                               | 0.17  |
| Mean right atrial pressure                   | 7 ± 4                  | 4 ± 3                            | 6 ± 2                          | 7 ± 2                         | 10 ± 5                        | <0.001|
| Right ventricular end-diastolic pressure sPAP| 40 ± 15                | 28 ± 5                           | 33 ± 5                         | 42 ± 11                       | 57 ± 16                       | <0.001|
| dpPAP                                         | 15 ± 8                 | 9 ± 3                            | 12 ± 3                         | 16 ± 4                        | 24 ± 8                        | <0.001|
| mPAP                                          | 25 ± 10                | 16 ± 3                           | 21 ± 3                         | 26 ± 5                        | 39 ± 10                       | <0.001|
| Pulmonary vascular resistance, WU             | 16 ± 8                 | 8 ± 2                            | 12 ± 1                         | 17 ± 1                        | 27 ± 6                        | <0.001|
| v wave                                        | 21 ± 12                | 11 ± 3                           | 16 ± 3                         | 22 ± 4                        | 37 ± 10                       | <0.001|
| TAPSE/sPAP, mm/mm Hg                          | 0.60 ± 0.28            | 0.87 ± 0.27                      | 0.69 ± 0.13                    | 0.54 ± 0.17                   | 0.34 ± 0.15                    | <0.001|
| Pulmonary vascular resistance, WU             | 2.2 ± 1.4              | 1.7 ± 0.8                        | 1.8 ± 0.7                      | 2.1 ± 1.4                     | 2.9 ± 19                      | <0.001|
| Diastolic pressure gradient                   | −1 (−3−2)              | 0 (−1−2)                         | 0 (−2−2)                      | −2 (−3−2)                    | −3 (−5−0)                     | <0.001|
| Pulmonary artery capacitance, ml/m² Hg        | 3.4 ± 2.0              | 4.4 ± 1.9                        | 3.8 ± 1.2                      | 3.5 ± 2.6                     | 2.0 ± 0.9                     | <0.001|
| Left ventricular end-diastolic pressure       | 21 ± 8                 | 17 ± 6                           | 18 ± 6                         | 23 ± 7                        | 27 ± 7                        | <0.001|
| ApPAWP−LVEDP                                  | −5 ± 7                 | −9 ± 6                           | −6 ± 6                         | −6 ± 7                        | 0 ± 8                         | <0.001|
| Systolic aortic pressure                     | 146 ± 25               | 145 ± 22                         | 143 ± 24                       | 153 ± 26                      | 144 ± 28                      | 0.06  |
| Diastolic aortic pressure                    | 68 ± 11                | 67 ± 12                          | 69 ± 11                        | 69 ± 10                       | 69 ± 12                       | 0.73  |
| Mean aortic pressure                         | 99 ± 14                | 97 ± 13                          | 98 ± 14                        | 101 ± 14                      | 99 ± 15                       | 0.22  |
| Systemic vascular resistance, WU              | 20.3 ± 5.1             | 19.1 ± 4.3                       | 19.6 ± 4.5                     | 20.5 ± 5.1                    | 22.0 ± 5.8                    | <0.001|
| Arterial oxygen saturation, %                | 95 (94−97)             | 96 (94−97)                       | 96 (94−97)                     | 95 (94−97)                    | 95 (92−96)                    | 0.04  |
| Mixed venous oxygen saturation, %            | 68 (64−72)             | 71 (67−74)                       | 69 (65−73)                     | 68 (64−71)                    | 63 (58−68)                    | <0.001|
| Cardiac output, L/min                         | 4.7 ± 1.1              | 5.0 ± 1.0                        | 4.8 ± 1.0                      | 4.9 ± 1.3                     | 4.2 ± 0.9                     | <0.001|
| Cardiac index, L/min/m²                       | 2.5 ± 0.5              | 2.7 ± 0.5                        | 2.5 ± 0.5                      | 2.6 ± 0.6                     | 2.2 ± 0.5                     | <0.001|
| Stroke volume index, ml/m²                    | 37 ± 10                | 42 ± 8                           | 39 ± 9                         | 39 ± 9                        | 30 ± 8                        | <0.001|

Data are given as n (%), mean ± standard deviation, and/or median (interquartile range). Pressures and gradients are given in mm Hg. ΔApPAWP−LVEDP, mathematical difference between mean pulmonary artery wedge pressure and left ventricular end-diastolic pressure; dpAP, diastolic pulmonary artery pressure; E/e†, ratio of peak early mitral inflow velocity to peak early mitral annular velocity; mPAP, mean pulmonary artery pressure; mPAWP, mean pulmonary artery wedge pressure; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion.

about the reliability of the mPAWP measurement. In the majority of patients, the LVEDP was higher than the mPAWP (mean difference: 5 mm Hg). In these patients, reliance on the LVEDP alone results in overestimation of the left heart disease contribution to pulmonary pressures. There were patients who were classified as having precapillary PH,
based on mPAWP, whereas based on LVEDP, they were classified as having postcapillary PH (example in Supplemental Fig. 1A). On the other hand, there were also patients with a lower LVEDP than mPAWP, and such patients were classified as having postcapillary PH based on mPAWP but as having precapillary PH based on classification using LVEDP. In these patients, the v wave contribution of left heart disease to PH is underestimated in relying on the LVEDP alone. These 2 scenarios accounted for a divergent classification using mPAWP vs LVEDP in 22 patients overall (mainly reclassification from precapillary PH to IpCH). Patients who by the 2015 PH definition were labeled as mild precapillary PH (example in Supplemental Fig. S2A) in the severe AS setting most likely have mild occult postcapillary PH (ie, an mPAWP slightly below 15 mm Hg due to diuretic therapy and/or fasting, and a normal PVR), and therefore, this change in classification had no prognostic impact.

Another factor seems to be more critical: in the absence of mPAWP, neither PVR nor DPG can be properly calculated. Current guidelines do not explicitly address how to deal with this issue when using the LVEDP for PH classification. O’Sullivan et al. have suggested resolving this problem by use of the calculation of DPGLVEDP as dPAP minus LVEDP. These researchers were able to show that such a PH classification, based on (i) LVEDP and (ii) DPGLVEDP, predicted mortality after transcatheter AVR. However, this method may still result in underestimation of the pulmonary vascular contribution to PH (by overestimation of mPAWP by LVEDP), and our data suggest that indeed patients with CpcPH may be missed by this approach (example in Supplemental Fig. S2B). This seems to be relevant given that the higher mortality of divergently classified patients was driven by patients who were classified as having CpcPH by the standard PAWP-based approach but were labelled as having IpCH (rather than CpcPH) based on the LVEDP-based approach. Notably, the poor prognosis of patients with AS and CpcPH undergoing AVR has been shown previously. However, given the small number of patients in this analysis, careful interpretation of the mortality data is required.
important prognostic markers in patients with AS21,22
sure (mPAWP) and left ventricular end-diastolic pressure (LVEDP; aortic valve replacement mortality) for patients in different quartiles but also did not provide any prognostic information at all.

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Interestingly, LVEDP not only was inferior to mPAWP with regard to the prediction of mortality, but also did not provide any prognostic information at all.

This important relationship between LVEDP and mPAWP can roughly be expressed by $\Delta_{mPAWP-LVEDP}$. Positive values for $\Delta_{mPAWP-LVEDP}$ reflect a situation in which the wedge pressure integrated over the entire cardiac cycle exceeds the LVEDP, owing to atrial fibrillation, mitral regurgitation, and atrial dysfunction. Patients with the highest $\Delta_{mPAWP-LVEDP}$ had not only the most severe mitral regurgitation and the highest v wave but also the highest PVR, the lowest pulmonary capacitance, and the worst right ventricular to pulmonary artery coupling (lowest TAPSE/ $sPAP$ ratio). A higher mPAWP than LVEDP in patients with atrial fibrillation5,10 dilated left atrium,5 and valve disease5 has also been found. However, the prognostic impact of this constellation in the specific setting of patients with severe AS has not been investigated previously. Patients with the highest $\Delta_{mPAWP-LVEDP}$ values had the worst prognosis in the present study, and interestingly, $\Delta_{mPAWP-LVEDP}$ even had a numerically higher area under the curve for the prediction of mortality than mPAWP.

Accordingly, the present data suggest that measurement of LVEDP alone does not allow PH classification. This is clinically important in the AS setting, as LVEDP measurement requires crossing of the stenotic aortic valve, a procedure associated with the risk of embolic events27 that is no longer recommended for purely diagnostic purposes unless the severity of AS cannot be determined non-invasively.28 This is now also the practice at our institution. The slightly larger area under the curve for $\Delta_{mPAWP-LVEDP}$ for the prediction of mortality than for mPAWP is interesting from a pathophysiological point of view, but it probably does not justify performing a potentially hazardous procedure. Thus, the study suggests that measurement of LVEDP in AS is not justified. In contrast, right heart catheterization with measurement of mPAP and mPAWP characterizes the hemodynamic situation and provides important prognostic information. The data may have even broader implications for patients with PH in the context of left heart diseases. Even if LVEDP is measured as a substitute for mPAWP (if there are doubts about the reliability of a measured mPAWP), this will not always allow understanding of the pathophysiology of PH or correct PH classification.

The study has some limitations. First, the number of patients was relatively low. Therefore, the outcome data require careful interpretation. However, we present a unique hemodynamic dataset that provides novel insights into the role of mPAP and LVEDP in PH categorization. Second, we have used the indirect Fick method to assess cardiac output, which is subject to error, as oxygen consumption is often inaccurately estimated.29 This issue can affect all cardiac output-based measures, including PVR. However, this technique is routinely used in clinical practice. Third, the wedge position was not routinely confirmed by aspiration of an arterialized

As a key finding, the study revealed that the mPAWP, but not the LVEDP, was a predictor of mortality. This finding is in line with results of a recent study in patients with heart failure with preserved ejection fraction,8 an entity characterized by a similar left ventricular phenotype as that seen in patients with AS and with a high prevalence of PH.25,26 These findings are intuitive, as the mPAWP is the pressure recorded closer to the point of mPAP measurement and thereby reflects the integrated hemodynamic burden of the pulmonary vein—left atrium—mitral valve—left ventricle continuum on the pulmonary circulation and finally the right ventricle.2,16 Indeed, there was a significantly closer correlation between mPAP and mPAWP than between mPAP and LVEDP. The inverse relationship between right ventricular function expressed as TAPSE, and the right ventricular to pulmonary artery coupling expressed as the TAPSE/sPAP ratio—both important prognostic markers in patients with AS21,22—were stronger for mPAWP than for LVEDP, also suggesting that mPAWP is the more “important” pressure from a pathophysiology point of view. Interestingly, LVEDP not only was inferior to mPAWP with regard to the prediction of mortality, but also did not provide any prognostic information at all.

This may be explained by the observation that patients with AS and clearly different hemodynamic profiles can have relatively similar LVEDP, as shown previously for patients with AS and sinus rhythm vs atrial fibrillation.13 In atrial fibrillation, LVEDP is relatively low compared to the mPAWP, owing to the presence of (atrial) mitral regurgitation and lack of atrial contraction, whereas in sinus rhythm, LVEDP is relatively high compared to the mPAWP, owing to atrial contraction and less/no mitral regurgitation.13

Figure 4. (A) Kaplan–Meier plots showing cumulative events (post—
aortic valve replacement mortality) for patients in different quartiles (Q) for the difference between mean pulmonary artery wedge pressure (mPAWP) and left ventricular end-diastolic pressure (LVEDP; $\Delta_{mPAWP-LVEDP}$), and (B) receiver operator characteristics curve showing the areas under the curve (AUC; with 95% confidence intervals [CIs]) for mPAWP, LVEDP, and $\Delta_{mPAWP-LVEDP}$ to predict mortality.
blood gas sample. We acknowledge that this lack of confirmation can also be a source of error. However, definition of wedge position by fluoroscopy and waveform analysis alone is current practice in many laboratories. Fourth, the setting of our study was selected because all patients underwent AVR early after cardiac catheterization, which affects hemodynamics owing to afterload reduction and thereby may have an impact on prognosis. Still, the data may add to our understanding of the pathophysiology of PH in patients with AS and other left heart diseases, and the role of mPAWP vs LVEDP in PH classification.

Conclusions
In severe AS, use of the LVEDP rather than the mPAWP results in a different PH classification of nearly every second patient, and these patients have a higher mortality compared with the non-reclassified patients. The poor outcome of differently classified patients is mediated by those patients classified as having CpcPH by the mPAWP-based approach being reclassified as IpcPH by the LVEDP-based approach. The mPAWP, but not the LVEDP, is a predictor of post-AVR mortality. This fact underscores the importance of using the mPAWP for classification and risk stratification in patients with PH in the context of left heart diseases.

Funding Sources
The authors have no funding sources to declare.

Disclosures
The authors have no conflicts of interest to disclose.

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Supplementary Material
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