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Research Article

Varying Transvenous Pressure Gradients in Different Entities of Aortic Stenosis

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Abstract

Aims: Enhanced left ventricular end-diastolic pressure (LVEDP) has been shown to be associated with worse outcome after acute myocardial infarction, cardiac surgery and in patients with severe aortic stenosis (AS) undergoing transcatheter aortic valve replacement (TAVR). Nowadays, pulmonary artery wedge pressure (PCWP) has largely replaced direct measurement of LVEDP but several patient series have demonstrated a poor agreement between both methods. Different AS-entities by the meaning of normal-flow high-gradient (NFHG), paradoxical and true low-flow low-gradient ((p)LFLG) AS may be also linked to high left ventricular filling pressures that can be measured by LVEDP and PCWP. Therefore, we analyzed 1) role and agreement of LVEDP and PCWP in patients with high-grade AS and 2) influence of AS-entities on LVEDP/PCWP pressure gradients.

Methods and Results: From 2009 to 2018, a total of 788 patients with high-grade AS prior to TAVR, completed hemodynamic status and echocardiographic data were retrospectively enrolled.

LVEDP was significantly higher as the PCWP (23.3 ± 8.4 vs. 19.0 ± 8.9; p<0.0001) and over-all LVEDP and PAWP showed medium correlation (r=0.37, 95%-CI=0.30-0.43; p<0.0001*). Surprisingly, patients with NFHG- (6.2 [4.8-7.5] mmHg) and pLFLG-AS (4.2 [3.2-5.1] mmHg) had a significantly higher transvenous pressure gradient than the LFLG-AS cohort (1.4 [-0.1-2.9] mmHg; p<0.0001 between LFLG- and NFHG-AS; p=0.0336 between LFLG- and pLFLG-AS). However, several influencing factors as main drivers for the transvenous pressure gradient were found in NFHG- and pLFLG-AS but not LFLG entity by multivariate analysis.

Conclusion: Our data indicate, that the influence on LVEDP/PCWP pressure gradients differ according to several AS-entities and the underlying pathologies with smallest LVEDP/PCWP pressure gradients in LFLG-AS, supposing that the use of PCWP should not be used unthinkingly as a surrogate for LVEDP.

Keywords: Aortic Stenosis; Pulmonary artery wedge pressure; Myocardial infarction

Abbreviations

AS=aortic stenosis

cpcPHT=combined postcapillary pulmonary hypertension

ipcPHT= isolated postcapillary pulmonary hypertension

LVEDP=left ventricular end-diastolic pressure

mPAP=mean pulmonary artery pressure

NFHG=normal-flow high-gradient

PCWP=pulmonary artery wedge pressure

(p)LFLG=(p) low-flow low-gradient

TAVR=Transcatheter Aortic Valve Replacement

Citation

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Introduction

Enhanced left ventricular end-diastolic pressure (LVEDP) has been shown to be associated with worse outcome after acute myocardial infarction [1], cardiac surgery [2] and in patients with severe aortic stenosis (AS) undergoing transcatheter aortic valve replacement (TAVR) [3]. Nowadays, pulmonary artery wedge pressure (PCWP) has largely replaced direct measurement of LVEDP but several patient series have demonstrated a poor -potentially multifactorial- agreement between both methods [4-6]. Looking at AS hemodynamics, different AS-entities by the meaning of normal-flow high-gradient (NFHG), paradoxical and true low-flow low-gradient ((p)LFLG) AS are well-known to be associated with different outcomes. These findings may be also linked to high left ventricular filling pressures that can be measured by LVEDP and PCWP. In this single-center study, we analyzed 1) role and agreement of LVEDP and PCWP in patients with high-grade AS and 2) influence of AS-entities on LVEDP/PCWP pressure gradients.

Material and Methods

From 2009 to 2018, a total of 788 patients with high-grade AS prior to TAVR, completed hemodynamic status and echocardiographic data were retrospectively enrolled. The study procedures were in accordance with the Declaration of Helsinki and the institutional Ethics Committee of the Heinrich-Heine University and is registered at clinical trials (NCT01805739). Patients underwent coronary angiography prior to TAVR according to current recommendations. Mean pulmonary artery pressure (mPAP), PCWP and LVEDP were recorded. Pulmonary hypertension (PHT) was classified as pre-capillary (precPHT), isolated post-capillary (IpcPHT) or combined entity (cpcPHT) according to current recommendations. Normal-flow high-gradient AS (NFHG-AS), low-flow low-gradient aortic stenosis (LFLG-AS) and paradoxical LFLG-AS (pLFLG-AS) were classified according to current guideline definitions. Continuous variables were compared using a Student's t-test or Kolmogorov-Smirnov. Analysis of variance (ANOVA) was calculated with appropriate post-hoc tests comparing more than 2 groups. For correlations of interest, Spearman correlation coefficients were calculated. Correlation coefficients of 0.8 to 1.0 and 0.5 to 0.8, respectively, indicate a very strong and strong positive correlation between two variables, whereas coefficients between 0.2 to 0.5 and 0.0 to 0.2 suggest medium and small correlations, respectively. The influence on LVEDP/PCWP pressure gradients was tested by univariate and multivariate regression analysis. The data analysis was performed using the statistical software SPSS (version 23.0, SPSS Inc., Chicago, IL, USA) and GraphPad Prism (version 6.0, Graphpad Software, San Diego, CA, USA). All statistical tests were 2-tailed, and a value of $p < 0.05$ was considered statistically significant.

Results

Over-all LVEDP was significantly higher as the PCWP (23.3 ± 8.4 vs. 19.0 ± 8.9; $p<0.0001$) and over-all LVEDP to PCWP showed only medium correlation in agreement ($r=0.37$, 95%-CI=0.30-0.43; $p<0.0001$). All patients were stratified into subgroups of AS-entity (NFHG-AS, pLFLG-AS and LFLG-AS). Surprisingly, patients with NFHG- (6.2 [4.8-7.5] mmHg) and pLFLG-AS (4.2 [3.2-5.1] mmHg) had a significantly higher transvenous pressure gradient than the LFLG-AS cohort (1.4 [-0.1-2.9] mmHg; $p<0.0001$ between LFLG- and NFHG-AS; $p=0.0336$ between LFLG- and pLFLG-AS). However, correlation of LVEDP and PCWP gradients within the several AS-entities remained at a medium level (Figure 1A).

LVEDP/PCWP gradients showed varying dependencies related to the particular AS-entities (please see Table 1): by multivariate regression analysis, ipcPHT (OR 0.27; 95%-CI 0.14-0.54; p<0.0001*) and cpcPHT (OR 0.34; 95%-CI 0.14-0.78; p=0.010*) were independently and inversely related to a pressure difference ≥5 mmHg between PCWP and LVEDP in NFHG-AS**.** Atrial fibrillation and multivalvular disease failed to reach significance. In pLFLG-AS, the LVEDP/PCWP pressure gradient was predominantly influenced by PAPm (OR 1.04; 95%-CI 1.01-1.07; p=0.013*), renal replacement therapy (OR 0.27; 95%-CI 0.10-0.74; p=0.011*), atrial fibrillation (OR 0.37; 95%-CI 0.23-0.59; p=<0.0001*), ipc- (OR 0.30; 95%-CI 0.16-0.55; p<0.0001*) and pcpPHT (OR 0.22; 95%-CI 0.10-0.59; p<0.0001*), whereas in LFLG-AS no relation to several influencing factors as main drivers for the transvenous pressure gradient were found (Figure 1B). Neither arterial hypertension, aortic valve area, cardiac index or previous surgical procedures took influence in this analysis.

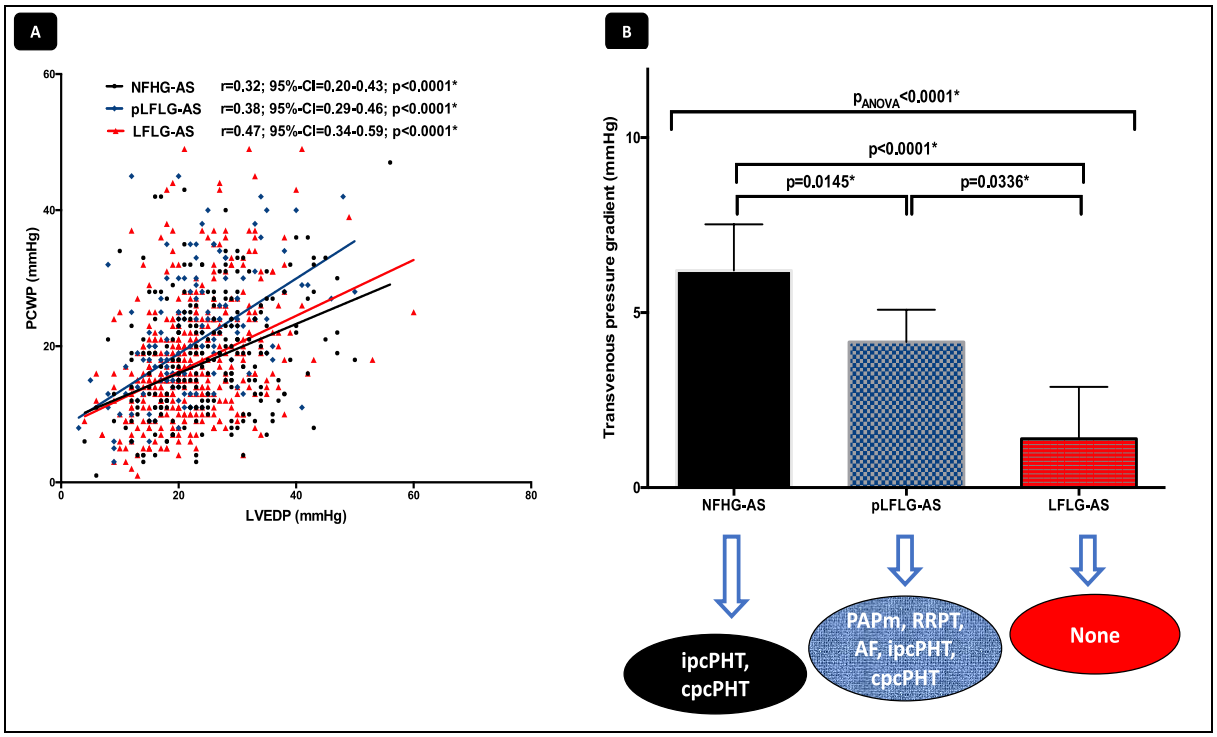

Figure 1: Correlation Curves of Mean PCWP and LVEDP

(A) Correlation curves are shown for PCWP and LVEDP stratified for subgroups of AS-entities (NFHG-AS, pLFLG-AS and LFLG-AS). **(B)** Cumulative transvenous pressure gradients (LVEDP/PCWP) according to AS-entity and influencing factors based on multivariate regression analysis. NFHG=normal-flow high-gradient; (p)LFLG=(paradoxical) low-flow low-gradient.

		Univariate analysis		Multivariate analysis	
A)	**NFHG-AS**	**Regression slope (95-CI)**	**p-value**	**Regression slope (95-CI)**	**p-value**
	mPAP	0.96 (0.94-0.99)	0.006*	-	-
	AF	0.42 (0.23-0.77)	0.005*	0.55 (0.29-1.05)	0.068
	Mv disease ≥ II°	0.45 (0.25-0.82)	0.009*	0.56 (0.30-1.06)	0.076
	precPHT	2.83 (0.81-9.89)	0.103	-	-
	ipcPHT	0.37 (0.21-0.67)	0.001*	**0.27 (0.14-0.54)**	**<0.0001***
	cpcPHT	0.50 (0.25-0.99)	0.048*	**0.34 (0.15-0.77)**	**0.0010***
A)	**pLFLG-AS**	**Regression slope (95-CI)**	**p-value**	**Regression slope (95-CI)**	**p-value**
	mPAP	0.98 (0.96-1.00)	0.063	**1.04 (1.01-1.07)**	**0.013***
	RRPT	0.29 (0.11-0.73)	0.009*	**0.27 (0.10-0.74)**	**0.011***
	DM	0.67 (0.44-1.02)	0.060	-	-
	AF	0.34 (0.22-0.52)	<0.0001*	**0.37 (0.23-0.59)**	**<0.0001***
	ipcPHT	0.53 (0.34-0.83)	0.005*	**0.30 (0.16-0.55)**	**<0.0001***
	cpcPHT	0.55 (0.33-0.92)	0.024*	**0.22 (0.10-0.59)**	**<0.0001***
B)	**LFLG-AS**	**Regression slope (95-CI)**	**p-value**	**Regression slope (95-CI)**	**p-value**
	-	-	-	-	-

Table 1: Parameters associated with the LVEDP-to-PCWP gap in patients with different AS-entities

AF=atrial fibrillation; aHT=arterial hypertension; DM=diabetes mellitus; mPAP=mean pulmonary artery pressure; cpcPHT=combined postcapillary pulmonary hypertension; ipcPHT=isolated postcapillary pulmonary hypertension; precPHT=precapillary pulmonary hypertension; mv=multivalvular

Discussion

The present study evaluating invasive hemodynamics of patients with severe AS revealed several findings:

1. Patients with LFLG-AS had the smallest LVEDP/PCWP pressure gradient.
2. Influence on LVEDP/PCWP pressure gradients differed according to several AS-entities and the underlying pathologies.

Clinically meaningful disagreement between PCWP and LVEDP is common, especially in patients with atrial fibrillation, valve diseases, and changing stroke volumes [7]. Just in patients with AS, ventricular filling pressures are often multifactorial influenced [8]. Therefore, we stratified all patients prior to TAVR into subgroups of AS-entity. In NFHG- and pLFLG-AS patients, LVEDP and PCWP pressures were significantly different, resulting in high pressure gradients between 4 to 6 mmHg, supposing that under normal and mildly reduced flow-conditions covariables exert more influence on LVEDP than on PCWP leading to a higher difference. Surprisingly, patients with LFLG-AS had the smallest transvenous pressure (2 mmHg), so in this cohort highest PCWP with nearly equal LVEDP based on the interaction of multiple and different weighted influencers seems to equalize this difference. *Weber et. al* confirmed, that cpcPHT, atrial fibrillation and severe mitral regurgitation were characterized by a smaller difference between LVEDP and PCWP indicating that left ventricular pressure is more strongly reflected backwards into the pulmonary circulation [8]. These findings are fundamental, suggesting multiple influencing hemodynamic, functional and structural factors, that may result in a landscape of complex interactions. To our knowledge, this is the first study on LVEDP/PCWP gradients that shows varying dependencies related to the particular AS-entities. However, our study has confirmed previous data that LVEDP and PCWP may significantly differ and added new value on differences between several AS-entities, supposing that the use of PCWP should not be used unthinkingly as a surrogate for LVEDP.

Conclusions

Our data indicate, that the influence on LVEDP/PCWP pressure gradients differ according to several AS-entities and the underlying pathologies with smallest LVEDP/PCWP pressure gradients in LFLG-AS.

Limitations

Several limitations have to be addressed: Data on cardiac catheterization were obtained from reports and database platform, facilitating mistakes in documentation. The calculation of cardiac output based on indirect Fick-method is error-prone and may have had impact on all cardiac output- and stroke volume-derived measurements. Furthermore, LVEDP and PCWP were not measured simultaneously, possibly affecting accuracy of the measurements. However, this is one of the largest studies on invasive hemodynamics in patients with AS and our center has a long experience in hemodynamic assessment.

Data Availability

The research data used to support the findings of this study are available from the corresponding author upon request.

Conflict of Interest (COI) statement

Verena Veulemans, Tobias Zeus, and Ralf Westenfeld have received consulting fees, travel expenses, or study honoraries from Medtronic and Edwards Lifesciences. All other authors have nothing to disclose with regard to this project.

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