ESC HEART FAILURE
ESC Heart Failure 2023; **10**: 274–283
Published online 7 October 2022 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.14192

ORIGINAL ARTICLE

Systemic blood pressure in severe aortic stenosis: Haemodynamic correlates and long-term prognostic impact

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Abstract

Aims Blood pressure (BP) targets in patients with aortic stenosis (AS) are controversial. This study sought to describe the haemodynamic profile and the clinical outcome of severe AS patients with low versus high central meaarterial pressure (MAP).

Methods and results Patients with severe AS (n = 477) underwent right and left heart catheterization prior to aortic valve replacement (AVR). The population was divided into MAP quartiles. The mean systolic BP, diastolic BP, and MAP in the entire population were 149 ± 25, 68 ± 11, and 98 ± 14 mmHg. Patients in the lowest MAP quartile had the lowest left ventricular ejection fraction (LVEF), systemic vascular resistance, and valvulo-arterial impedance, whereas there were no significant differences in mean right atrial pressure, mean pulmonary artery wedge pressure, pulmonary vascular resistance, and stroke volume index across MAP quartiles. However, left ventricular stroke work index (LVSWI) was lowest in patients in the lowest and highest in those in the highest MAP quartile. After a median (interquartile range) post-AVR follow-up of 3.7 (2.6–5.2) years, mortality was highest in patients in the lowest MAP quartile [hazard ratio 3.08 (95% confidence interval 1.21–7.83); P = 0.02 for lowest versus highest quartile]. In the multivariate analysis, lower MAP [hazard ratio 0.78 (95% confidence interval 0.62–0.99) per 10 mmHg increase; P = 0.04], higher mean right atrial pressure and lower LVEF were independent predictors of death.

Conclusions In severe AS patients, lower MAP reflects lower systemic vascular resistance and valvulo-arterial impedance, which may help to preserve stroke volume and filling pressures despite reduced left ventricular performance, and lower MAP is a predictor of higher long-term post-AVR mortality.

Keywords Aortic stenosis; Blood pressure; Haemodynamics; Stroke work index; Valvulo-arterial impedance

Received: 29 July 2022; Revised: 10 September 2022; Accepted: 21 September 2022
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Introduction

In patients with aortic stenosis (AS), there is an important interaction between valve disease and blood pressure (BP).[1,2] On the one hand, hypertension contributes to the progression of valve calcification and stenosis severity.[2] On the other hand, hypertension adds to the load of the left ventricle because it represents an additional resistance that is located distally to the valvular stenosis.[3,4] Historically, there was great reluctance to administer vasodilators to AS patients because of the fear of profound hypotension in presence of a fixed valvular stenosis.[3] However, experts now concur that hypertension should also be treated in AS patients to protect the left ventricle from additional damage.[1,2,4] This is based on mechanistic studies showing that the acute administration of potent vasodilators such as nitroprusside and sildenafil was well tolerated and associated with favourable haemodynamic effects.[5–7] There is also evidence from observational studies that long-term antihypertensive therapy, particularly based on inhibitors of the

renin-angiotensin aldosterone system (RAASi), is beneficial in AS patients both before and after aortic valve replacement (AVR).[8,9] However, blood pressure (BP) goals in AS patients remain controversial.[1,2,10,11] Importantly, a low rather than a high BP early after AVR has been shown to be associated with increased mortality,[10,11] which is similar to patients with heart failure, where low BP is a marker of a poor prognosis even in the current treatment era,[12] presumably because this indicates a low stroke volume. In patients with AS, however, the differential contribution of stroke volume and vascular resistance on BP on the one hand and the prognostic impact of BP on the other hand have been incompletely characterized. In the present invasive study, we assessed the detailed haemodynamic profile of low versus high mean arterial pressure (MAP) in patients with severe AS undergoing left and right heart catheterization prior to AVR as well as the prognostic impact of low versus high MAP on long-term post-AVR mortality. We hypothesized that a low MAP is a marker of poor left ventricular performance and thereby poor prognosis.

Methods

Study population

This is a retrospective analysis of prospectively and systematically collected data on cardiac catheterization in patients with severe AS undergoing a highly standardized evaluation process prior to AVR in a single center between January 2011 and January 2016 (entire cohort: *n* = 503) with a post-AVR follow-up of several years.[13] For this analysis, we included 477 patients undergoing left and right heart catheterization in whom an invasively assessed central arterial blood pressure was available. All patients subsequently underwent surgical (SAVR) or transcatheter (TAVR) AVR. The study was approved by the local ethics committee. A waiver of consent was granted.

Cardiac catheterization

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 five or six French catheters via the femoral or radial artery and right heart catheterization using six French Swan Ganz catheters via femoral or brachial access. The midthoracic level was used as zero reference point. Right atrial pressure, right ventricular pressure, pulmonary artery pressure (PAP), and pulmonary artery wedge pressure were measured. The wedge position was confirmed by fluoroscopy and waveform analysis. Measurements were obtained at end-expiration, the mean pulmonary artery wedge pressure (mPAWP) was calculated over the entire cardiac cycle, and v waves were included to determine mPAWP. This practice leads to higher values compared to the measurement of the end-diastolic pulmonary artery wedge pressure.[14] However, for the estimation of the impact of the left heart contribution to pulmonary pressures and calculation of pulmonary vascular resistance (PVR), respectively, the mPAWP is preferred.[15] In patients with atrial fibrillation, at least five cardiac cycles were used to assess PAP and pulmonary artery wedge pressure (sinus rhythm: usually three cycles). Cardiac output (CO) was assessed by the indirect Fick method based on blood gases, which were collected simultaneously and in duplicate from the arterial catheter and the pulmonary artery. After completion of right heart catheterization a coronary or a pigtail catheter was advanced into the ascending aorta. Systolic BP, diastolic BP, and MAP were measured. In approximately two-third of the population (*n* = 327), the aortic valve was crossed with a stiff wire, and the left ventricular end-diastolic pressure (LVEDP) was measured using a pigtail catheter within a few minutes after the right heart catheter measurements and before coronary angiography. All pressure readings were double-checked by the operator by manual review of the pressure tracings before they were entered into the report and used for haemodynamic calculations, respectively.

Haemodynamic calculations and definitions

The transpulmonary gradient (TPG) was calculated as mPAP − mPAWP. Pulmonary vascular resistance [in Wood units (WU)] was calculated as TPG/CO, and pulmonary artery compliance was calculated as stroke volume/(systolic PAP − diastolic PAP), where stroke volume is CO/heart rate. Right ventricular stroke work index (RVSVI) was calculated as 0.0125*SVI*(mPAP − mRAP), where SVI is stroke volume index, which is obtained by the division of stroke volume by body surface area, and mRAP is mean right atrial pressure. Indexed arterial elastance as a measure of total arterial load was calculated as 0.9*systolic BP/SVI.[16] Pulsatile arterial load was described by pulse pressure, that is, systolic BP – diastolic BP, and systemic arterial compliance, which was calculated as SVI divided by pulse pressure.[17] Resistive arterial load was described by the systemic vascular resistance (SVR, in WU), which was calculated as (MAP − mRAP)/CO. Valvulo-arterial impedance (Z_{VA}) as a measure of the global haemodynamic load to the left ventricle was calculated as (systolic BP + dp mean)/SVI, where where dp mean is the mean aortic pressure gradient as assessed by echocardiography.[18] We assessed left ventricular stroke work index (LVSWI) as a measure of global left ventricular performance.[19] Given that mPAWP was available for the entire cohort whereas LVEDP was available only in a subset of patients, LVSWI was

calculated as 0.0136*SVI*(MAP + dp mean − mPAWP).[20] However, we performed a subgroup analysis of patients with available LVEDP. For this analysis, LVSWI was calculated as 0.0136*SVI*(MAP + dp mean − LVEDP).[21]

Echocardiography

All patients had an echocardiogram prior to cardiac catheterization as a basis for the referral. Echocardiograms were performed by experienced cardiologist according to contemporary guidelines but not according to a specific study protocol. The data were retrospectively obtained from the reports.

Follow-up

All patients underwent surgical (71%) or transcatheter (29%) AVR following a median interval of 21 (12–35) days post-catheterization. Information on long-term follow-up was obtained by a research assistant from patients, general practitioners, and hospital or practice cardiologists. The 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. Clinical characteristics and echocardiographic and haemodynamic data across the four MAP quartiles were compared using analysis of variance, Kruskal–Wallis test, or χ^2 tests as appropriate. Survival of patients in different MAP and LVSWI quartiles were compared using Kaplan–Meier plots and log-rank tests. Cox regression was applied to describe the association between variables of interest and mortality. A *P*-value <0.05 was considered statistically significant. Analyses were performed using SPSS statistical package version 25.0 (SPSS Inc., Chicago, IL, USA).

Results

Study population

We studied 477 patients with mean age 74 ± 10 years (57% males). The mean indexed aortic valve area was 0.43 ± 0.12 cm^2/m^2, and the mean left ventricular ejection fraction (LVEF) was 58 ± 12%. The mean systolic BP, diastolic BP, and MAP in the entire population were 145 ± 25 mmHg, 68 ± 11 mmHg, and 98 ± 14 mmHg. Detailed clinical, echocardiographic, and haemodynamic characteristics of the entire study population are shown in *Tables 1* and *2*.

Clinical characteristics according to MAP quartiles

Patients in the lowest MAP quartile (MAP ≤88 mmHg) were the most likely to be female and to be treated with digoxin and loop diuretics and had the highest B-type natriuretic peptide (BNP) plasma concentrations, whereas they were the least likely to be treated with angiotensin converting enzyme inhibitors (ACE-I)/angiotensin receptor blockers (ARB) compared to the patients in the other MAP quartiles (*Table 1*). There were some additional minor differences across MAP quartiles but no clear trend (*Table 1*).

Echocardiography findings and haemodynamics according to MAP quartiles

The mean aortic valve gradient and the indexed aortic valve area did not differ across MAP quartiles (*Table 2*). However, patients in the lowest MAP quartile had the lowest LVEF and numerically the largest left atrial area. There were no significant differences in mRAP, mPAP, mPAWP, PVR, pulmonary artery compliance, and RVSWI across MAP quartiles. There was no significant difference in SVI across MAP quartiles either. However, patients in the lowest MAP quartile not only had the lowest systolic and diastolic BP but also the lowest pulse pressure, SVR, and Z_{VA}. In addition, LVSWI was lowest in patients in the lowest MAP quartile and highest in those in the fourth quartile (*Table 2* and *Figure 1*). In the subgroup of patients with available LVEDP and LVSWI calculation based on LVEDP rather than mPAWP, findings were unchanged (*Tables S1* and *S2*).

MAP and mortality

After a median (interquartile range) follow-up of 3.7 (2.6–5.2) years after AVR, there were 42 deaths. Mortality was highest in patients in the lowest and was lowest in those in the highest MAP quartile (*Figure 2*). Patients in the lowest MAP quartile had a three-fold risk of death compared to patients in the highest quartile [hazard ratio (HR) 3.08 (95% confidence interval [95% CI] 1.21–7.83); *P* = 0.02]. When used as a continuous variable, lower MAP was also associated with higher mortality [HR 0.75 (95% CI 0.60–0.94) per 10 mmHg increase; *P* = 0.01]. These results were driven by the larger subgroup of patients undergoing SAVR: HR 3.39 (95% CI 1.09–10.52); *P* = 0.04 for lowest versus highest MAP quartile in the SAVR subgroup, and HR 2.48 (95% CI

Table 1 Clinical characteristics of the entire study population and according to mean arterial pressure (MAP) quartiles

	All (n = 477)	Q1 (n = 115) MAP ≤88 mmHg	Q2 (n = 121) MAP 89–97 mmHg	Q3 (n = 125) MAP 98–107 mmHg	Q4 (n = 116) MAP ≥108 mmHg	P value
Age (years)	74 ± 10	74 ± 11	73 ± 11	74 ± 10	77 ± 8	0.02
Gender (male)	272 (57%)	78 (68%)	69 (57%)	73 (58%)	52 (44%)	0.006
Body mass index (kg/m^2)	27.8 ± 5.1	27.7 ± 5.1	28.2 ± 5.5	28.3 ± 5.1	27.1 ± 4.6	0.24
eGFR (mL/min/1.73 m^2)	73 ± 29	70 ± 32	75 ± 29	78 ± 29	69 ± 25	0.04
Haemoglobin (g/L)	134 ± 17	134 ± 18	132 ± 18	137 ± 17	133 ± 17	0.13
Diabetes	96 (20%)	30 (26%)	19 (16%)	26 (21%)	21 (18%)	0.23
Stroke	28 (6%)	4 (3%)	6 (5%)	7 (6%)	11 (9%)	0.25
Chronic obstructive lung disease	56 (12%)	20 (17%)	13 (11%)	14 (11%)	9 (8%)	0.14
FEV1 (% predicted)	86 ± 20	83 ± 20	86 ± 23	89 ± 20	88 ± 19	
Heart rhythm						0.67
Sinus rhythm	414 (87%)	95 (83%)	108 (89%)	110 (88%)	101 (87%)	
Atrial fibrillation	48 (10%)	16 (14%)	9 (8%)	10 (8%)	13 (11%)	
Pacemaker	15 (3%)	4 (3%)	4 (3%)	5 (4%)	2 (2%)	
Heart rate (b.p.m.)	69 ± 12	69 ± 14	68 ± 12	68 ± 11	72 ± 2	0.02
Medication						
Oral anticoagulation	92 (19%)	24 (21%)	19 (16%)	26 (21%)	23 (20%)	0.71
Aspirin	289 (61%)	70 (61%)	77 (64%)	80 (64%)	62 (53%)	0.31
Loop diuretics	235 (49%)	70 (61%)	56 (46%)	56 (45%)	54 (47%)	0.04
Beta-blocker	224 (47%)	50 (43%)	59 (49%)	61 (49%)	54 (47%)	0.83
ACEI/ARB	264 (55%)	54 (47%)	60 (50%)	70 (56%)	80 (69%)	0.003
Digoxin	30 (6%)	17 (15%)	3 (2%)	4 (3%)	6 (5%)	<0.001
Spironolactone	23 (5%)	9 (8%)	6 (5%)	6 (5%)	2 (2%)	0.20
B-type natriuretic peptide (BNP; ng/L)	181 (76–446)	362 (92–844)	180 (72–368)	165 (70–348)	140 (73–289)	0.04
ln BNP	5.2 ± 1.3	5.6 ± 1.4	5.1 ± 1.3	5.1 ± 1.1	5.0 ± 1.1	0.03
Symptoms						
Dyspnea NYHA class						0.13
I	92 (19%)	18 (16%)	22 (18%)	26 (21%)	26 (22%)	
II	238 (50%)	51 (44%)	66 (55%)	67 (54%)	54 (47%)	
III	126 (26%)	35 (30%)	29 (24%)	29 (23%)	33 (28%)	
IV	21 (5%)	11 (10%)	4 (3%)	3 (2%)	3 (3%)	
Mode of AVR						0.80
Surgical AVR	339 (71%)	78 (68%)	87 (72%)	92 (74%)	82 (71%)	
Transcatheter AVR	138 (29%)	37 (32%)	34 (28%)	33 (26%)	34 (29%)	

Note: Data are given as numbers and percentages, mean ± standard deviation, or median (interquartile range).
Abbreviations: ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; AVR, aortic valve replacement; eGFR, estimated glomerular filtration rate: FEV1, forced expiratory volume within the first second; NYHA, New York Heart Association.

0.48–12.82); P = 0.28 for lowest versus highest MAP quartile in the TAVR subgroup. For the analysis with MAP as a continuous variable, the results were as follows: HR 0.68 (95% CI 0.50–0.93) per 10 mmHg increase; P = 0.02 for the SAVR group, and HR 0.85 (95% CI 0.62–1.16); P = 0.30 for the TAVR group.

In a multivariate Cox regression analysis, lower MAP [HR 0.78 (95% CI 0.62–0.99) per 10 mmHg increase; P = 0.04], higher mean right atrial pressure [HR 1.08 (95% CI 1.01–1.17) per 1 mmHg increase; P = 0.04], and lower LVEF [HR 0.97 (95% CI 0.95–0.99) per 1% increase; P = 0.01] were independent predictors of death (*Table 3*). Indexed arterial elastance [HR = 1.11 (95% CI 0.86–1.44) per 1 mmHg/mL*m^2 increase; P = 0.40], pulse pressure [HR = 0.90 (95%CI 0.79–1.03) per 10 mmHg increase; P = 0.13], systemic arterial compliance [HR 0.59 (95% CI 0.11–3.12) per 1 mL/m^2/mmHg increase; P = 0.54], SVR [HR 1.01 (95% CI 0.95–1.07) per 1 WU increase; P = 0.85], and Z_{VA} [HR 1.02 (95% CI 0.85–1.23) per 1 mmHg/mL*m^{-2} increase; P = 0.81] were not significantly associated with post-AVR mortality.

LVSWI and mortality

In the subgroup of patients with available LVEDP (n = 327), the correlation between LVSWI values calculated with the use of the mPAWP or the LVEDP was very strong (r = 0.99). As shown in *Figure 3*, mortality in the entire population (n = 477) was highest in patients in the lowest LVSWI (mPAWP-based) quartile [HR 2.65 (95% CI 1.11–6.33); P = 0.03 compared with the highest quartile]. When used as a continuous variable, lower LVSWI was also significantly associated with higher mortality (*Table 3*). In the subgroup with available LVEDP, LVSWI as a continuous variable was also associated with mortality, and this was independent of the method of LVSWI calculation: mPAWP-based: HR 0.83 (95% CI 0.73–0.95); P = 0.006; LVEDP-based: HR 0.84 (95% CI 0.73–0.97); P = 0.02. In the Kaplan–Meier analysis, mortality was highest in patients in the lowest LVSWI quartile, but this analysis reached statistical significance only for the mPAWP-based LVSWI calculation (P = 0.016) but not for the LVEDP-based LVSWI calculation (P = 0.065) (*Figures* S1 and S2).

Table 2 Data from echocardiography and cardiac catheterization of the entire study population and according to mean arterial pressure (MAP) quartiles

	All (n = 477)	Q1 (n = 115) MAP ≤88 mmHg	Q2 (n = 121) MAP 89–97 mmHg	Q3 (n = 125) MAP 98–107 mmHg	Q4 (n = 116) MAP ≥108 mmHg	P value
Echocardiography						
Left ventricular end-diastolic diameter (mm)	47 ± 8	48 ± 8	48 ± 8	48 ± 7	45 ± 7	0.008
Indexed left ventricular end-diastolic diameter	25 ± 4	26 ± 5	26 ± 4	25 ± 4	25 ± 3	0.16
Left ventricular ejection fraction (%)	58 ± 12	54 ± 14	58 ± 11	58 ± 10	60 ± 10	0.004
E/e'	16.7 ± 8.4	18.6 ± 11.3	15.3 ± 6.7	16.3 ± 7.0	16.9 ± 8.6	0.26
Left atrial area (cm^2)	25 ± 7	27 ± 9	24 ± 7	24 ± 6	25 ± 6	0.11
Indexed left atrial area (cm^2/m^2)	13.3 ± 3.7	14.5 ± 4.4	12.6 ± 3.5	13.2 ± 3.5	13.2 ± 3.3	0.10
Tricuspid annular plane systolic excursion (mm)	21 ± 5	21 ± 5	21 ± 4	21 ± 5	21 ± 6	0.86
Estimated sPAP (mmHg)	40 ± 13	43 ± 15	39 ± 12	38 ± 10	38 ± 12	0.08
Mean aortic valve gradient (mmHg)	47 ± 17	48 ± 19	48 ± 17	47 ± 18	45 ± 16	0.53
Aortic valve area (cm^2)	0.80 ± 0.23	0.81 ± 0.27	0.79 ± 0.24	0.79 ± 0.22	0.80 ± 0.21	0.87
Indexed aortic valve area (cm^2/m^2)	0.43 ± 0.12	0.43 ± 0.13	0.42 ± 0.12	0.42 ± 0.12	0.43 ± 0.11	0.73
Mitral regurgitation						0.03
No	225 (47%)	45 (39%)	66 (54%)	58 (46%)	56 (48%)	
Mild	204 (43%)	48 (42%)	47 (39%)	59 (47%)	50 (43%)	
Moderate	39 (8%)	17 (15%)	7 (6%)	6 (5%)	9 (8%)	
Severe	9 (2%)	5 (4%)	1 (1%)	2 (2%)	1 (1%)	
Coronary artery disease						0.39
No coronary artery disease	251 (53%)	62 (54%)	65 (54%)	63 (50%)	61 (53%)	
1-vessel disease	84 (18%)	17 (15%)	23 (19%)	18 (14%)	26 (22%)	
2-vessel disease	63 (13%)	17 (15%)	19 (16%	16 (13%)	11 (9%)	
3-vessel disease	79 (16%)	19 (16%)	14 (11%)	28 (23%)	18 (16%)	
Invasive hemodynamics						
Mean right atrial pressure (mmHg)	6 ± 4	7 ± 4	6 ± 3	7 ± 3	7 ± 4	0.63
Right ventricular end-diastolic pressure (mmHg)	8 ± 4	8 ± 4	8 ± 4	8 ± 4	8 ± 4	0.95
sPAP (mmHg)	40 ± 15	41 ± 16	37 ± 15	39 ± 13	42 ± 14	0.10
dPAP (mmHg)	15 ± 7	16 ± 8	14 ± 7	15 ± 6	16 ± 7	0.11
mPAP (mmHg)	25 ± 10	26 ± 11	23 ± 10	25 ± 9	27 ± 10	0.07
mPAWP (mmHg)	16 ± 8	17 ± 8	14 ± 7	16 ± 7	17 ± 8	0.05
Transpulmonary gradient (mmHg)	9+/-4	9 ± 5	9 ± 4	9 ± 4	10 ± 4	0.58
Pulmonary vascular resistance (Wood units)	2.1 ± 1.2	2.3 ± 1.6	2.0 ± 1.3	2.0 ± 1.0	2.1 ± 1.1	0.31
Pulmonary artery compliance (mL/mmHg)	3.3 ± 1.6	3.5 ± 2.3	3.5 ± 1.4	3.3 ± 1.2	3.0 ± 1.4	0.24
Left ventricular end-diastolic pressure (mmHg), n = 327	21 ± 8	21 ± 8	21 ± 8	21 ± 7	21 ± 7	0.91
Systolic aortic pressure (mmHg)	145 ± 25	121 ± 16	137 ± 15	151 ± 13	174 ± 18	<0.001
Diastolic aortic pressure (mmHg)	68 ± 11	56 ± 9	65 ± 9	71 ± 6	80 ± 8	<0.001
Mean aortic pressure (mmHg)	98 ± 14	81 ± 6	93 ± 3	102 ± 3	117 ± 7	<0.001
Pulse pressure (mmHg)	77 ± 23	64 ± 21	72 ± 21	80 ± 18	94 ± 22	<0.001
Systemic vascular resistance (Wood units)	20.3 ± 5.2	17.4 ± 4.9	18.9 ± 4.4	20.8 ± 3.9	24.1 ± 5.1	<0.001
Arterial oxygen saturation (%)	95 (95–97)	95 (93–96)	96 (94–97)	95 (93–96)	95 (93–97)	0.28
Mixed venous oxygen saturation (%)	68 (64–72)	66 (62–71)	69 (63–72)	69 (65–72)	70 (66–73)	0.003
Cardiac output (l/min)	4.7 ± 1.0	4.5 ± 1.2	4.8 ± 1.0	4.8 ± 0.9	4.8 ± 1.1	0.24
Cardiac index (l/min/m^2)	2.5 ± 0.5	2.4 ± 0.5	2.5 ± 0.5	2.5 ± 0.4	2.6 ± 0.5	0.04
Stroke volume index (mL/m^2)	37 ± 10	37 ± 11	39 ± 10	37 ± 8	37 ± 10	0.44
RVSWI (g*min*m^{-2})	8.3 ± 3.4	8.1 ± 3.4	7.9 ± 3.1	8.4 ± 3.4	8.7 ± 3.5	0.25
LVSWI (g*min*m^{-2})	91 ± 31	77 ± 30	91 ± 30	93 ± 26	103 ± 33	<0.001
Valvulo-arterial impedance (mmHg/mL*m^{-2})	5.4 ± 1.6	5.0 ± 1.7	5.1 ± 1.7	5.5 ± 1.2	6.3 ± 1.5	<0.001
Indexed arterial elastance (mmHg/mL*m^2)	3.7 ± 1.1	3.2 ± 1.1	3.4 ± 1.0	3.8 ± 0.8	4.5 ± 1.1	<0.001
Systemic arterial compliance (mL/m^2/mmHg)	0.52 ± 0.20	0.61 ± 0.25	0.57 ± 0.18	0.48 ± 0.14	0.41 ± 0.14	<0.001

Note: Data are given as numbers and percentages, mean ± standard deviation, and/or median (interquartile range).
Abbreviations: dPAP, diastolic pulmonary artery pressure; E/e', ratio of peak early mitral inflow velocity to peak early mitral annular velocity; LVSWI, left ventricular stroke work index; mPAP, mean pulmonary artery pressure; mPAWP, mean pulmonary artery wedge pressure; RVSWI, right ventricular stroke work index; sPAP, systolic pulmonary artery pressure.

Discussion

The present detailed invasive study with a clinical post-AVR follow-up of several years provides novel insights into the role of BP in patients with severe AS. First, low MAP was associated with low LVEF and high BNP. Patients with low MAP had similar indexed aortic valve area, SVI, LVEDP, mPAWP, mPAP, and PVR as patients with higher MAP, but this occurred in the context of a more unloaded left ventricle as expressed by low SVR and Z_{VA}. The LVSWI, an important invasive measure of global left ventricular performance, was lowest in patients in the lowest MAP quartile. Second and very importantly, low pre-AVR MAP was an independent predictor of mortality late after AVR (graphical abstract).

Figure 1 Indexed aortic valve area (AVAi) and key haemodynamic parameters in patients in different mean arterial pressure (MAP) quartiles. Error bars represent means and standard deviations. LVEDP, left ventricular end-diastolic pressure; LVSWI, left ventricular stroke work index; mPAWP, mean pulmonary artery wedge pressure; SVI, stroke volume index; SVR, systemic vascular resistance. The scale/units are: mm^2/m^2 (AVAi), mL/m^2 (SVI), $g*min*m^{-2}$ (LVSWI), mmHg (LVEDP, mPAWP, and MAP), and Wood units (SVR).

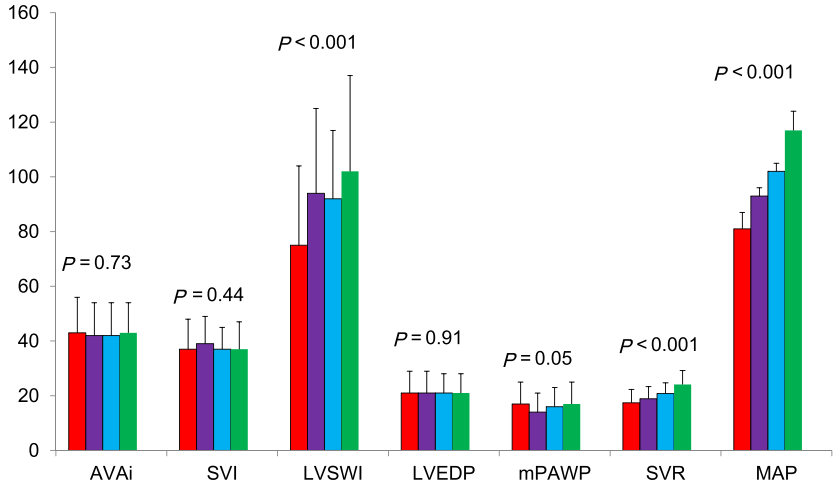
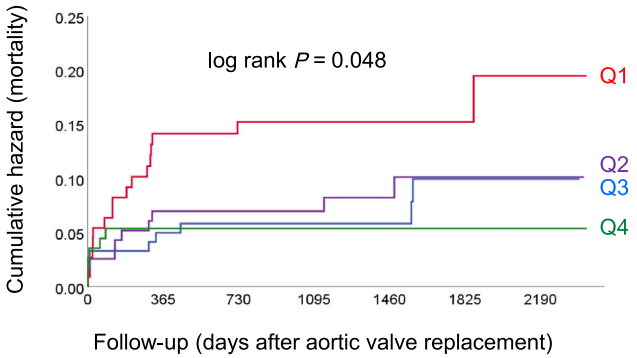


Figure 2 Kaplan–Meier plots showing cumulative events (mortality) for patients in different mean arterial pressure (MAP) quartiles. Q1: MAP ≤88 mmHg, Q2: MAP 89–97 mmHg, Q3: MAP 98–107 mmHg, Q4: MAP ≥108 mmHg.



The changes in demographics in the population with severe AS—that is, a shift towards older patients with co-morbidities including hypertension—has resulted in a new interest in the management of hypertension in AS patients.[3,4] In addition, it has been proposed that early (i.e., prior to the time point of AVR) pharmacological interventions may favourably impact on the maladaptive changes of the left ventricle in severe AS (i.e., hypertrophy and fibrosis).[22] Data from observational studies suggest that RAASi may indeed have a beneficial effect.[8] A new approach (first proposed for the post-AVR setting) is the use of sodium glucose co-transporter-2 inhibitors.[23] All these drugs have an effect on BP, but the optimal BP in AS patients is unknown, and this applies for both the pre-AVR and post-AVR setting. Experts now recommend a systolic BP 130–139 mmHg and a diastolic BP 70 (80) to 90 mmHg for AS patients.[1,2] This recommendation is derived from a *post hoc* analysis of the Simvastatin Ezetimibe in Aortic Stenosis (SEAS) trial, which however included asymptomatic patients with mild or moderate asymptomatic AS rather than symptomatic patients with severe AS.[24] In the present study, prognosis was clearly worst in patients in the lowest MAP quartile, that is, a MAP of 81 ± 6 mmHg. These patients had a central systolic BP of 121 ± 16 mmHg and a central diastolic BP of 56 ± 9 mmHg at the time of cardiac catheterization, which was probably higher than under everyday conditions, when these patients had taken their ACE-I/ARB and diuretics and were free of the adrenergic drive related to an invasive procedure. In a contemporary trial in patients with heart failure and reduced LVEF, those in the lowest BP stratum (systolic BP < 110 mmHg) also had the worst prognosis. These patients had a peripheral systolic BP of 102 ± 4 mmHg, and a peripheral diastolic BP of 65 ± 7 mmHg.[12]

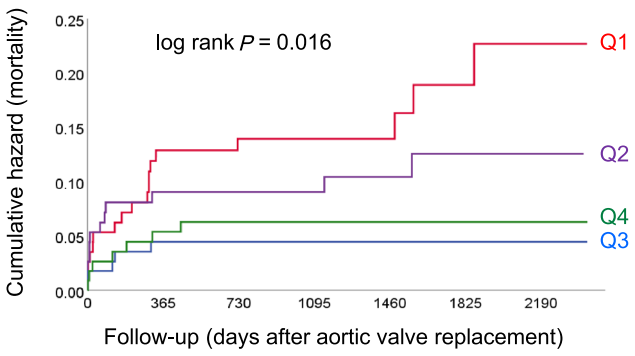
To the best of our knowledge, our data on the prognostic role of MAP in severe AS represent a new finding. The findings are however in line with an analysis of the Placement of Aortic Transcatheter Valve (PARTNER) I trial, where a lower systolic BP measured 30 days after TAVR was associated with higher mortality.[10] In this study, high indexed arterial elastance and low systemic arterial compliance but not SVR, that is, high total and pulsatile but not resistive arterial load, were also associated with increased 1 year mortality.[10] An analysis in a different population of patients undergoing SAVR or TAVR confirmed these findings.[11] In the present study, indexed arterial elastance and systemic arterial compliance

Table 3 Univariate and multivariate Cox regression with mortality as the dependent variable

	Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Chronic obstructive pulmonary disease	2.54 (1.25–5.16)	0.01		
Estimated glomerular filtration rate (eGFR)	0.85 (0.75–0.96) per 10 mL/min/1.73 m^2	0.009		
Oral anticoagulation	2.73 (1.47–5.10)	0.002		
Left ventricular ejection fraction	0.96 (0.94–0.98) per 1%	<0.001	0.97 (0.95–0.99) per 1%	0.01
Tricuspid annular plane systolic excursion	0.91 (0.83–1.00) per 1 mm	0.05		
Mitral regurgitation	2.02 (1.41–2.90) per grade	<0.001		
Coronary artery disease	1.32 (1.04–1.68) per number of affected vessels	0.02		
Mean arterial pressure	0.75 (0.60–0.94) per 10 mmHg	0.01	0.78 (0.62–0.99) per 10 mmHg	0.04
Mean right atrial pressure	1.10 (1.03–1.18) per 1 mmHg	0.007	1.08 (1.01–1.17) per 1 mmHg	0.04
Right ventricular end-diastolic pressure	1.08 (1.01–1.16) per 1 mmHg	0.03		
Mean pulmonary artery pressure	1.05 (1.03–1.08) per 1 mmHg	<0.001		
Mean pulmonary artery wedge pressure	1.05 (1.01–1.08) per 1 mmHg	0.008		
Pulmonary vascular resistance	1.50 (1.29–1.75) per 1 WU	<0.001		
Pulmonary artery compliance	0.63 (0.49–0.82) per 1 mL/mmHg	<0.001		
Stroke volume index	0.70 (0.50–0.99) per 10 mL/m^2	0.04		
Right ventricular stroke work index	1.08 (1.004–1.16) per 1 g*min*m^{-2}	0.04		
Left ventricular stroke work index	0.85 (0.77–0.95) per 10 g*min*m^{-2}	0.003		
Ln B-type natriuretic peptide	1.94 (1.34–2.81) per ln unit	<0.001		

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval.

Figure 3 Kaplan–Meier plots showing cumulative events (mortality) for patients in different left ventricular stroke work index (LVSWI) quartiles in the entire population (LVSWI calculated using the mean pulmonary artery wedge pressure; for details see text). Q1: LVSWI ≤68.79 g*min*m^{-2}, Q2: LVSWI 68.80–90.83 g*min*m^{-2}, Q3: LVSWI 90.84–109.82 g*min*m^{-2} Q4: LVSWI ≥109.83 g*min*m^{-2}.



were not associated with mortality, which may be explained by the different setting and methodology. First, we studied patients in the pre-AVR rather than the post-AVR setting. The PARTNER investigators have shown that TAVR leads to significant albeit relatively small changes in systolic and diastolic BP, pulse pressure, indexed arterial elastance, and SVR.[10] Second, we measured central BP invasively, whereas other studies including the PARTNER trial typically used non-invasive brachial BP.[10] Difference in central and peripheral BP are well known,[25] and the studies are therefore not directly comparable. In addition, the TAVR subgroup in our study was relatively small. Thus, the two studies overall provided complimentary rather than contradictory findings.

To understand the role of BP in AS and particularly its prognostic impact, we performed an analysis of a very detailed and unique invasive dataset. We found that a low MAP was not simply reflective of a low SVI and/or a low SVR although at the first glance, low MAP was primarily the effect of reduced SVR. This finding is somewhat counterintuitive because a high rather than a low SVR is typically considered to be an unfavourable haemodynamic marker. At the same time, Z_{VA} was lowest in patients with the lowest MAP, which we would consider a favourable constellation.[18] However, despite reduced afterload central haemodynamics including LVEDP, mPAWP, mPAP, and SVI were not 'better' in patients with low MAP compared to those in the other MAP quartiles suggesting a deficit in left global ventricular performance among patients with low MAP given that the indexed aortic valve area was also similar across MAP quartiles. To describe this in a single parameter, we used the LVSWI as an invasive measure of global left ventricular performance taking into account preload and afterload.[19] In daily practice, LVSWI is not a frequently used parameter because it requires a full right and left heart catheterization and thereby is not suitable for bedside and repeated measurements. In addition, in patients with AS, retrograde passage of the aortic valve is potentially hazardous[26] and not recommended for purely diagnostic purposes on a routine basis.[27] We currently only selectively perform this procedure and are not proposing LVSWI measurement for routine use in AS patients. However, for the purpose of the present mechanistic study, LVSWI is a key parameter as it best characterizes left ventricular perfor-

mance in this context. We showed first that LVSWI was lowest in patients in the first MAP quartile and its calculation thereby unmasked the reduced left ventricular performance, and second that low LVSWI was also associated in increased mortality.

In the present study, there was no systematic 30 days and 6 months follow-up as this was the case in PARTNER. Therefore, the haemodynamic situation after AVR remains speculative. A recent small invasive study showed however that TAVR resulted in an immediate reduction in mean aortic valve gradient and thereby Z_{VA}, end-systolic wall stress, and LVSWI, whereas LVEDP, mPAP, and SVI remained acutely unchanged.[20] This was accompanied by a modest increase in systolic BP by 11 mmHg but no change in diastolic BP and MAP.[20] The PARTNER study showed that the BP behaviour after TAVR was variable in that 55% of the population experienced an increase while 45% had a decrease in systolic BP 30 days post-TAVR, and 46% had an increase in diastolic BP while 54% had a decrease.[10] Overall, there were a moderate increase in systolic BP from pre-TAVR to 6 months post-TAVR by less than 10 mmHg and a small decrease in diastolic BP by less than 5 mmHg.[10] Interestingly, the patients with a systolic BP 100–129 mmHg 30 days post-TAVR, who had a higher mortality than those with a systolic BP 130–170 mmHg, also had lower LVEF (and slightly lower SVI) but also lower indexed arterial elastance, SVR, and Z_{VA}, and higher systemic arterial compliance,[10] which is exactly in line with our pre-AVR study. We therefore hypothesize that the pre-AVR MAP and the associated haemodynamic constellation are overall reflective of the early and mid-term post-AVR situation.

Limitations

A number of limitations must be considered. First, the number of patients was relatively small for a study looking at clinical endpoints, and therefore the mortality data are hypothesis-generating only. This is particular true for the subgroup analysis of SAVR versus TAVR patients. However, given the invasive nature of the study the number of patients was sizeable. Second, two aspects related to medical treatment must be considered: on the one hand, our practice of withholding diuretics and ACE inhibitors/ARBs may have had impact of BP during cardiac catheterization in that BP may have been higher than under everyday conditions. However, given that the proportion of patients treated with ACE-I/ARBs was highest in the highest and lowest in the lowest MAP quartile, and the opposite was the case for diuretics, the overall effect was probably small. On the other hand, long-term medical therapy may have affected prognosis.[8] The relatively low proportion of patients under ACEi/ARBs in the lowest MAP quartile is probably explained by their low BP but this may have contributed to the poor outcome of these patients. However, the cross-sectional nature of the present study does not allow definite conclusion. Importantly, in patients with heart failure and reduced LVEF, prognosis is worst in those with the lowest BP, but these patients derive the same relative and the largest absolute benefit from modern medical therapy, for example, sacubitril/valsartan.[12] Whether this is also the case in AS patients pre- and/or post-AVR will have to be tested prospectively. Third, we and others have shown that mPAWP and LVEDP can differ substantially.[28,29] This can have impact of the haemodynamic classification of pulmonary hypertension where a few millimetres of mercury can be relevant around the cut-off value of 15 mmHg.[28] Therefore, calculation of LVSWI based on mPAWP is not absolutely accurate. However, in this setting the systolic left ventricular pressure is much higher than mPAWP and LVEDP, and the differences between the two are less relevant. We demonstrated a tight correlation between LVSWI calculated based on the two methods, and all findings were very similar in the entire population and the two thirds of the population with available LVEDP. Fourth, cardiac catheterization and echocardiography were not performed simultaneously, which may have introduced certain errors in the calculation of LVSWI and Z_{VA}. Still, the availability of a broad set of invasive parameters is a strength of the study.

Conclusions

In severe AS patients, lower MAP reflects lower SVR and Z_{VA}, which may help to preserve stroke volume and filling pressures despite reduced left ventricular performance, which is reflected by low LVSWI. Low MAP is a predictor of high post-AVR mortality, which may be explained by reduced left ventricular reserve.

Conflict of interest

None.

Funding

None.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Kaplan Meier plots showing cumulative events (mortality) for patients in different left ventricular stroke work index (LVSWI) quartiles in the subgroup with available LVEDP (LVSWI calculated using the mPAWP; for details see text). Q1: LVSWI ≤68.49 g*min*m^{-2}, Q2: LVSWI 68.50–89.71 g*min*m^{-2}, Q3: LVSWI 89.72–107.79 g*min*m^{-2} Q4: LVSWI ≥107.80 g*min*m^{-2}.
mPAWP = mean pulmonary artery wedge pressure.

Figure S2. Kaplan Meier plots showing cumulative events (mortality) for patients in different left ventricular stroke work index (LVSWI) quartiles in the subgroup with available LVEDP (LVSWI calculated using the LVEDP; for details see text). Q1: LVSWI ≤67.25 g*min*m^{-2}, Q2: LVSWI 67.26–87.30 g*min*m^{-2}, Q3: LVSWI 87.31–103.25 g*min*m^{-2}, Q4: LVSWI ≥103.26 g*min*m^{-2}.
LVEDP = left ventricular end-diastolic pressure.

Table S1. Clinical characteristics of the entire subgroup of patients with available left ventricular end-diastolic pressure (LVEDP) and according to mean arterial pressure (MAP) quartiles.

Table S2. Data from echocardiography and cardiac catheterization of the entire subgroup of patients with available left ventricular end-diastolic pressure (LVEDP) and according to mean arterial pressure (MAP) quartiles.

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