

Paradoxical Low Flow, Low Gradient in Aortic Valve Stenosis

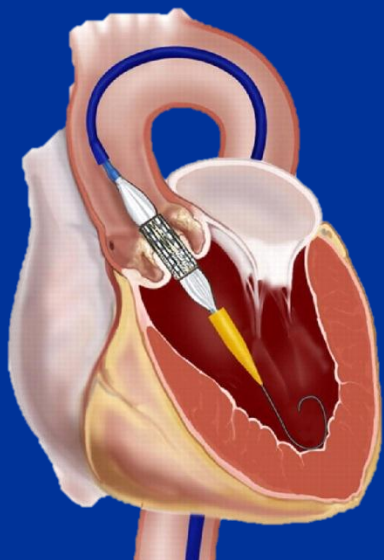
Jean G. Dumesnil, MD, FRCPC, FACC, FASE(Hon)

Quebec Heart and Lung Institute,
Laval University, Quebec, Canada

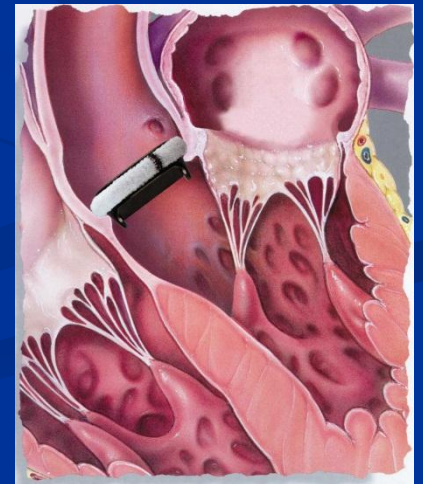
Indication for AVR in AS

SEVERE AORTIC STENOSIS

- Peak aortic jet velocity $\geq 4 \text{ m/s}$
- Mean gradient: $\geq 40 \text{ mmHg}$
- Aortic valve area (AVA): $\leq 1.0 \text{ cm}^2$
- Indexed AVA: $\leq 0.6 \text{ cm}^2/\text{m}^2$



+ SYMPTOMS
 $\pm \text{LVEF} < 50\%$
= AVR (Class I)



A new entity

Paradoxical Low-Flow, Low-Gradient Severe Aortic Stenosis Despite Preserved Ejection Fraction Is Associated With Higher Afterload and Reduced Survival

Zeineb Hachicha, MD; Jean G. Dumesnil, MD; Peter Bogaty, MD; Philippe Pibarot, DVM, PhD

(Circulation. 2007;115:2856-2864.)

Paradoxical low flow and/or low gradient severe aortic stenosis despite preserved left ventricular ejection fraction: implications for diagnosis and treatment

Jean G. Dumesnil^{1*}, Philippe Pibarot^{1*}, and Blase Carabello²

European Heart Journal (2010) **31**, 281–289

Case Study: 57 y.o. Male First Seen 04-07 for Systolic Murmur + Recent Onset Angina

- Rest echo: Max/Mean Gradients : 32/18 mm Hg, AVA:1.2 cm² (BSA = 2.2 cm², indexed EOA: 0.54 cm²/m²)
- Stress echo (Bruce): Onset angina 3 min., strongly positive ECG, normal wall motion rest + exercise, LVH noted
- BP during exercise 160/95

Case Study: Cardiac Cath 05-2007

LVSP: 170 mm Hg

LVEDP: 22 mm Hg

Aortic BP: 150/76

P-to-P gr: 20 mm Hg

**AVA: 1.0 cm² (0.45
cm²/m²)**

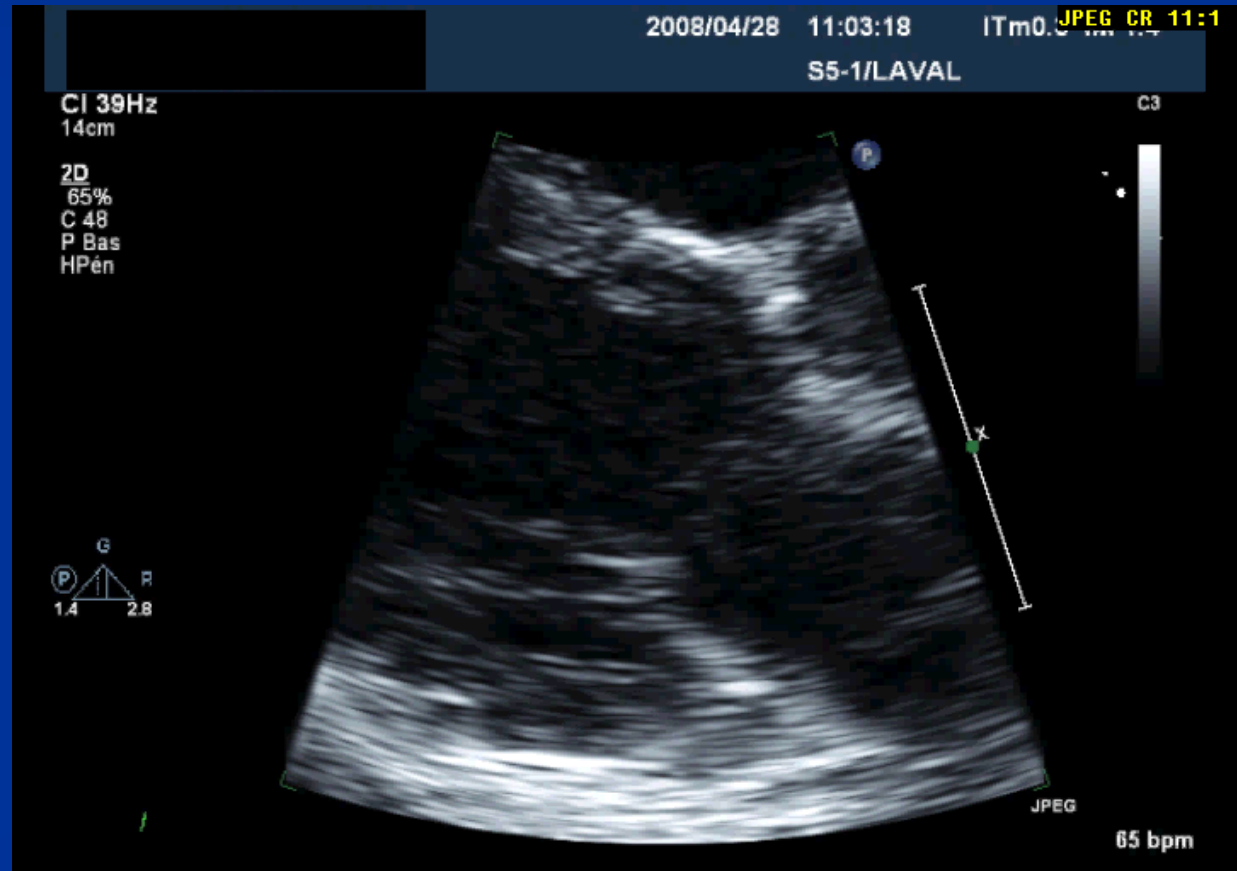
**Angio: 25% stenosis
on distal LAD**

**Dismissed on medical
Rx**

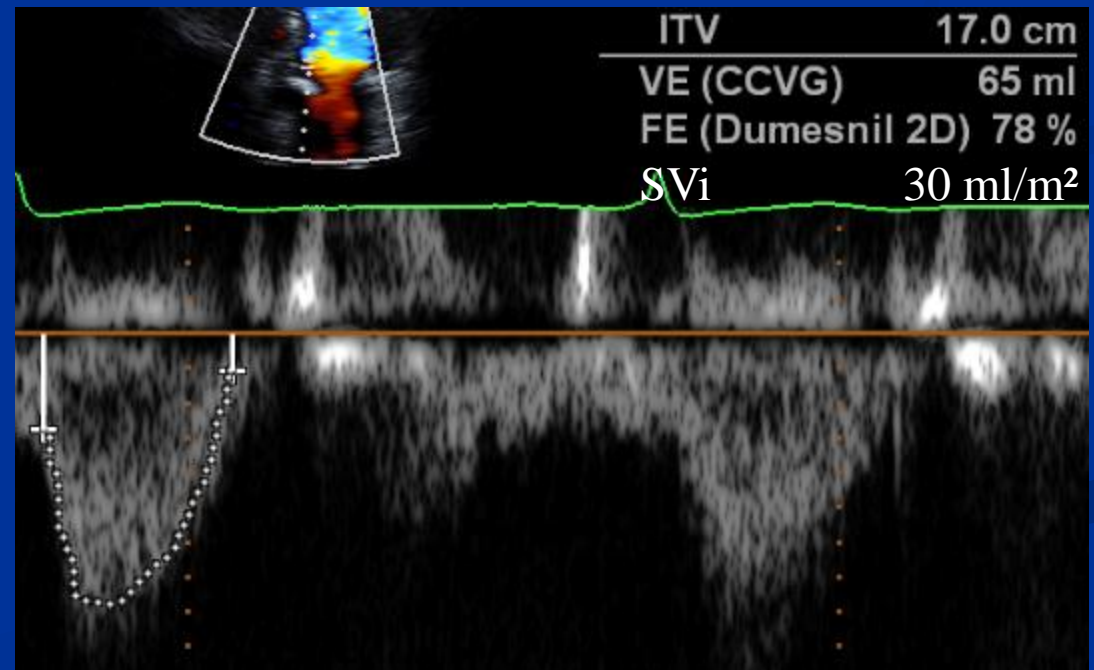
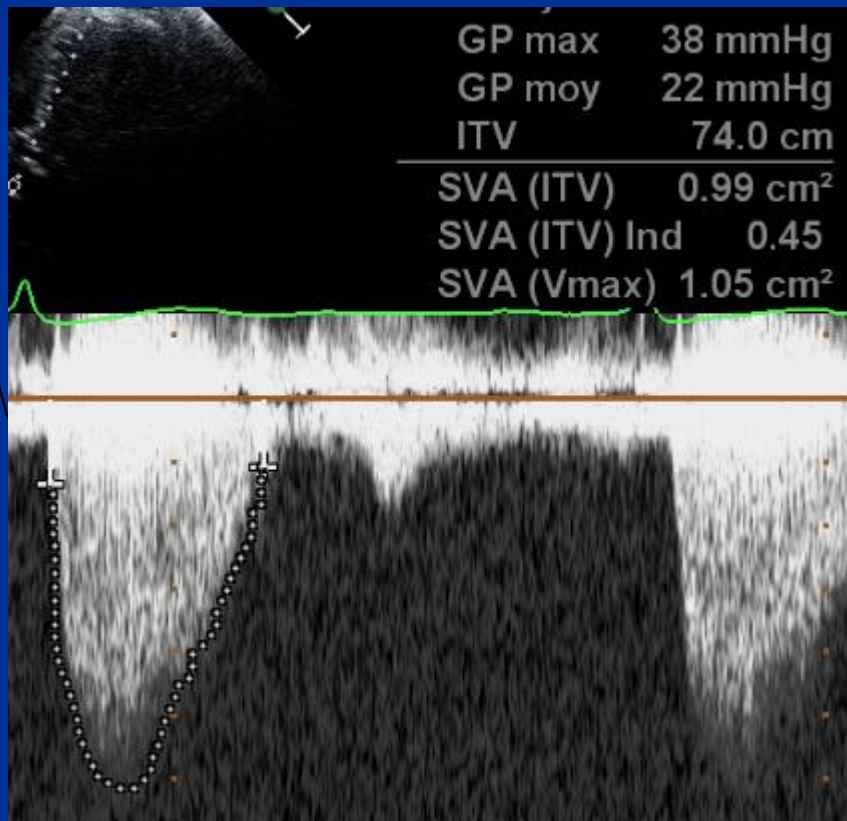


Case Study: Control Echo One Year Later, Persistent III/IV Angina

LVIDd=43 mm
S Th= 12 mm
PW Th= 12 mm
LVEDV=83 ml
LVEDVi=38 ml/m²
(N=35-75 ml/m²)
RWTh=0.55



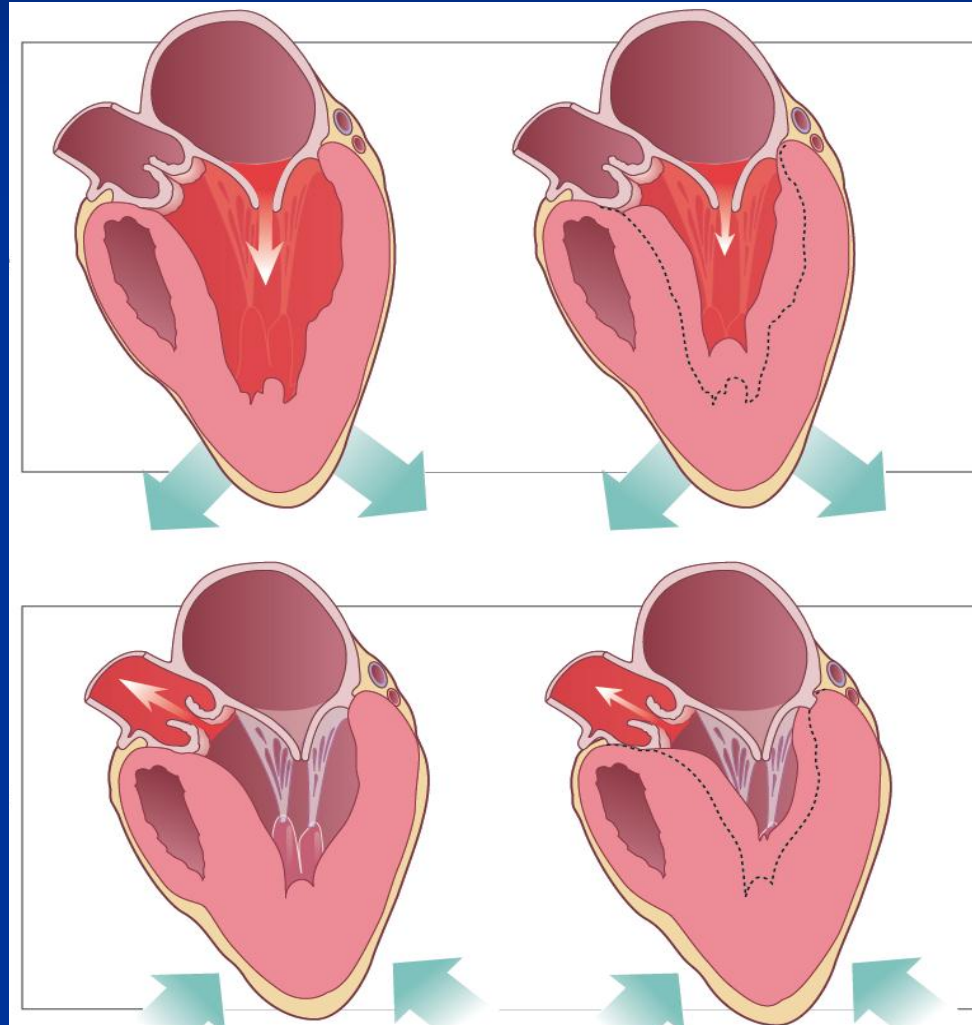
Case Study: Control Echo One Year Later, Persistent III/IV Angina



Pathophysiology of Paradoxical Low Flow AS

Normal flow AS

Paradoxical low flow AS



LVEDV: 115 ml

LVEF: 60%

SV = 70 ml

SVi = 39 ml/m²

AVA = 0.7 cm²

ΔP_{mean} = 45 mmHg

LVEDV: 85 ml

LVEF: 60%

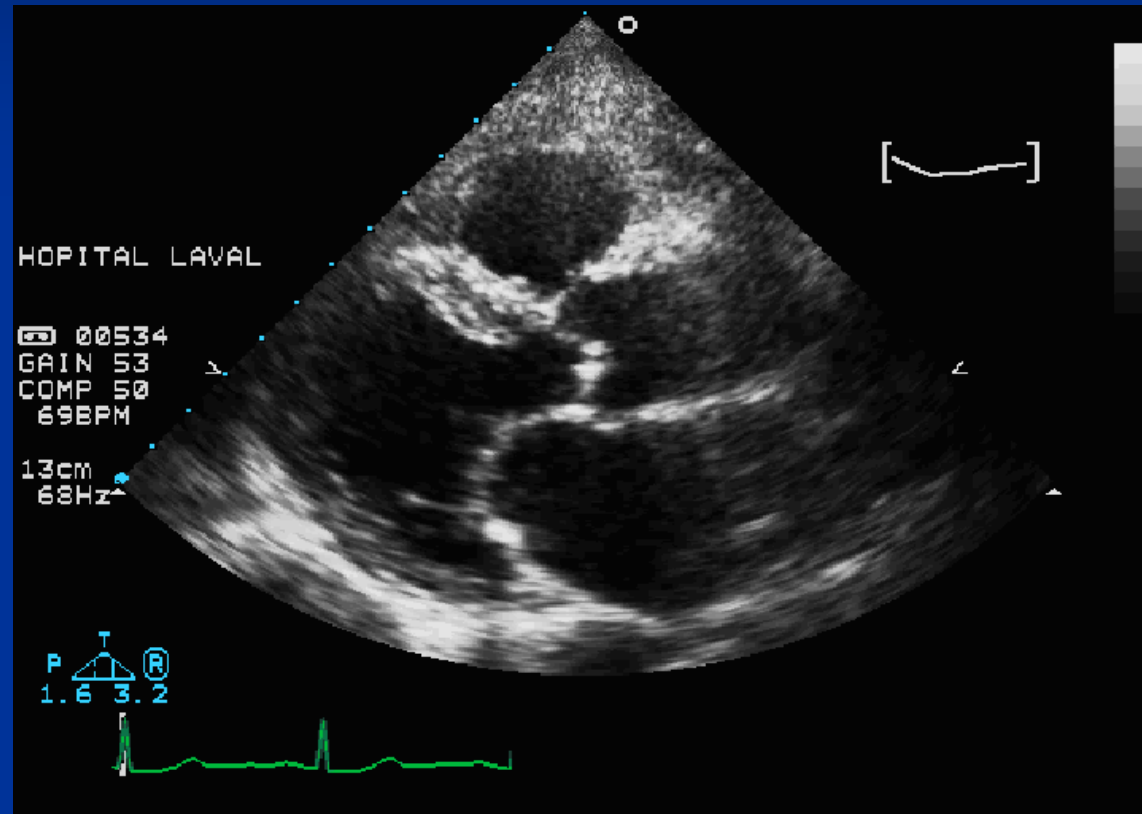
SV = 50 ml

SVi = 28 ml/m²

AVA = 0.7 cm²

ΔP_{mean} = 25 mmHg

Degenerative AS: often not an Isolated Disease of the Valve



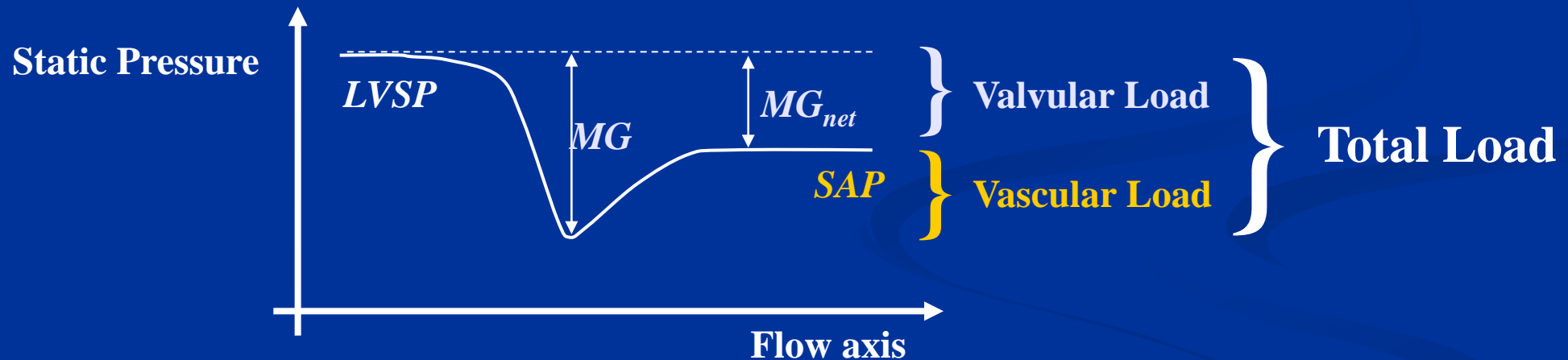
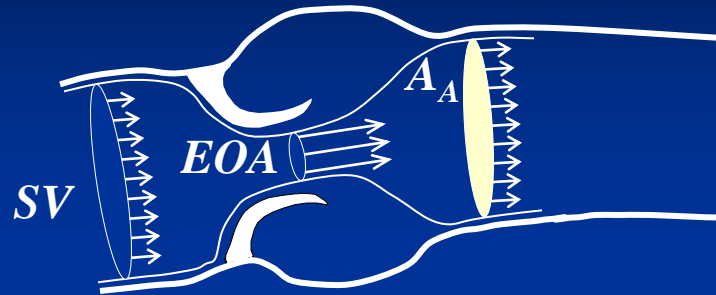
Up to 40 % of patients with AS have reduced systemic arterial compliance and systolic hypertension

Briand et al., JACC, 2005;46:291-8.

Impact of Reduced SAC on LV Hemodynamic Load

	<u>AS+nBP</u>	<u>AS+HTN</u>
Blood Pressure	120/80	180/80
EOA (cm ²)	0.80	0.80
Indexed EOA(cm ² /m ²)	0.44	0.44
Mean Gradient (mm Hg)	50	50
LV systolic pressure	170	230

Valvulo-Arterial Impedance (Zva) as a Measure of Global LV Load



Valvulo-Arterial Impedance

$$Z_{va} = \frac{LVSP}{SV_i} = \frac{MG_{net} + SAP}{SV_i}$$

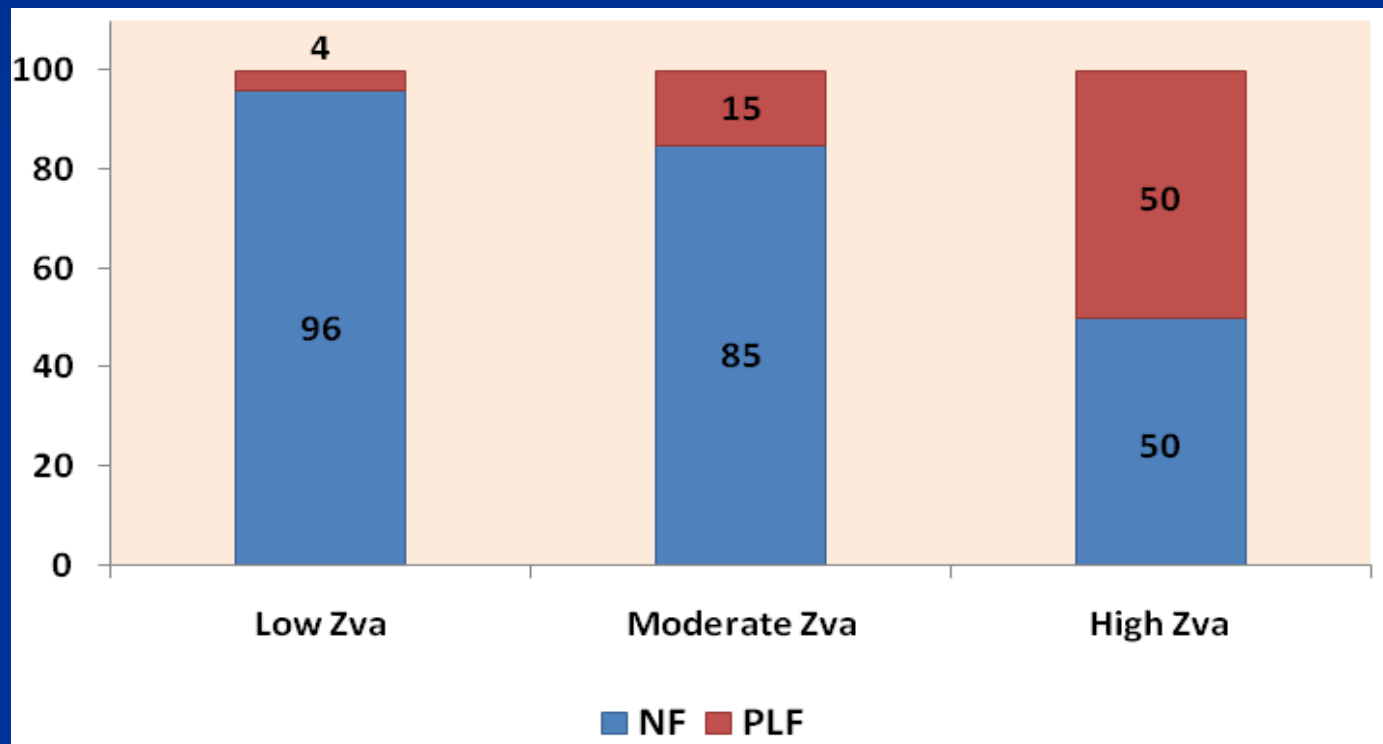
In our patient, Zva = 5,7 mm Hg/ml/m²

Briand et al., JACC,
46:291-8, 2005

Hachicha et al., Circulation,
115:2856-2864, 2007

Valvulo-Arterial Impedance and Prevalence of PLF

544 Asymptomatic Pts. \geq moderate AS



Low $Z_{va} = < 3.5$
mmHg/ml/m²

Moderate $Z_{va} = 3.5 \leq Z_{va} < 4.5$
mmHg/ml/m²

High $Z_{va} = \geq 4.5$
mmHg/ml/m²

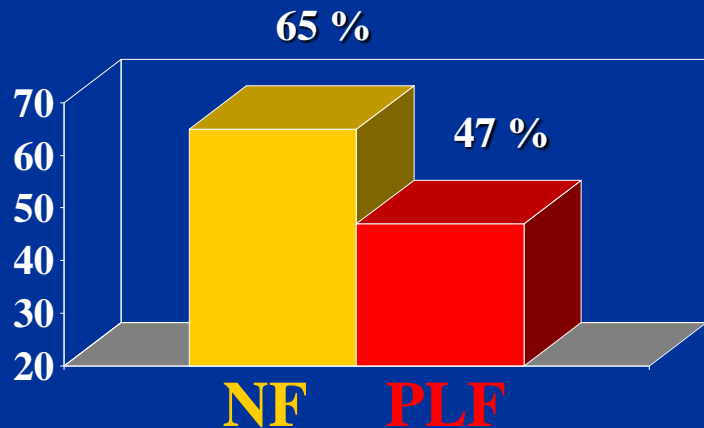
NF: Normal Flow

PLF: Paradoxical Low Flow

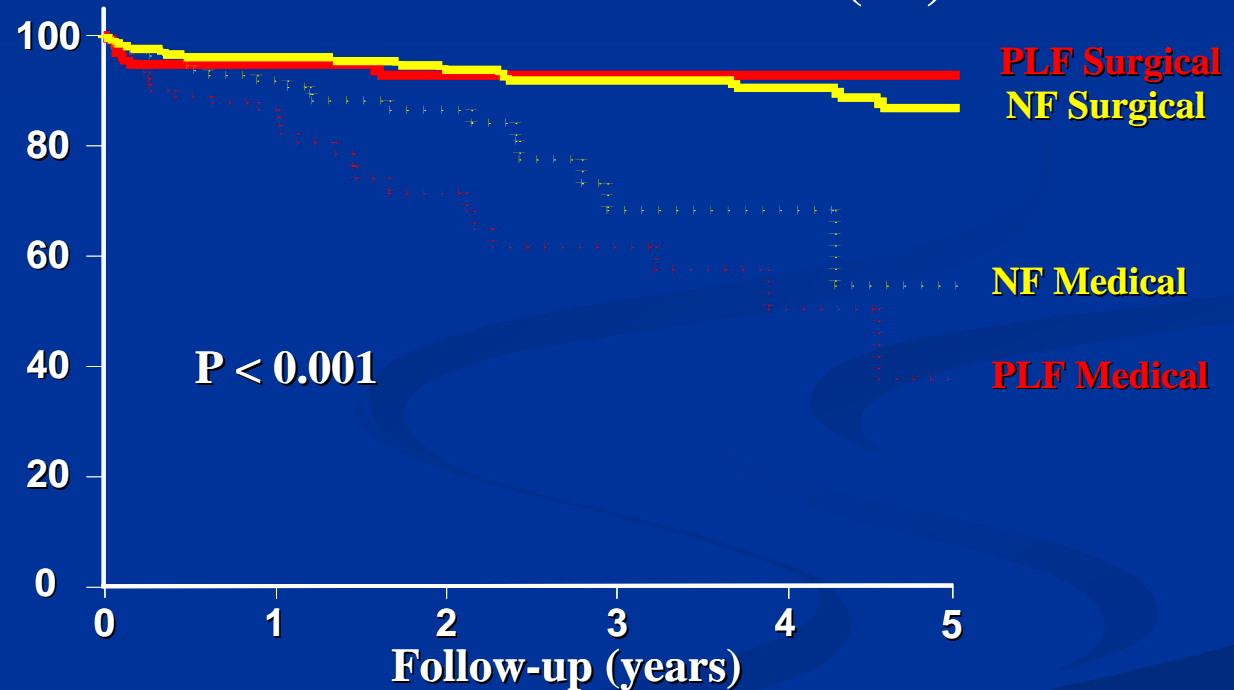
Outcome of Patients with Paradoxical Low Flow, Low Gradient Severe AS

512 Patients with LVEF $\geq 50\%$

Percentage of Patients Treated Surgically



Overall Survival (%)

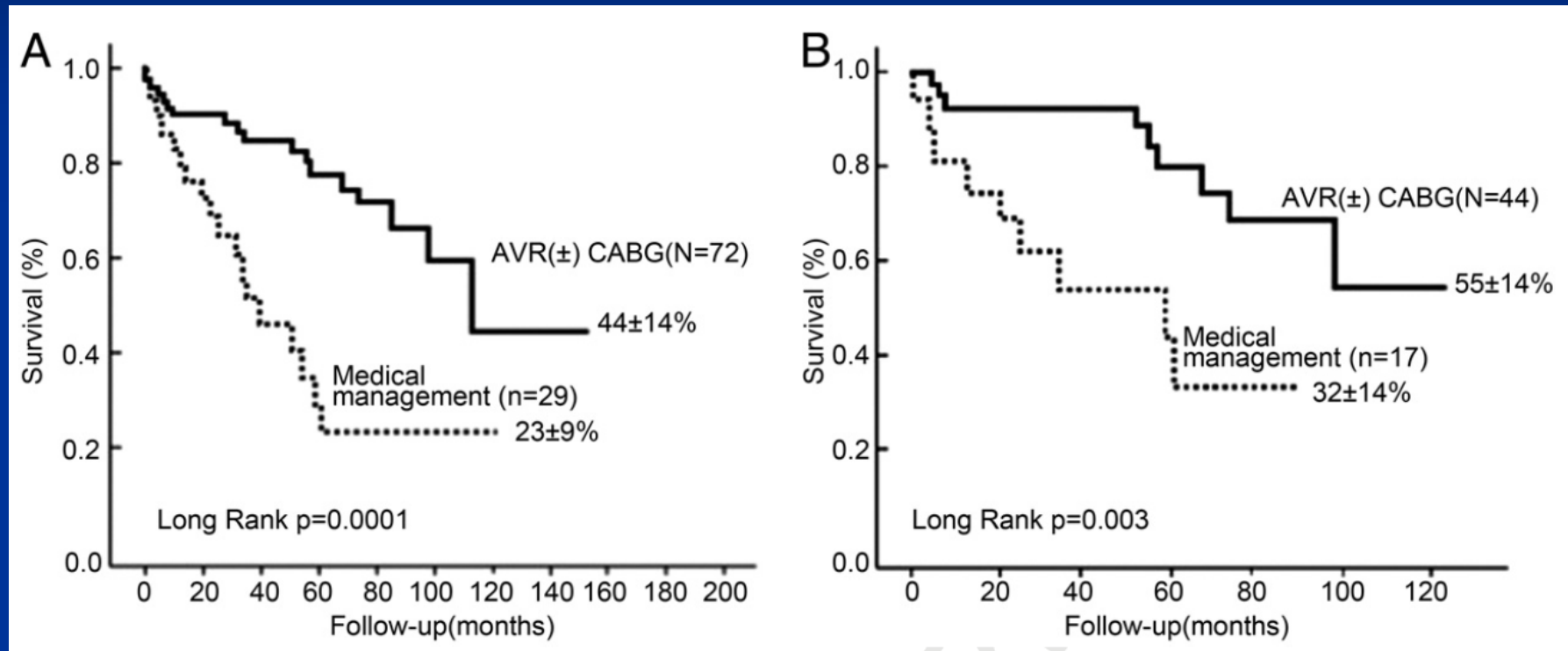


Hachicha Z et al., Circulation.
115:2856-2864, 2007

NF: Normal Flow: SVI > 35 (65%)

PLF: Paradoxical Low Flow: SVI ≤ 35 (35%)

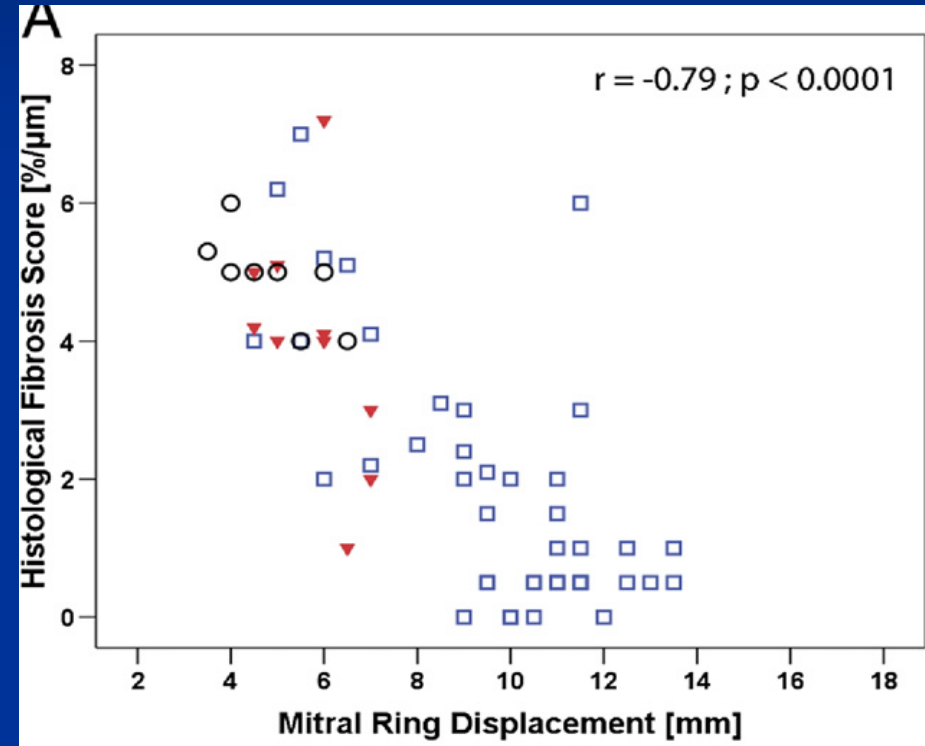
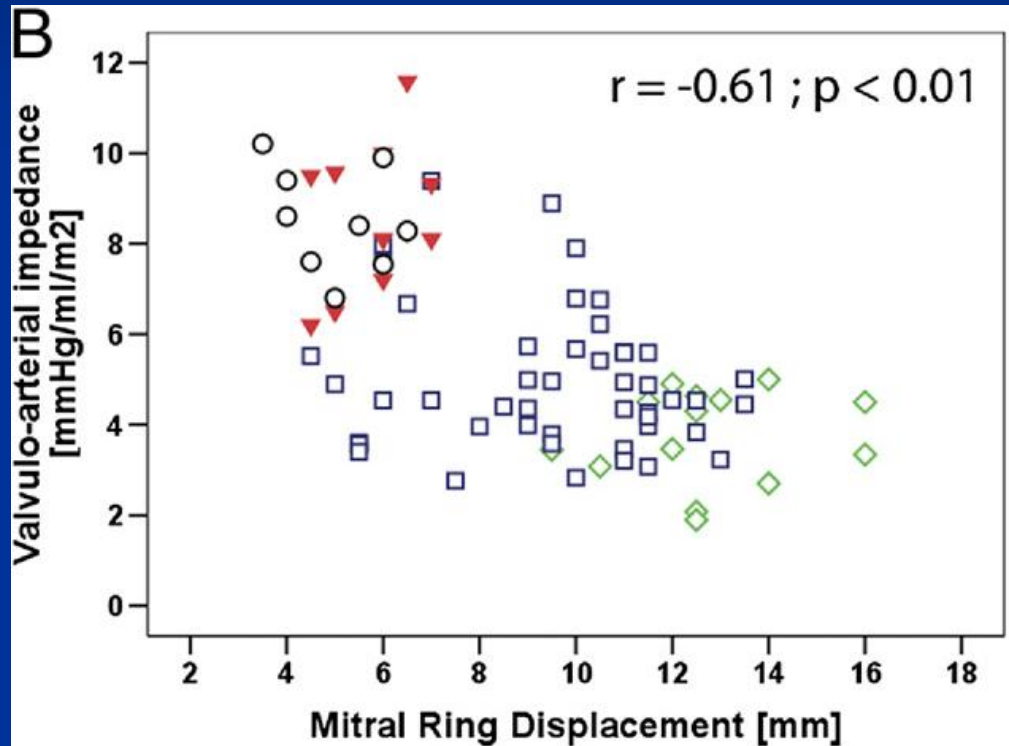
Impact of AVR on Survival in Patients With Paradoxical LF-LG AS



Entire Cohort (n = 101)

Propensity Score Matched
Patients (n = 61).

Interaction between Zva, Longitudinal Shortening and Myocardial Fibrosis

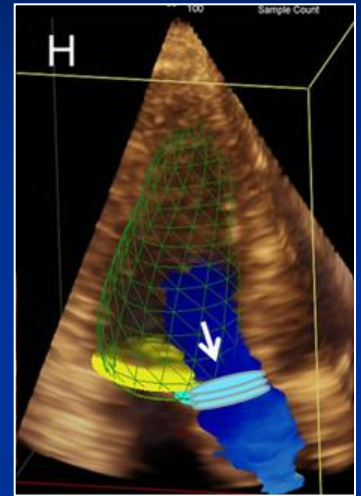


- ◇ Moderate AS
- Severe AS High Gradient
- ▼ Severe AS Low Gradient EF ≥ 50%
- Severe AS Low Gradient EF < 50%

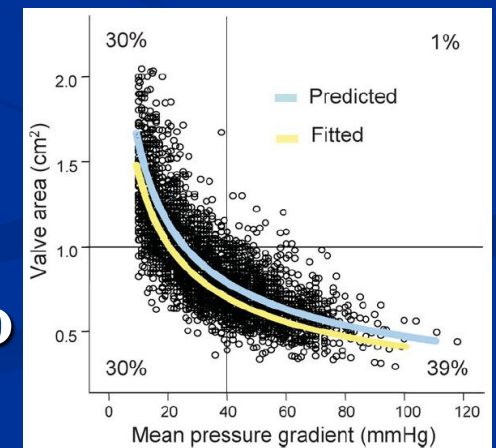
Herrman et al, JACC
2011;58:402-12

Differential Diagnosis of Low Gradient in Pts. With Severe AS and Preserved LVEF

- Paradoxical **LOW FLOW**, low gradient AS
 - Identify typical Doppler-echo features
- Measurement errors (underestimation of SV)
 - Use other methods / imaging modalities to corroborate measures of SV and AVA
- Large or small body size
 - Calculate indexed AVA
- **NORMAL FLOW** low gradient AS due to inconsistency in guidelines criteria



Thavendiranathan
JASE 2012



Paradoxical low flow and/or low gradient severe aortic stenosis despite preserved left ventricular ejection fraction: implications for diagnosis and treatment

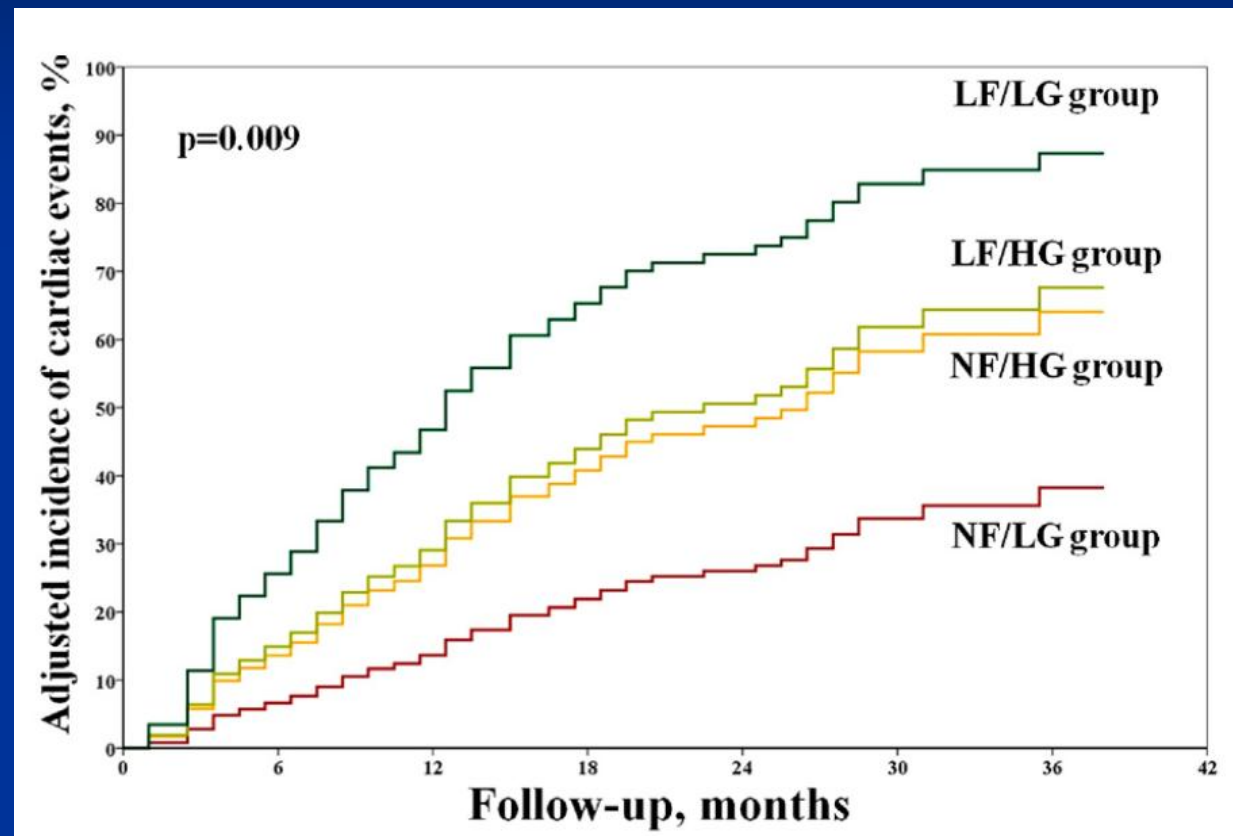
Jean G. Dumesnil^{1*}, Philippe Pibarot^{1*}, and Blase Carabello²

<p>Group 1 'Normal flow, high gradient' $SV_i > 35 \text{ mL/m}^2$ $\text{Gradient} > 40 \text{ mmHg}$ $n = 152 (30\%)$ $\text{Indexed AVA} = 0.4 \pm 0.1 \text{ cm}^2/\text{m}^2$ $\text{LVEDD} = 48 \pm 5 \text{ mm}$ $\text{LVEDVI} = 59 \pm 13 \text{ mL/m}^2$ $Z_{va} = 4.2 \pm 0.8 \text{ mmHg/mL/m}^2$ $\text{AVR} = 80\%$</p>	<p>Group 2 'Normal flow, low gradient' $SV_i > 35 \text{ mL/m}^2$ $\text{Gradient} \leq 40 \text{ mmHg}$ $n = 193 (38\%)$ $\text{Indexed AVA} = 0.5 \pm 0.1 \text{ cm}^2/\text{m}^2$ $\text{LVEDD} = 48 \pm 5 \text{ mm}$ $\text{LVEDVI} = 58 \pm 13 \text{ mL/m}^2$ $Z_{va} = 4.0 \pm 0.6 \text{ mmHg/mL/m}^2$ $\text{AVR} = 53\%$</p>
<p>Group 3 'Low flow, high gradient' $SV_i \leq 35 \text{ mL/m}^2$ $\text{Gradient} > 40 \text{ mmHg}$ $n = 44 (8 \%)$ $\text{Indexed AVA} = 0.3 \pm 0.1 \text{ cm}^2/\text{m}^2$ $\text{LVEDD} = 43 \pm 5 \text{ mm}$ $\text{LVEDVI} = 48 \pm 12 \text{ mL/m}^2$ $Z_{va} = 6.0 \pm 1.2 \text{ mmHg/mL/m}^2$ $\text{AVR} = 68\%$</p>	<p>Group 4 'Low flow, low gradient' $SV_i \leq 35 \text{ mL/m}^2$ $\text{Gradient} \leq 40 \text{ mmHg}$ $n = 123 (24\%)$ $\text{Indexed AVA} = 0.5 \pm 0.1 \text{ cm}^2/\text{m}^2$ $\text{LVEDD} = 46 \pm 5 \text{ mm}$ $\text{LVEDVI} = 53 \pm 11 \text{ mL/m}^2$ $Z_{va} = 5.2 \pm 1.3 \text{ mmHg/mL/m}^2$ $\text{AVR} = 36\%$</p>

Clinical Outcome in Asymptomatic Severe Aortic Stenosis: Insights From the New Proposed Aortic Stenosis Grading Classification

Patrizio Lancellotti, Julien Magne, Erwan Donal, Laurent Davin, Kim O'Connor, Monica Rosca, Catherine Szymanski, Bernard Cosyns, and Luc A. Piérard

J. Am. Coll. Cardiol. 2012;59;235-243



NF/LG (referent)	1.00	1.00-1.00	NA	1.00	1.00-1.00	NA
NF/HG	1.01	0.42-2.38	0.38	2.12	0.80-5.83	0.14
LF/HG	1.51	0.74-3.12	0.08	2.24	1.02-5.47	0.043
LF/LG	4.54	1.99-11.1	0.001	5.22	2.02-14.1	0.001

Outcome of Patients With Low-Gradient “Severe” Aortic Stenosis and Preserved Ejection Fraction

Nikolaus Jander, MD*; Jan Minners, MD, PhD*; Ingar Holme, PhD; Eva Gerds, MD, PhD;

(*Circulation*. 2011;123:887-895.)

	Low-Gradient “Severe” (AVA <1.0 cm ² ; MPG ≤40 mm Hg) (n=435)	Moderate (AVA 1.5–1.0 cm ² ; MPG 25–40 mm Hg) (n=184)	P
Stroke volume, mL	63.8±13.1	97.5±13.9	<0.01
Stroke volume index, mL/m	35.1±7.3	50.7±8.5	<0.01
Cardiac output, L/min	4.3±1.0	6.6±1.2	<0.01
Cardiac index, L/min	2.4±0.56	3.4±0.71	<0.01
LV			
LV ejection fraction, %	66.9±5.7	66.7±5.8	0.68
LV end-diastolic diameter, mm	49.0±6.1	50.7±5.6	<0.01
LV end-diastolic diameter index, mm/m	26.9±3.4	26.3±3.2	0.04
LV end-diastolic volume, mL	115.3±32.7	124.4±31.1	<0.01
LV end-diastolic volume index, mL/m	63.0±16.5	64.3±15.6	0.36
LV end-systolic diameter, mm	31.0±5.1	31.6±5.0	0.18
LV end-systolic diameter index, mm/m	17.0±2.7	16.4±2.7	<0.01
Fractional shortening, %	36.8±5.6	37.8±6.0	0.05
LV end-diastolic septum thickness, mm	11.4±2.8	12.3±2.9	<0.01
LV end-diastolic posterior wall thickness, mm	8.8±1.9	9.4±1.9	<0.01
LV mass, g	182.3±63.6	211.6±67.5	<0.01
LV mass index, g/m	98.9±30.6	108.9±33.3	<0.01
Relative wall thickness, %	36.5±9.5	37.3±8.9	0.30

Conclusion: “Patients with low-gradient “severe” aortic stenosis and normal ejection fraction have an outcome similar to that in patients with moderate stenosis.”

Baseline echocardiographic measures in 610 patients included in the SEAS trial¹⁴ according to assessment of aortic

Paradoxical Low Flow Low Gradient AS despite Preserved LVEF

Conclusions

- Frequent pattern (10-25% of patients)
- More advanced stage of the disease
- Poorer prognosis if treated medically
- Often misdiagnosed (→ inappropriate delays for AVR)
- Need for more comprehensive evaluations including BP, Zva, LV geometry, Echo stress test, BNP, CT scan
- Main pitfalls in diagnosis = 1) Underestimation of SV and AVA; 2) Variations in BSA; 3) Confusion with normal flow LG severe AS

Low-Flow Aortic Stenosis in Asymptomatic Patients: Valvular Arterial Impedance and Systolic Function From the SEAS Substudy

Dana Cramariuc, Giovanni Cioffi, Åshild E. Rieck, Richard B. Devereux, Eva M. Staal, Simon Ray, Kristian Wachtell, and Eva Gerds
J. Am. Coll. Cardiol. Img. 2009;2;390-399

Table 3. Clinical and Echocardiographic Characteristics of Patients With Low-Flow AS and Severely Reduced Energy Loss Index Versus the Remaining Study Population

	Stroke Volume Index ≤22 ml/m ^{2.04} and Energy Loss Index ≤0.55 cm ² /m ² (n = 100)	Stroke Volume Index >22 ml/m ^{2.04} and/or Energy Loss Index >0.55 cm ² /m ² (n = 1,491)
Age (yrs)	69 ± 9	67 ± 10
Women (%)	49†	38
Body mass index (kg/m ²)	26.3 ± 3.9	26.9 ± 4.3
Heart rate (beats/min)	68 ± 10†	66 ± 12
End-diastolic LV volume (ml)	94 ± 33*	112 ± 45
End-systolic LV volume (ml)	33 ± 16*	39 ± 22
LV mass index (g/m ^{2.7})	41 ± 12*	46 ± 15
Relative wall thickness (%)	44 ± 12*	35 ± 9
Mean transaortic gradient (mm Hg)	29 ± 8*	22 ± 8
Net mean transaortic gradient (mm Hg)	25 ± 8*	18 ± 8
Energy loss index (cm ² /m ²)	0.45 ± 0.07*	0.81 ± 0.34
Global LV load (mm Hg/ml-m ^{2.04})	9.66 ± 2.23*	6.38 ± 2.04
Stroke volume index (ml/m ^{2.04})	19 ± 3*	28 ± 7
Ejection fraction (%)	65 ± 7	66 ± 7
Stress-corrected midwall shortening (%)	78.5 ± 14.6*	98.5 ± 19.1

Data are mean ± SD. *p < 0.001 and †p < 0.05 between the 2 groups.
 Abbreviations as in Table 2.

Conclusion: LV myocardial systolic dysfunction is common in asymptomatic AS in particular in patients with low-flow AS and increased valvuloarterial afterload,

Outcome of Patients With Low-Gradient “Severe” Aortic Stenosis and Preserved Ejection Fraction

Nikolaus Jander, MD*; Jan Minners, MD, PhD*; Ingar Holme, PhD; Eva Gerds, MD, PhD;

(*Circulation*. 2011;123:887-895.)

	Low-Gradient “Severe” (AVA <1.0 cm ² ; MPG ≤40 mm Hg) (n=435)*	Moderate (AVA 1.5–1.0 cm ² ; MPG 25–40 mm Hg) (n=184)	P
Stroke volume, mL	63.8±13.1	97.5±13.9	<0.01
Stroke volume index, mL/m	35.1±7.3	50.7±8.5	<0.01
Cardiac output, L/min	4.3±1.0	6.6±1.2	<0.01
Cardiac index, L/min	2.4±0.56	3.4±0.71	<0.01
LV			
LV ejection fraction, %	66.9±5.7	66.7±5.8	0.68
LV end-diastolic diameter, mm	49.0±6.1	50.7±5.6	<0.01
LV end-diastolic diameter index, mm/m	26.9±3.4	26.3±3.2	0.04
LV end-diastolic volume, mL	115.3±32.7	124.4±31.1	<0.01
LV end-diastolic volume index, mL/m	63.0±16.5	64.3±15.6	0.36
LV end-systolic diameter, mm	31.0±5.1	31.6±5.0	0.18
LV end-systolic diameter index, mm/m	17.0±2.7	16.4±2.7	<0.01
Fractional shortening, %	36.8±5.6	37.8±6.0	0.05
LV end-diastolic septum thickness, mm	11.4±2.8	12.3±2.9	<0.01
LV end-diastolic posterior wall thickness, mm	8.8±1.9	9.4±1.9	<0.01
LV mass, g	182.3±63.6	211.6±67.5	<0.01
LV mass index, g/m	98.9±30.6	108.9±33.3	<0.01
Relative wall thickness, %	36.5±9.5	37.3±8.9	0.30

- *Severe AS and SVi < 35 mL/m² = 223pts vs 100 pts for Cramariuc et al. in same cohort
- Different methodology for SV
- 64 mL/m² (LVEDvol) X 0.67 (LVEF) = 42 mL/m² (SVi) rather than 35 mL/m²
- Measurement error ?

Baseline echocardiographic measures in 610 patients included in the SEAS trial¹⁴ according to assessment of aortic

Outcome of Patients With Low-Gradient “Severe” Aortic Stenosis and Preserved Ejection Fraction

Nikolaus Jander, MD*; Jan Minners, MD, PhD*; Ingar Holme, PhD; Eva Gerds, MD, PhD;

(*Circulation*. 2011;123:887-895.)

*Severe AS
and SVi <
35mL/m² =
223/(435+) vs
100/359 pts for
Cramariuc et
al. in same
cohort.

	Low-Gradient “Severe” (AVA <1.0 cm ² ; MPG ≤40 mm Hg) (n=435) *	Moderate (AVA 1.5–1.0 cm ² ; MPG 25–40 mm Hg) (n=184)	P
Stroke volume, mL	63.8±13.1	97.5±13.9	<0.01
Stroke volume index, mL/m	35.1±7.3	50.7±8.5	<0.01
Cardiac output, L/min	4.3±1.0	6.6±1.2	<0.01
Cardiac index, L/min	2.4±0.56	3.4±0.71	<0.01
LV			
LV ejection fraction, %	66.9±5.7	66.7±5.8	0.68
LV end-diastolic diameter, mm	49.0±6.1	50.7±5.6	<0.01
LV end-diastolic diameter index, mm/m	26.9±3.4	26.3±3.2	0.04
LV end-diastolic volume, mL	115.3±32.7	124.4±31.1	<0.01
LV end-diastolic volume index, mL/m	63.0±16.5	64.3±15.6	0.36
LV end-systolic diameter, mm	31.0±5.1	31.6±5.0	0.18
LV end-systolic diameter index, mm/m	17.0±2.7	16.4±2.7	<0.01
Fractional shortening, %	36.8±5.6	37.8±6.0	0.05
LV end-diastolic septum thickness, mm	11.4±2.8	12.3±2.9	<0.01
LV end-diastolic posterior wall thickness, mm	8.8±1.9	9.4±1.9	<0.01
LV mass, g	182.3±63.6	211.6±67.5	<0.01
LV mass index, g/m	98.9±30.6	108.9±33.3	<0.01
Relative wall thickness, %	36.5±9.5	37.3±8.9	0.30

Baseline echocardiographic measures in 610 patients included in the SEAS trial¹⁴ according to assessment of aortic

GUIDELINES AND STANDARDS

Echocardiographic Assessment of Valve Stenosis: EAE/ASE Recommendations for Clinical Practice

Helmut Baumgartner, MD,[†] Judy Hung, MD,[‡] Javier Bermejo, MD, PhD,[†]
John B. Chambers, MD,[†] Arturo Evangelista, MD,[†] Brian P. Griffin, MD,[‡] Bernard Iung, MD,[†]
Catherine M. Otto, MD,[‡] Patricia A. Pellikka, MD,[‡] and Miguel Quiñones, MD[‡]

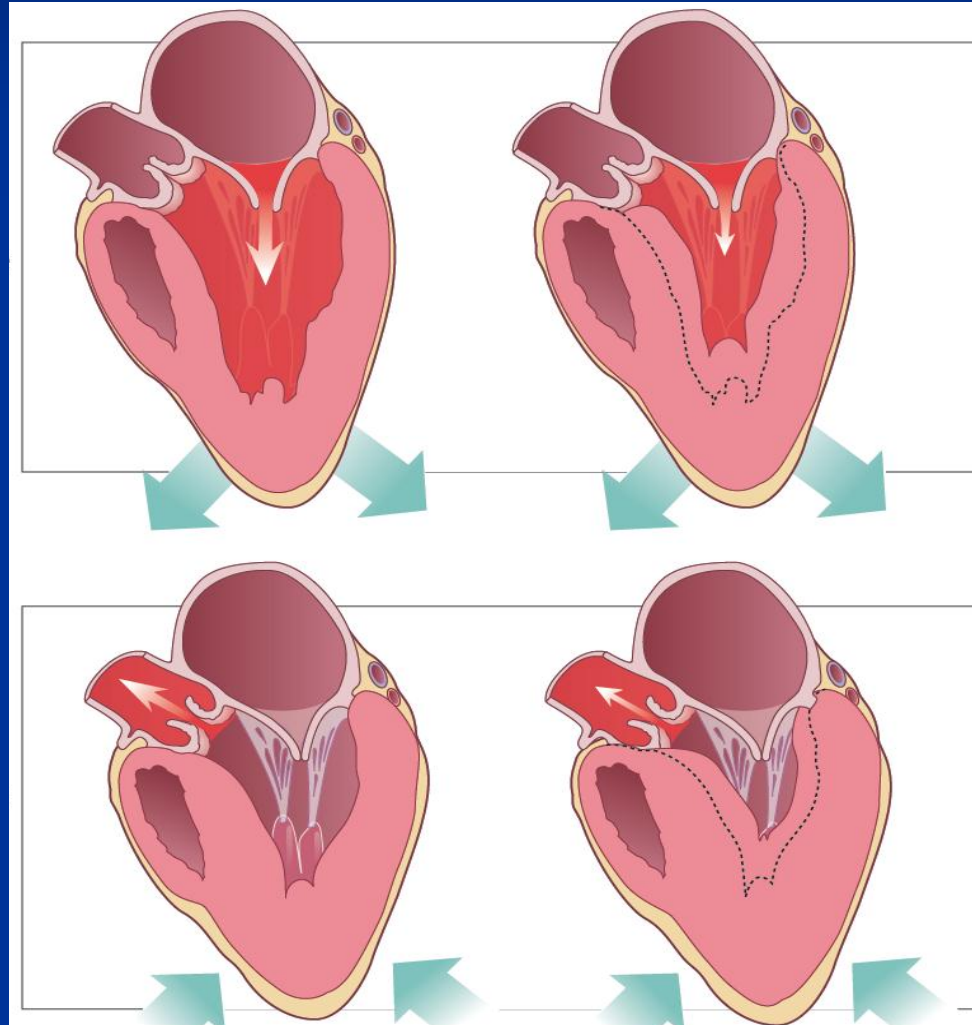
Table 2 Measures of AS severity obtained by Doppler echocardiography

	Units	Formula / Method	Cutoff for Severe	Concept	Advantages	Limitations
Valvulo-Arterial Impedance ³¹	mm Hg/ml/m ²	$Z_{VA} = \frac{\overline{\Delta P_{net}} + SBP}{SVI}$	5	Global systolic load imposed to the LV, where the numerator represents an accurate estimation of total LV pressure	Integrates information on arterial load to the hemodynamic burden of AS, and systemic hypertension is a frequent finding in calcific-degenerative disease.	Although named "impedance", only the steady-flow component (i.e. mean resistance) is considered. No longitudinal prospective study available.

LV Remodelling in Normal vs Paradoxical Low Flow AS

Normal flow AS

Paradoxical low flow AS



LVEDV: 115 ml
LVEF: 60%
SV = 70 ml
SVi = 39 ml/m²
AVA = 0.7 cm²
 $\Delta P_{\text{mean}} = 45 \text{ mmHg}$

LVEDV: 85 ml
LVEF: 60%
SV = 50 ml
SVi = 28 ml/m²
AVA = 0.7 cm²
 $\Delta P_{\text{mean}} = 25 \text{ mmHg}$

LF LG Severe Aortic Stenosis despite Preserved LV Ejection Fraction

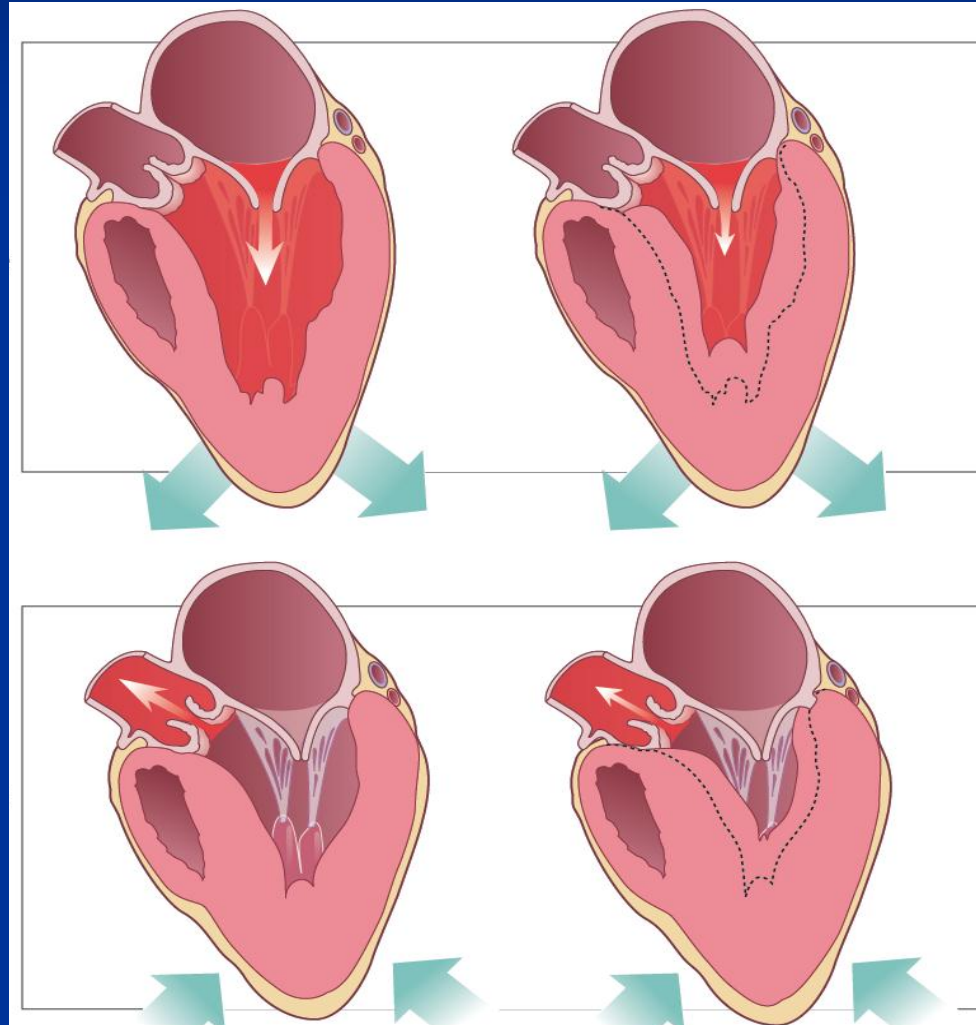
Characteristics

- Severe AS (indexed AVA $< 0.6\text{cm}^2/\text{m}^2$)
- Low mean gradient (20-40 mm Hg)
- SVi $< 35\text{ ml}/\text{m}^2$
- Preserved EF ($>50\%$)
- Hypertension frequent (BP may be pseudo-normalized)
- Higher global LV overload ($Z_{va} > 4.5$)
- More severe LV remodeling, smaller LV cavity
- More frequent in females

Pathophysiology of Paradoxical Low Flow Low Gradient AS

Normal flow AS

Paradoxical low flow AS

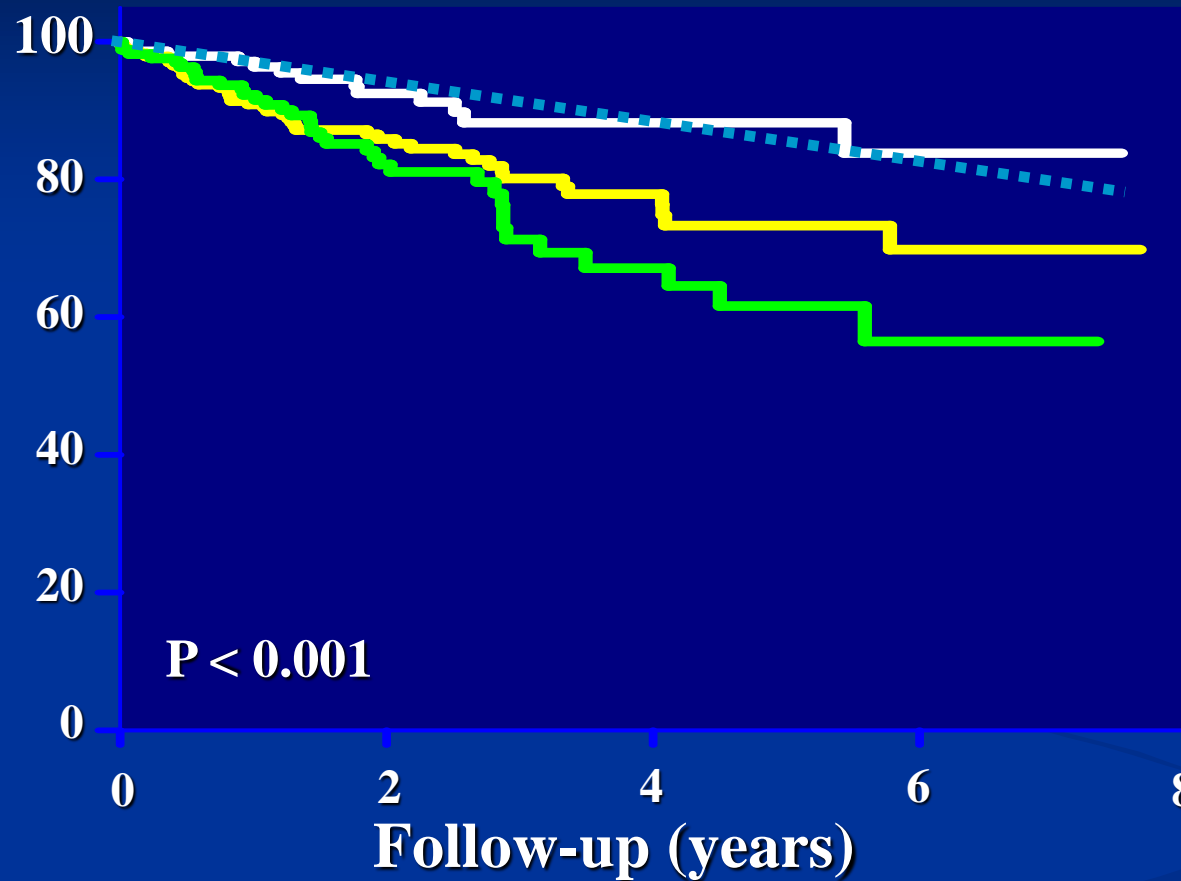


LVEDV: 115 ml
LVEF: 60%
SV = 70 ml
SVi = 39 ml/m²
AVA = 0.7 cm²
 $\Delta P_{\text{mean}} = 45 \text{ mmHg}$
 $Z_{\text{va}} = 4.2 \text{ mmHg/ml.m}^{-2}$

LVEDV: 85 ml
LVEF: 60%
SV = 50 ml
SVi = 28 ml/m²
AVA = 0.7 cm²
 $\Delta P_{\text{mean}} = 25 \text{ mmHg}$
 $Z_{\text{va}} = 5.2 \text{ mmHg/ml.m}^{-2}$

Impact of Valvulo-Arterial Impedance on Overall Survival

Survival
(%)



Adjusted Hazard Ratios:

$3.5 \leq Z_{va} < 4.5$: 1.7 (95% CI: 1.4-5.6); $p=0.01$

$Z_{va} \geq 4.5$: 2.0 (95% CI: 1.4-6.6); $p=0.006$

Hachicha Z et al.,
JACC, 2009;54;1003

Risk stratification in asymptomatic moderate to severe aortic stenosis: the importance of the valvular, arterial and ventricular interplay

Patrizio Lancellotti,¹ Erwan Donal,² Julien Magne,¹ Marie Moonen,¹ Kim O'Connor,¹ Jean-Claude Daubert,² Luc A Pierard¹

Heart 2010;**96**:1364–1371

