



«Paradoxical» low-flow, low-gradient AS with preserved LV function: *A Silent Killer*

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None except that...

Gilbert Habib is a very good friend!



None except that...

Gilbert Habib is a very good friend!

This is a very hot topic!







There's No Smoke without Fire





Burning Questions about Paradoxical Low-Flow, Low-Gradient AS:

Does it exist?

Does it have impact on survival?

Does AVR help?



Paradoxical Low-Flow, Low-Gradient AS: Does it exist?

Two Different Patterns of Low-Flow, Low-Gradient AS

NORMAL-LVEF NORMAL-FLOW HIGH-GRADIENT



NORMAL-LVEF «PARADOXICAL» LOW-FLOW LOW-GRADIENT

10-15%



5-10%

LOW-LVEF

Pibarot & Dumesnil JACC, 2012



- > 78 y.o. female with history of calcific AS
- > NYHA class III
- Mild hypertension
- > No evidence of obstructive CAD
- ➢ LVEF: 60%
- > AS severity on echo:
 - ► AVA: 0.7 cm²
 - ▷ BSA: 1.7 m², indexed AVA: 0.4 cm²/m²
 - > Peak/mean gradient: 51/29 mmHg

Case Study: Discrepancy between AVA and Gradient



LVEF: 60% Small LV cavity: LVEDD: 39 mm LVEDV: 79 ml



Dobutamine Stress Echocardiography

15 μg/kg/min



Heavy Aortic Valve Leaflet Calcification

Multislice CT

Coronary Artery Calcification

 Peak ΔP: 94 mmHg

 Mean ΔP: 57 mmHg

 AVA: 0.77 cm²

Valve Calcium score: 1900 AU

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



Patients with paradoxical low-flow AS have abnormal myocardial systolic function



Lancellotti et al. Eur J Echo 2010

Deterioration of Myocardial Function in Paradoxical Low-Flow Severe Aortic Stenosis: Two-Dimensional Strain Analysis

Seung-Pyo Lee, MD, Yong-Jin Kim, MD, PhD, Ji-Hyun Kim, MD, Kyungil Park, MD, Kyung-Hee Kim, MD, Hyung-Kwan Kim, MD, PhD, Goo-Yeong Cho, MD, PhD, Dae-Won Sohn, MD, PhD, Byung-Hee Oh, MD, PhD, and Young-Bae Park, MD, PhD, Seoul and Seongnam, Korea

Lee et al. J Am Soc Echocardiogr, 2011

Low-Flow, Low-Gradient Severe Aortic Stenosis Despite Normal Ejection Fraction Is Associated with Severe Left Ventricular Dysfunction as Assessed by Speckle-Tracking Echocardiography: A Multicenter Study

Jérôme Adda, Christopher Mielot, Roch Giorgi, Frédéric Cransac, Xavier Zirphile, Erwan Donal, Catherine Sportouch-Dukhan, Patricia Réant, Stéphane Lafitte, Stéphane Cade, Yvan Le Dolley, Franck Thuny, Nathalie Touboul, Cécile Lavoute, Jean-François Avierinos, Patrizio Lancellotti and Gilbert Habib

Circ Cardiovasc Imaging published online November 22, 2011;

Adda et al. Circulation CV Imaging, 2012



Pibarot & Dumesnil, Circulation 2013

Normal Flow AS

LVEDV: 115 ml

LVEF: 60% SV: 70 ml AVA: 0.7 cm² ΔP: 45 mmHg





Paradoxical Low-Flow AS

> LVEDV: 85 ml

LVEF: 60%

SV: 50 ml AVA: 0.7 cm² Δ**P: 25 mmHg**





Prevalence of Paradoxical Low-Flow, Low-Gradient AS



Paradoxical Low-Flow, Low-Gradient AVA<1.0 cm^{2;} MG<40 mmHg LVEF>50%; SVi<35 mL/m²

Invasive Hemodynamic Characteristics of Low-Flow, Low-Gradient Severe AS Despite Preserved LVEF



Occurrence of paradoxical low-flow, low-gradient AS was confirmed by invasive hemodynamics and was not the result of a systematic bias in the echo calculation of AVA

Lauten et al. JACC 2013

Circulation Cardiovascular Imaging



Learn and Live

JOURNAL OF THE AMERICAN HEART ASSOCIATION

Low-Flow, Low-Gradient Severe Aortic Stenosis Despite Normal Ejection Fraction Is Associated with Severe Left Ventricular Dysfunction as Assessed by Speckle-Tracking Echocardiography: A Multicenter Study

Jérôme Adda, Christopher Mielot, Roch Giorgi, Frédéric Cransac, Xavier Zirphile, Erwan Donal, Catherine Sportouch-Dukhan, Patricia Réant, Stéphane Lafitte, Stéphane Cade, Yvan Le Dolley, Franck Thuny, Nathalie Touboul, Cécile Lavoute, Jean-François Avierinos, Patrizio Lancellotti and Gilbert Habib

Circ Cardiovasc Imaging published online November 22, 2011; DOI: 10.1161/CIRCIMAGING.111.967554 Circulation: Cardiovascular Imaging is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514 Copyright © 2011 American Heart Association. All rights reserved. Print ISSN: 1941-9651. Online ISSN: 1942-0080

Conclusions—LFLG AS is observed in 9% of patients with severe AS and normal ejection fraction and is associated with high global afterload and reduced longitudinal systolic function. Patients with normal-flow low-gradient AS are more frequent and present with less severe AS, normal afterload, and less severe longitudinal dysfunction. Severe left ventricular longitudinal dysfunction is a new explanation to the concept of LFLG AS. (*Circ Cardiovasc Imaging*. 2012;5:27-35.)



Paradoxical Low-Flow, Low-Gradient AS: Does it have impact on survival?

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



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

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

150 Pts with asymptomatic severe (AVA<1.0 cm²) AS LVEF>50%



Lancellotti P, Magne J et al. J Am Coll Cardiol. 59:235–43, 2012

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



Eleid et al. Circulation 2013

Ozkan Circulation 2013

Outcome in Paradoxical Low-Flow, Low-Gradient Severe Aortic Stenosis and Preserved LVEF A Cardiac Catheterization Study



Mohty et al. Circulation 2013

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

Case Match Study: 3 × 187 patients



Clavel et al. JACC 2012

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



Conclusions:

Patients with paradoxical LFLG AS exhibit marked concentric remodelling, impaired LV longitudinal function and worse prognosis

Normal-flow, low-gradient AS patients have outcomes similar to moderate AS

Mehrota et al. Eur Heart J 2013



Outcome of Patients With Low-Gradient "Severe" Aortic Stenosis and Preserved LVEF A Substudy of the SEAS trial



Jander et al. Circulation. 2011;123:887-895.

No. at Risk

Potential Causes of Discordance between AVA (e.g. 0.8) and gradient (e.g. 30) in Pts. With Preserved LVEF

> Measurement errors



Small body size

> Inconsistency in guidelines criteria

> Paradoxical low-flow, low-gradient severe AS





Table 1. Baseline Characteristics

	Aortic Valve Stenosis		
	Low-Gradient "Severe" (AVA $<$ 1.0 cm ² ; MPG \leq 40 mm Hg) (n=435)	Moderate (AVA 1.5–1.0 cm ² ; MPG 25–40 mm Hg) (n=184)	Р
Age, y	69.8±9.2	66.8±9.2	< 0.01
Female gender, n (%)	240 (55.2)	50 (27.2)	< 0.01
Height, cm	167.2±8.8	173.2±8.7	< 0.01
Weight, kg	74.4±13.6	80.2±13.1	< 0.01
Body surface area, m ²	1.83±0.2	1.94 ± 0.2	< 0.01
Body mass index, kg/m ²	26.6±4.3	26.7±3.9	0.69

- > Paradoxical low flow severe AS
- > Measurement error
- Small body size
- Inconsistency in guidelines criteria

Jander et al. Circulation. 2011;123:887-895.

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able 2. Baseline Echocardiographic Parameters

	Aortic Valve Stenosis			
	Low-Gradient "Severe" (AVA $<$ 1.0 cm ² ; MPG \leq 40 mm Hg) (n=435)	Moderate (AVA 1.5–1.0 cm ² ; MPG 25–40 mm Hg) (n=184)	P	
Aortic valve				
Peak aortic jet velocity, m/s	3.3 ± 0.5	$3.6 {\pm} 0.3$	< 0.01	
Transaortic peak pressure gradient, mm Hg	44.8±11.9	53.0±7.4	< 0.01	
Transaortic mean pressure gradient, mm Hg	26.2±7.3	31.2±4.1	< 0.01	
Aortic valve area, cm	0.82±0.13 1.0	1.19±0.13 1.0	< 0.01	
Aortic valve area index, cm /m	0.46 ± 0.08	0.63 ± 0.09	<0.01	
Velocity time integral aortic valve, cm	78.0±13.0	82.0±10.0	< 0.01	
Dimensionless velocity index	0.26 ± 0.06	0.30 ± 0.06	< 0.01	
Stroke volume				
LV outflow tract diameter, mm	20.2±0.2	22.8±0.2	< 0.01	
Velocity time integral LV outflow tract, cm	20.1±4.1	24.2±4.9	< 0.01	
Stoke volume, mL	63.8±13.1 77	97.5±13.9 83	< 0.01	
Stoke 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	

	Aortic Valve Stenosis			
	Low-Gradient "Severe" (AVA $<$ 1.0 cm ² ; MPG $<$ 40 mm Hq)	Moderate (AVA 1.5–1.0 cm ² ; MPG 25–40 mm Hg)		
	(n=435)	(n=184)	Р	
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	

Criteria for Paradoxical low-flow AS ≻EDD<47 mm EDV< 55 mL/m² ≻RWT ratio > 0.50





Aortic Valve Area, Stroke Volume, Left Ventricular Hypertrophy, Remodeling and Fibrosis in Aortic Stenosis Assessed by Cardiac MRI: Comparison Between High and Low Gradient, and Normal and Low Flow Aortic Stenosis

Gilles Barone-Rochette, Sophie Piérard, Stéphanie Seldrum, Christophe de Meester de Ravenstein, Julie Melchior, Frédéric Maes, Anne-Catherine Pouleur, David Vancraeynest, Agnes Pasquet, Jean-Louis Vanoverschelde and Bernhard L. Gerber



Barone-Rochette, Circ CV Imaging 2013

Low-Gradient Aortic Valve Stenosis

Myocardial Fibrosis and Its Influence on Function and Outcome

Sebastian Herrmann, MD,*† Stefan Störk, MD, PHD,*† Markus Niemann, MD,*† Volkmar Lange, MD,§ Jörg M. Strotmann, MD,* Stefan Frantz, MD,*† Meinrad Beer, MD,†|| Stefan Gattenlöhner, MD,‡ Wolfram Voelker, MD,*† Georg Ertl, MD,*† Frank Weidemann, MD*† *Würzburg, Germany*

CME

Table 3 Baseline Left Heart Catheterization, Magnetic Resonance Imaging, Myocardial Histology, and Cardiac Biomarkers					
		Severe AS, High Gradient $(n = 49)$	Severe AS, Low Gradient, EF \geq 50% (n = 11)	Severe AS, Low Gradient, EF $<50\%$ (n = 9)	
Left heart catheterization	1				
Aortic valve area, cm ²		0.7 ± 0.1	0.7 ± 0.2	0.8 ± 0.1	
Indexed aortic valve ar	ea, cm²·m ⁻²	0.39 ± 0.12	$\textbf{0.41} \pm \textbf{0.14}$	$\textbf{0.46} \pm \textbf{0.11}$	
Pulmonary capillary we	edge pressure, mm Hg	14 ± 7	15 ± 7	18 ± 7	
Stroke volume, ml		72 ± 12	56 ± 13	63 ± 13	
Stroke volume index, r	nl∙m ^{−2}	40 ± 5	31 ± 4	34 ± 3	
Mean aortic pressure g	(radient, mm Hg	53 ± 8	37 ± 8*	$27\pm8^{\star}$ †	
Transvalvular flow rate	, ml/s	241 ± 40	179 ± 30*	$184 \pm \mathbf{20*}$	
Central venous oxygen	saturation, %	69 ± 4	63 ± 4*	$59 \pm 4 \star \dagger$	
cMRI					
Ejection fraction, %		55 ± 13	56 ± 12	38 ± 17*†	
Late enhancement-po	sitive segments: 0/1/>1, %	47/19/34	0/20/80	0/23/77	
Myocardial histology					
Interstitial fibrosis, %		1.8 ± 0.8	3.9 ± 0.6*	$4.8 \pm 0.6 \star$	
Myocyte diameter, μ m		12.2 ± 1.3	13.1 ± 1.5	$13.7 \pm 1.3 \star$	
Cardiac biomarkers					
NT-proBNP, pg/ml		1,418 (377-1,505)	3,730 (1,858-5,671)*	5,016 (4,182-5,704)*	
PIIINP, μ g/ml		3.4 ± 0.8	$\textbf{4.6} \pm \textbf{0.4}$	$5.0 \pm 1.3*$	

EUROECHO 20 & other Imaging Modalities

Abstract: P252

Budapest

7-10 December

Low-flow Low-gradient aortic stenosis: prognosis and effect of surgery.

Authors:

J Adda¹, C Mielot², F Cransac¹, X Zirphile³, P Reant³, C Sportouch-Dukhan¹, S Lafitte³, E Donal⁴, P Lancellotti⁵, G Habib², ¹University Hospital of Montpellier - Montpellier - France, ²la Timone Hospital - Marseille - France, ³University Hospital of Bordeaux - Bordeaux -France, ⁴University of Rennes - Rennes - France, ⁵university of Liège - Liège - Belgium,

Topic(s):

Aortic stenosis

Citation:

Eur J Echocardiography Abstracts Supplement (2011) 12 (S2), ii13

Background: Low-flow low-gradient aortic stenosis with preservedejection fraction is a recently described entity, but its prognosis and influence of surgery are uncertain.

Methods: In amulticentre study, 362 patients with severeaortic stenosis (aortic valve area $\leq 0.6 \text{ cm}^2/\text{m}^2$), and preserved LV function (LVEF $\geq 50\%$) were prospectively included. Four groups were defineddepending on flow and gradient: low flow was defined as a stroke volume index(SVi) $\leq 35 \text{ ml/m}^2$, and low gradient as a mean gradient (MG) $\leq 40 \text{ mmHg}$. Results: Group 1 (normal flow high gradient) represented themajority of our patients (231 patients, 63.5%). 3-year survival was 87%.Referral rate for surgery was 75%. There was a significant improvement of survival among the surgery group (88% vs75% in the medical group, p=0.035). Group 2 (low flow high gradient) included 46 patients(12.6%). 3-year survival was 95% (p=ns vsgroup 1). Referral rate for surgery was 76%. There was a significant improvement of survival among the surgery group (100% vs 76% in the medical group, p=0.01). Group 3 (high flow low gradient) included 57 patients(15.7%). 3-year survival was 85% (p=ns vsgroup 1). Referral rate for surgery was 55%. There was a significant improvement of survival among the surgery group (100% vs 76% in the medical group, p=0.01). Group 3 (high flow low gradient) included 57 patients(15.7%). 3-year survival was 85% (p=ns vsgroup 1). Referral rate for surgery was 55%. There was a significant improvement of survival among the surgery group (90.6% vs 74.7% in the

Conclusion: Paradoxical low-flow, low-gradient AS is a associated with severe prognosis

EUROECHO 20 & other Imaging Modalities

Abstract: P252

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J Adda¹, C Mielot², F Cransac¹, X Zirphile³, P Reant³, C Sportouch-Dukhan¹, S Lafitte³, E Donal⁴, P Lancellotti⁵, G Habib², ¹University Hospital of Montpellier - Montpellier - France, ²la Timone Hospital - Marseille - France, ³University Hospital of Bordeaux - Bordeaux -France, ⁴University of Rennes - Rennes - France, ⁵university of Liège - Liège - Belgium,

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Conclusion: Paradoxical low-flow, low-gradient AS is associated with severe prognosis. Its prognosis does not seem to be improved by surgery.



Paradoxical Low-Flow, Low-Gradient AS: Does AVR help?

Outcome of Patients with Paradoxical Low-Flow AS



Impact of AVR on Survival in Patients with Paradoxical Low-Flow, Low-Gradient AS



Clavel et al. JACC 2012

Impact of AVR on Survival According to LVEF in Patients with Low Gradient



Impact of AVR on Survival in Patients with Low-Gradient Severe AS and Preserved LVEF

102 patients, AVA<1.0 cm^2 $\Delta P_{Mean} < 40 mmHg$ LVEF $\geq 50\%$

Whole Cohorts



Propensity Score-Matched Cohorts



Tarantini et al. Ann Thorac Surg, 91:1808-15, 2011

Impact of AVR on Outcome of Symptomatic Patients with Severe Stenosis, Low Gradient, and Preserved LVEF

260 symptomatic Pts Severe AS (AVAi<0.6 cm²/m²) Low gradient (<40 mmHg) Preserved LVEF (>50%)



Ozkan et al. Circulation 2013

Impact of AVR on Outcome of Symptomatic Patients with Severe Stenosis, Low Gradient, and Preserved LVEF

Table 5. Multivariable Predictors of All-Cause Mortality					
Variable	RR	Lower 95%	Upper 95%	<i>P</i> Value	
Flow-gradient patterns					
NF/LG no AVR	1.00	Referen	ce group		
NF/LG+AVR	0.86	0.518	1.414	0.54	
LF/LG no AVR	3.26	1.713	6.217	0.0003	
LF/LG+AVR	0.94	0.384	2.297	0.89	
NF/HG no AVR	2.81	1.905	4.140	<0.0001	
NF/HG+AVR	0.69	0.450	1.048	0.08	
LF/HG no AVR	1.55	0.615	3.904	0.35	
LF/HG+AVR	0.89	0.396	1.994	0.77	
Clinical					
Age	1.02	1.012	1.034	<0.0001	
Male sex	1.46	1.169	1.821	0.0008	
Obesity	1.51	1.214	1.885	0.0002	
Hypertension	1.42	1.076	1.868	0.01	
Previous HF	1.29	0.984	1.684	0.07	
Echocardiographic					
Aortic valve area	0.07	0.026	0.163	<0.0001	
Ejection fraction	0.98	0.968	1.000	0.05	

AVR indicates aortic valve replacement; HF, heart failure; HG, high gradient; LF, low flow; LG, low gradient; HG, high gradient; NF, normal flow; and RR, relative risk.

1704 Patients

Eleid et al. Circulation 2013

PARTNER-I (Cohorts A+B) Paradoxical LF, NEF, and LG (12% of cohort)





Herrmann et al. Circulation 2013

2012 ESC/EACTS Guidelines on Management of VHD: Indications for AVR in AS

		Class ^a	Level ^b		
"The new	AVR is indicated in patients with severe AS and any symptoms related to A ^r . WR is indicated in patients with severe AS undergoing CABG, surgery of the aslending aorta or another valve.	llo	w- ¦fl	ow, lov	W -
gradient A	A/R is indicated in usemptionatic protects with callare/ Sland systolic 17 dysfunction (1755-550%) not due to another cause.	l at	tent	ion be	ecause
of the limi	AVR is a dicated in asymptomatic patients with fevere KS and abnormal exercise test showing symptoms on exercise ck and, r late t o \$1.1001111110110110110101010101010101010	l his	stor	y and	
outcome a	AVR should be considered in high risk patients with severe symptomatic AS who are suitable for TAVI, but in whom all get γ is taken to all the form the individual risk profile and anatomic suitability.	lla	В		
	AVR should be considered in asymptomatic patients with severe AS and abnormal exercise test showing fall in blood pressure below baseline.	lla	с		
	AVR should be considered in patients with moderate AS ^d undergoing CABG, surgery of the ascending aorta or another valve.	lla	с		
AVR should be considered	I in symptomatic patients with low flow, low gradient (<40 mmHg) AS with n of severe AS°	ormal El	⁻ only	lla	С
alter careful confirmation	AVR should be considered in symptomatic patients with severe AS, low flow, low gradient with reduced EF, and evidence of flow reserve. ^f	lla	с		
	 AVR should be considered in asymptomatic patients, with normal EF and none of the above mentioned exercise test abnormalities, if the surgical risk is low, and one or more of the following findings is present: Very severe AS defined by a peak transvalvular velocity >5.5 m/s or, Severe valve calcification and a rate of peak transvalvular velocity progression ≥0.3 m/s per year. 	lla	с		
	AVR may be considered in symptomatic patients with severe AS low flow, low gradient, and LV dysfunction without flow reserve. ^f	IIb	с		
Vahanian et al.	 AVR may be considered in asymptomatic patients with severe AS, normal EF and none of the above mentioned exercise test abnormalities, if surgical risk is low, and one or more of the following findings is present: Markedly elevated natriuretic peptide levels confirmed by repeated measurements and without other explanations Increase of mean pressure gradient with exercise by >20 mmHg Excessive LV hypertrophy in the absence of hypertension. 	lib	с		

Va





Answers to Burning Questions: Paradoxical low-flow, low-gradient AS

- Does it exist: YES! this a real entity that occurs in 10-15% of AS patients
- > Does it have impact on survival: YES!
- Does AVR help: YES! AVR improves outcome in patients with <u>true</u> paradoxical low-flow, lowgradient <u>severe</u> AS
- > TAVR may provide a valuable alternative to SAVR

Key Messages: Paradoxical Low-Flow AS

> When confronted to AVA-gradient discordance:

- **1- Rule out measurement errors**
- 2- Rule out small body size
- **3- Document the presence of low-flow: SVi<35 ml/m²**
- 4- Identify typical echo features of paradoxical LFLG:

Small LV with concentric remodeling, impaired filling, reduced longitudinal function

5- Identify other causes of low flow:

AFib, MR, TR, MS, bradychardia

6- Rule out pseudo-severe AS:

MSCT and stress echo



