SUPPLEMENTARY MATERIAL

Supplementary Table 1: Reported comparisons of physiological measures in AS (presented in chronological order)

	CORONARY INDICES				SYSTEMIC/VALVE HEMODYNAMIC INDICES		MYOCARDIAL INDICES		ISCHEMIC/OTHER INDICES
Fallen EL et al 1967[1]									
Left heart and coronary sinus catheterization with baseline and hyperemic measurements using Isoproterenol in 18 patients with severe AS (7 patients without angina, 5 patients with angina but without CAD, and 6 patients with angina and CAD)									
	Hyperemic CBF						**Hyperemic myocardial oxygen extraction**		**Lactate production during hyperemia**
No angina	+						-		o
Angina without CAD	o						o		+
Angina with CAD	+						-		+
Marcus ML et al 1982[2]									
Coronary reactive hyperemia response following 20 second LAD occlusion in 14 symptomatic severe AS patients during SAVR									
	Peak-resting velocity ratio		**Repayment- debt area ratio**						
Controls	o		o						
Severe AS	-		-						
Omran H et al 1996[3]									
TEE Doppler of the LAD in 46 patients (34 symptomatic, 12 asymptomatic) with moderate-severe AS									
	Peak coronary systolic velocity	**Peak coronary diastolic velocity**	**Systolic VTI**	**Diastolic acceleration time**	**AVA**	**Pressure gradient**	**LVMI**	**LV wall stress**	
Controls	o	o	o	o			o		
All AS	-	-	-	+			+		
Symptomatic vs asymptomatic AS	Lower	Higher	Smaller	Longer	Smaller	Higher	Higher	Higher	
Julius BK et al 1997[4]									
Invasive rest and dipyridamole stress data from patients with severe AS and angina (n=18), without angina (n=11) and control patients (n=7)									

	CFR	Coronary resistance per 100g LVMM	LV peak systolic pressure	Mid-wall stress	Resting CS blood flow	Max CS blood flow	ST depression on exercise electrocardiogram
Controls	o	o	o	Low	o	o	
AS - angina	-	o	+	Moderate	+	-	
AS + angina	--	o	++	High	+	--	More pronounced

Hildick-Smith et al 2000[5]

Echocardiographic rest and hyperemic LAD Doppler data from 24 patients with severe AS pre- and 6-months post-SAVR

	CFR	Hyperemic peak systolic velocity	Hyperemic peak diastolic velocity	LVMI
Pre-SAVR	-	-	-	+
Post-SAVR	o	o	o	o

Rajappan et al 2002[6]

CMR, ECHO and PET data from 20 patients with moderate-severe AS (asymptomatic and symptomatic)

	CFR	AVA	hDPT	hTransmural MBF
Controls	o			o
Mod-severe AS	-	Increase linearly related to hMBF	Significant correlation with hMBF and CFR	-

Davies et al 2006[7]

Invasive coronary physiology at the time of angiography in 20 patients without aortic stenosis (10 controls, 10 with LVH)

	Mean CBFV	BEW	BEW/FCW
Controls	o	o	o
LVH	o	-	-

Galiuto et al 2006[8]

Contrast and Doppler echocardiographic in 11 patients with severe symptomatic AS awaiting SAVR, LV biopsy during SAVR

	Baseline CBFV	CBFVI	CFR	LVMI	SI*β	Apoptosis
Controls	o	o	o	o	o	o
Severe AS + LVH	+	-	-	+	-	+

Davies et al 2011[9]

Invasive coronary physiology at baseline and during rapid pacing before and after TAVI in 11 patients with severe symptomatic AS

	BEW	Flow velocity	Pressure time integral
Pre-TAVI baseline	+	o	o
Pre-TAVI 120bpm	o	o	-
Post-TAVI baseline	o	o	o
Post-TAVI 120bpm	+	o	-

Steadman et al 2012[10]

Cardiopulmonary exercise testing, CMR and echocardiography in 46 patients with severe AS awaiting SAVR (9 asymptomatic, 37 symptomatic)

	Peak AVG	MPR	LVMI	Septal E/e'	Resting MBF	LGE
Association with perfusion reserve (p value)	0.02		<0.001	0.03		0.002
Association with peak VO_2 (p value)	0.24	0.004	0.89	0.02	0.001	0.73

Mahmod M et al 2014[11]

CMR in 28 patients with severe AS (3 asymptomatic, 25 symptomatic) - 14 of the 25 symptomatic patients were rescanned 8 months after SAVR

	MPRI	Circumferential strain	Blood O2 level dependent signal intensity change	PCr/ATP
Controls	o	o	o	o
Severe AS	-	-	-	-
Post-SAVR	o	o	o	o

Ben-Dor I et al 2014[12]

Doppler LAD flow using TEE during TAVI in 90 patients with severe AS

	Peak systolic coronary velocity	Peak diastolic coronary velocity	Systolic VTI	Diastolic VTI
Pre-TAVI	o	o	o	o
Post-TAVI	+	+	+	+

Wiegerinck et al 2015[13]

Invasive coronary physiology immediately pre- and post-TAVI in 27 patients with severe AS)

	bCFV	hCFV	CFR	bMR	hMR	hAPV

Controls	o	o	o	o	o	o						
Pre-TAVI	+	-	-	-	o	-						
Post-TAVI	+	o	o	-	-	o						
Gutierrez-Barrios A et al 2015[14].												
Invasive coronary physiology in 35 patients with severe AS (unknown symptoms)												
	IMR						**AVA**		**LVMI**			**BNP**
Correlation with CFR (1.39+/-0.57)	r=-04, p0.03						CFR < 2 0.63+/-0.05 p0.04		r=0.38, p0.08			r=-0.38, p0.02
Ahn JH et al 2016 [15]												
CMR in 84 patients with severe AS (43 with angina, 41 without angina)												
									MPRI	**LVMI**	**CI**	**LGE**
Controls									o	o	o	o
AS - angina									-	+	+	+
AS + angina									--	++	++	+
Rolandi et al 2016[16]												
Invasive coronary physiology immediately pre- and post-TAVI in 15 patients with severe AS												
	CFR	**bBEW**	**hBEW**	**Coronary pulse pressure (bPPd and hPPd)**	**Systolic VTI rest and hyperemia**							
Controls	o	o	o	o	o							
Pre-TAVI	-	+	-	o	+							
Post-TAVI	-	++	o	+	++							
Singh et al[17]												
Exercise test, echocardiography and CMR in 174 asymptomatic patients with moderate-severe AS												
							AVA	**AVG**	**Global MPR**	**Stroke volume**	**LVMI**	**Fibrosis**	**NT-proBNP**
No event							o	o	o	o	o	o	o
Event							-	+	-	-	Predicted outcome	o	+
Lumley et al 2016[18]												

Rest and exercise coronary physiology in 22 patients with severe symptomatic AS and 38 healthy controls with stress echocardiography in 13 AS patients								
	Hyperemic CBF	**Fall in MR with hyperemia**	**Exercise CFR**	**Hyperemic CFR**		**Myocardial workload at rest**	**Myocardial workload during exercise**	
Controls	o	-	o	o		o	o	
AS patients	-	--	o	-		+	+	
Gutiérrez-Barrios et al 2017[19]								
Rest and hyperemic coronary physiology in 36 patients with severe AS and 10 healthy controls								
	CFR	**Tmn_{rest}**	**Tmn_{hyp}**	**IMR**	**Br**			
Controls	o	o	o	o	o			
AS patients	-	Faster	Slower	+	-			

Online Table 1: Comparison of outcomes from relevant studies.

Abbreviations: AS: aortic stenosis, AVA: aortic valve area, AVG: aortic valve gradient, BEW: backward expansion wave, bMR: baseline microvascular resistance, BNP: b-type natriuretic peptide, bPPD: baseline coronary pulse pressure in diastole, Br: baseline resistance, CBF: coronary blood flow, CBFV: coronary blood flow velocity, CBFVI: coronary blood flow velocity indexed for LV mass, CFR: coronary flow reserve, CI: cardiac index, CMR: cardiac magnetic resonance, CS: coronary sinus, ECHO: echocardiography, FCW: forward compression wave, hAPV: hyperemic average peak flow velocity, hDPT: hyperemic diastolic perfusion time, hMR: hyperemic microvascular resistance, hPPd: hyperemic pulse pressure in diastole, hTransmural MBF: hyperemic transmural myocardial blood flow, IMR: index of microvascular resistance, LAD: left anterior descending artery, LGE: late-gadolinium enhancement, LVMI: indexed left ventricular mass, LVMM: left ventricular muscle mass, MPR: myocardial perfusion reserve, MPRI: indexed myocardial perfusion reserve, PCr/ATP: phosphocreatine/adenosine triphosphate, PET: positron emission tomography, PW: pulse wave spectral Doppler, SAVR: surgical aortic valve replacement, SI*β: peak signal intensity (SI)

multiplied by the rate of signal rise, TEE: transesophageal echocardiography, Tmn_{hyp}: transit mean times during hyperemia, Tmn_{rest}: transit mean times at rest, Zva: valvulo-arterial impedance.

Physiological assessment of coronary stenoses in the setting of AS

Symptomatology overlaps in patients with AS and epicardial coronary disease, and distinction may be clinically impossible. Physiological assessment of epicardial coronary stenoses in this setting is challenging due to compounding factors that contribute to myocardial ischemia, such as LVH and excess afterload. Functional evaluation of isolated coronary artery disease is well validated[20,21] and strongly linked with clinical outcomes but a clear understanding of the pitfalls amidst AS is important for clinicians.

The results of coronary physiological assessment should be interpreted with caution in AS since it is not a true resting state. Distorted values may be caused by several factors:

1. Elevation of coronary sinus outflow and distal coronary pressure[22] which may underestimate the significance of a coronary stenosis
2. Secondary LVH which causes reduced capillary density and abnormal vasoreactivity[23]
3. Elevated right atrial pressure[24]

LVH causes fixed elevation of coronary resistance which may also be increased by neurohumoral factors that influence the response to adenosine[25] - these include α-adrenoceptor agonists, angiotensin and vasopressin[26], the levels of which may be modulated by medication - adenosine infusion is safe and well-tolerated in patients with AS[18,27,28]. LVH is also associated with a lower ischemic threshold as a result of capillary rarefaction[29] and transmural steal (with disproportionately high subepicardial blood flow). A higher cut-off value level of FFR to indicate myocardial ischemia is therefore appropriate in patients with AS[30,31].

Although data are scarce, two recent publications on the role of fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) in the setting of AS and epicardial coronary disease provide important insights. One study found that diagnostic accuracy of iFR was significantly lower in patients with AS when the standard iFR threshold of 0.89 (to correlate with FFR 0.8) was used[28]. The authors found that the best iFR threshold to predict an FFR ≤0.8 in the setting of AS was 0.83 (although iFR values were widely scattered). Another study found that iFR was not subject to change after TAVI ($p=0.94$) unlike FFR which fell significantly after intervention ($p=0.0008$)[32]. Positive FFR values worsen after TAVI whilst negative FFR values tend to improve[33].

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