Università Vita-Salute San Raffaele

Coronary flow in Aortic Stenosis: Pathophysiological and Clinical Insights

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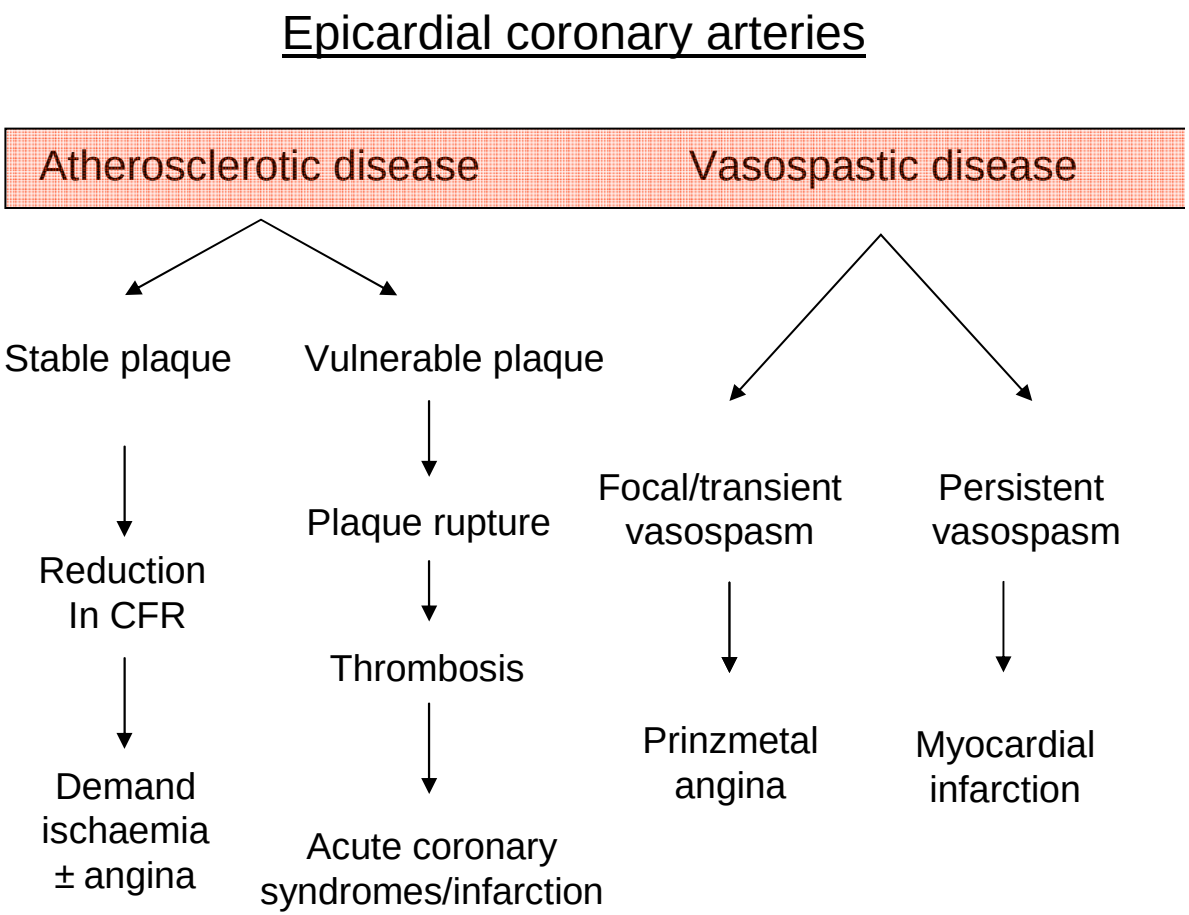
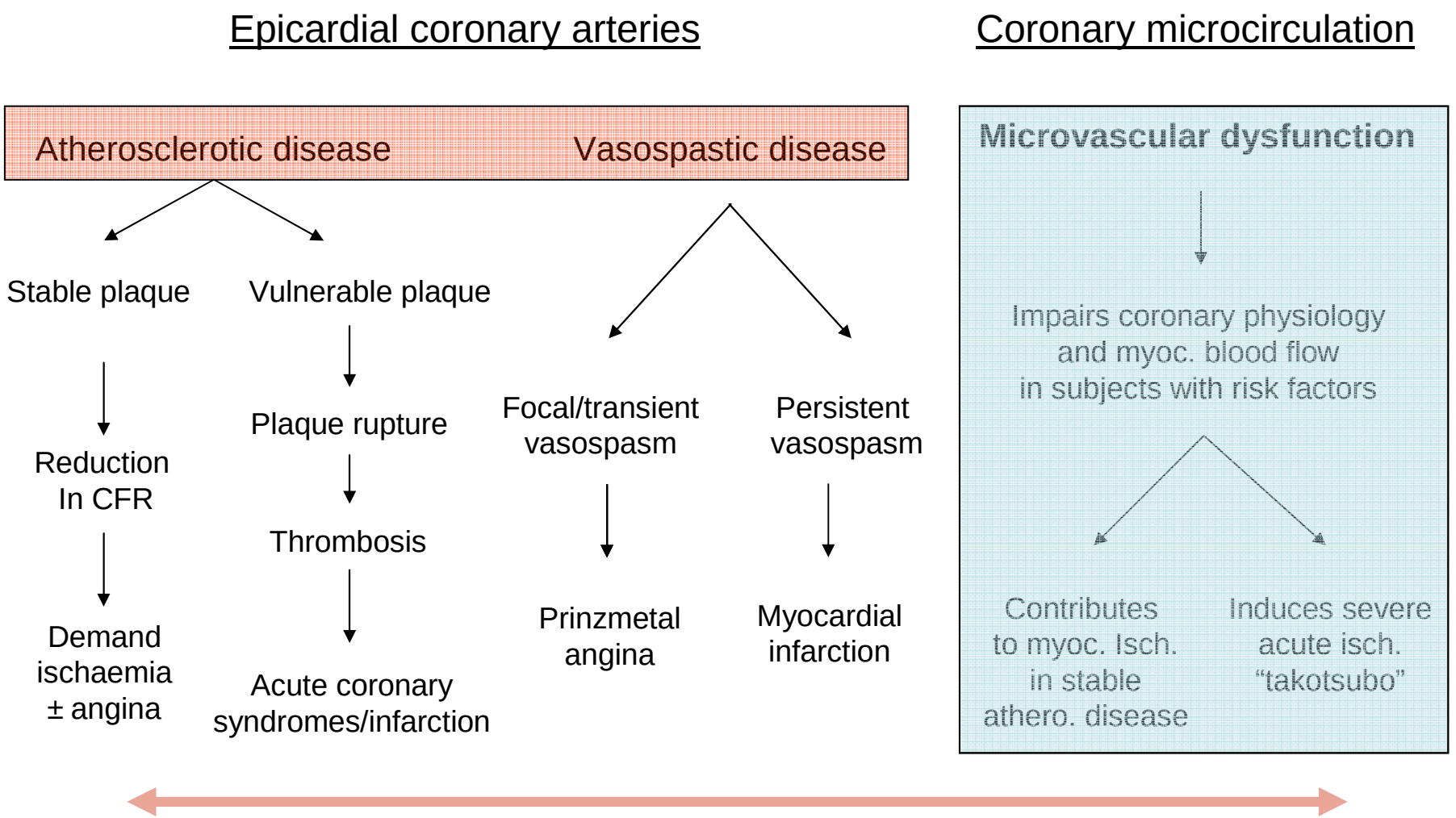
JOINT E.A.E./S.I.E.C. TEACHING COURSE
UPDATE IN VALVULAR HEART DISEASES:
FROM CLINICAL IMAGING
TO THERAPEUTIC INNOVATIONS

Mechanisms of myocardial ischaemia



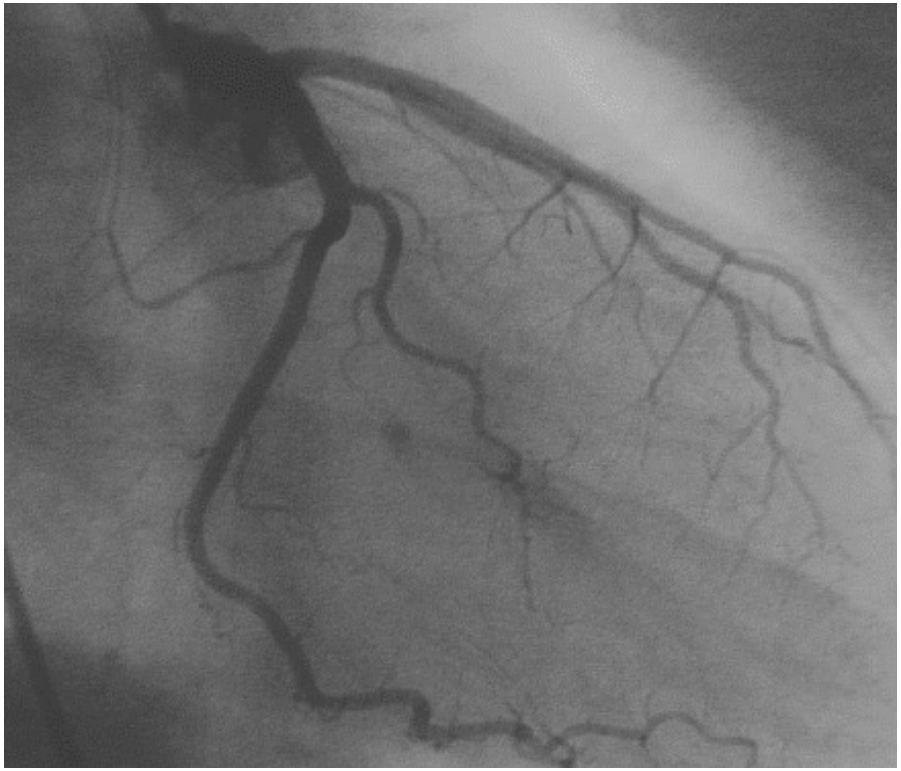
Mechanisms of myocardial ischaemia



These three mechanisms can overlap

The emerging concept of coronary “microvascular disease”

The tip of the iceberg - Resolution >500μm

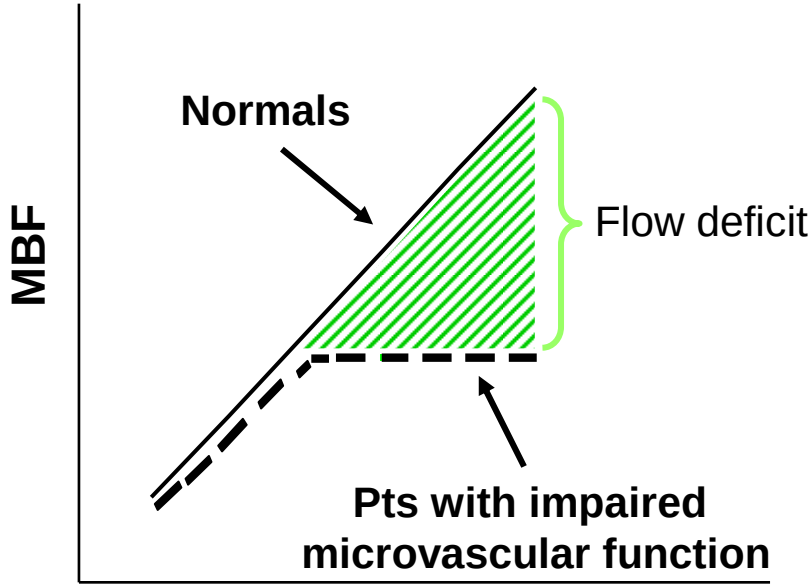


Resolution <500μm

Courtesy of M Gibson MD

Maximum myocardial blood flow is an index of microvascular function

In normal subjects myocardial blood flow (MBF) increases 3-5 fold during near-maximal pharmacologic vasodilatation (i.v. adenosine)

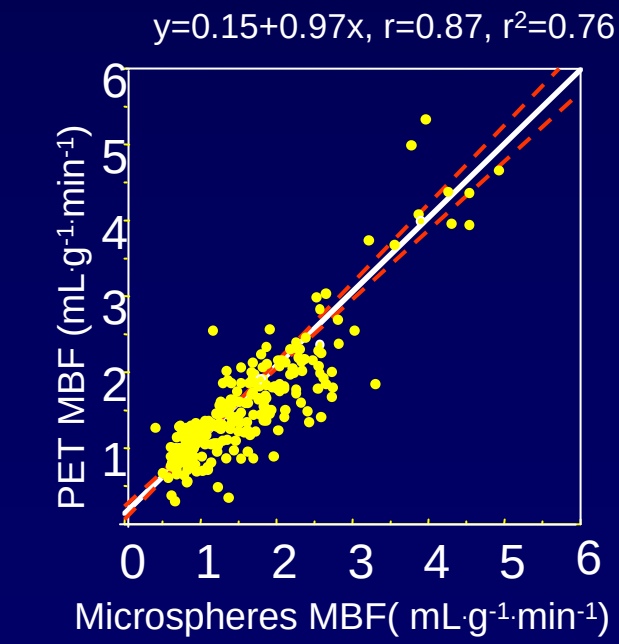


In the absence of coronary stenosis, maximum MBF reflects microvascular function

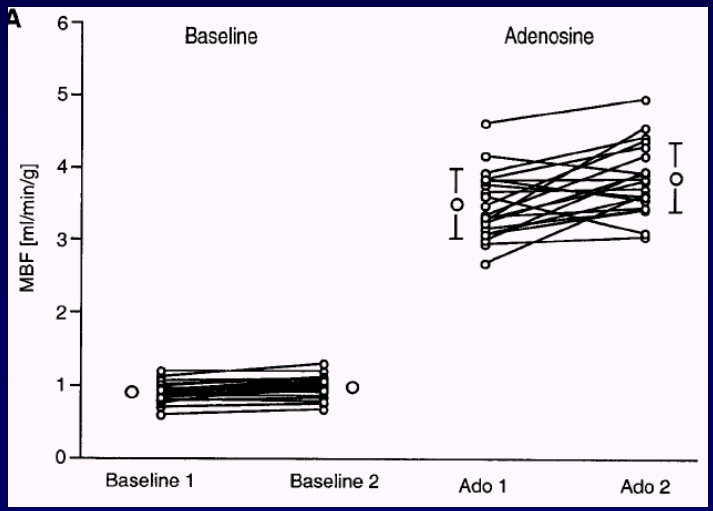
PET: the gold standard for the noninvasive measurement of myocardial blood flow

PET with $H_2{}^{15}O$ or $^{13}NH_3$ allows accurate, reproducible and non-invasive measurement of absolute (ml/min/g) myocardial blood flow in man

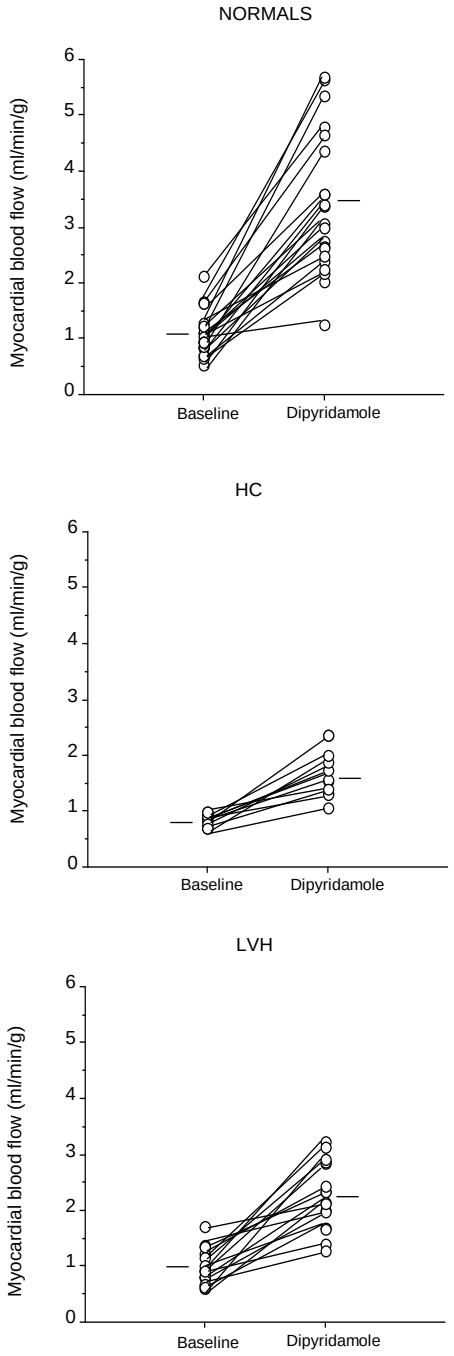
Accuracy of PET MBF measurement



Reproducibility of PET MBF measurement



Camici PG and Rimoldi OE. J Nucl Med. 2009; 50:1076–1087



Ischemia in patients with LVH

- Angina and/or ischemic signs on ECG are common in patients with primary or secondary LVH
- In the majority of cases patients with LVH suffer from angina despite angiographically normal coronary arteries
- Coronary flow reserve is reduced suggesting dysfunction of the microcirculation

Camici et al. Eur Heart J 1997; 18: 108-116

Table 1. Clinical Classification of Coronary Microvascular Dysfunction.

Coronary microvascular dysfunction in the absence of obstructive CAD and myocardial diseases	This type represents the functional counterpart of traditional coronary risk factors (smoking, hypertension, hyperlipidemia, and diabetes and insulin-resistant states). It can be identified by noninvasive assessment of coronary flow reserve. This type is at least partly reversible, and coronary flow reserve can also be used as a surrogate end point to assess efficacy of treatments aimed at reducing the burden of risk factors.
Coronary microvascular dysfunction in the presence of myocardial diseases	This type is sustained in most instances by adverse remodeling of intramural coronary arterioles. It can be identified by invasive or noninvasive assessment of coronary flow reserve and may be severe enough to cause myocardial ischemia. It has independent prognostic value. It remains unclear whether medical treatment may reverse some cases. It is found with primary (genetic) cardiomyopathies (e.g., dilated and hypertrophic) and secondary cardiomyopathies (e.g., hypertensive and valvular).
Coronary microvascular dysfunction in the presence of obstructive CAD	This type may occur in the context of either stable CAD or acute coronary syndromes with or without ST-segment elevation and can be sustained by numerous factors. It is more difficult to identify than the first two types and may be identified through the use of an integrated approach that takes into account the clinical context with the use of a combination of invasive and noninvasive techniques. There is some early evidence that specific interventions might prevent it or limit the resultant ischemia.
Iatrogenic coronary microvascular dysfunction	This type occurs after coronary recanalization and seems to be caused primarily by vasoconstriction or distal embolization. It can be identified with the use of either invasive or noninvasive means on the basis of a reduced coronary flow reserve, which seems to revert spontaneously in the weeks after revascularization. Pharmacologic treatment has been shown to promptly restore coronary flow reserve, and it may also change the clinical outcome. The likelihood of distal embolization can be reduced by the use of appropriate devices during high-risk procedures.

N Engl J Med. 2007;356:830-40

Table 2. Pathogenetic Mechanisms of Coronary Microvascular Dysfunction.

Alterations	Causes
Structural	
Luminal obstruction	Microembolization in acute coronary syndromes or after recanalization
Vascular-wall infiltration	Infiltrative heart disease (e.g., Anderson–Fabry cardiomyopathy)
Vascular remodeling	Hypertrophic cardiomyopathy, arterial hypertension
Vascular rarefaction	Aortic stenosis, arterial hypertension
Perivascular fibrosis	Aortic stenosis, arterial hypertension
Functional	
Endothelial dysfunction	Smoking, hyperlipidemia, diabetes
Dysfunction of smooth-muscle cell	Hypertrophic cardiomyopathy, arterial hypertension
Autonomic dysfunction	Coronary recanalization
Extravascular	
Extramural compression	Aortic stenosis, hypertrophic cardiomyopathy, arterial hypertension
Reduction in diastolic perfusion time	Aortic stenosis

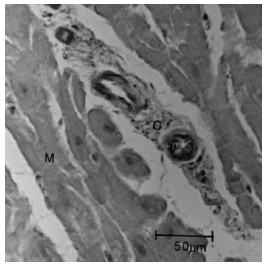
N Engl J Med 2007;356:830-40.

Mechanisms of CMD in LVH

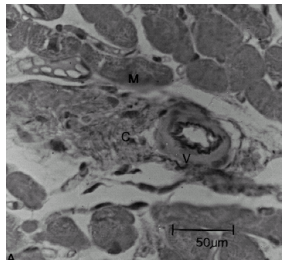
CFR is reduced in patients with hypertrophic cardiomyopathy (HCM) and those with LVH secondary to systemic hypertension.

In these 2 patient groups, the reduction of CFR is primarily sustained by an increase in the vascular component of resistance because of anatomic changes in the intramural coronary arteries.

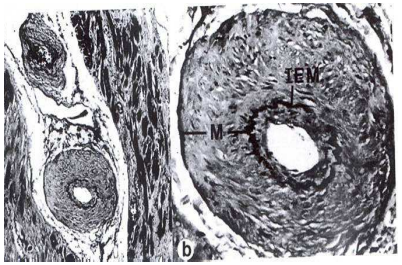
Normal subject



Hypertensive

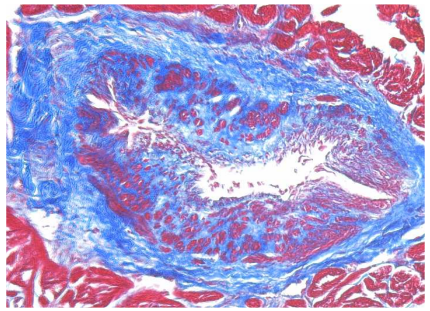


HCM

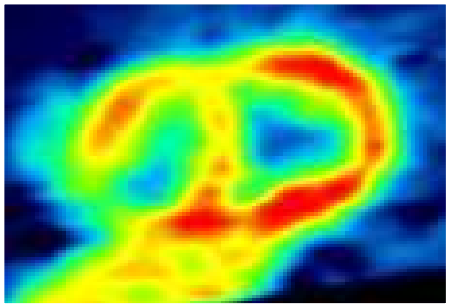


- Myocites hypertrophy
- Perimyocitic fibrosis
- Thickening of the wall of intramyocardial arterioles: increased wall/lumen ratio

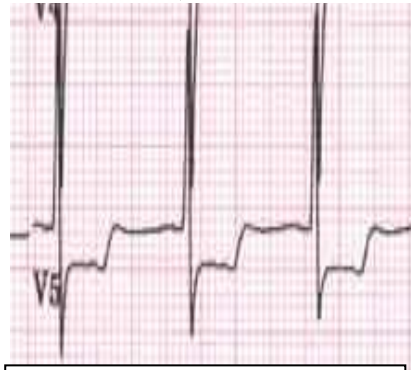
Camici & Crea N Engl J Med. 2007;356:830-40



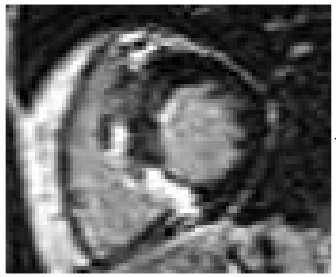
Microvascular Remodeling



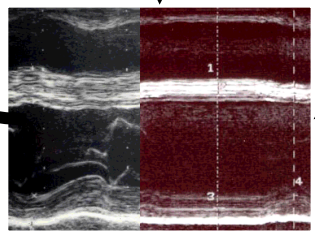
Microvascular Dysfunction



Myocardial Ischemia



Myocardial Fibrosis



LV Remodeling
Diastolic and Systolic Dysfunction

Atrial Fibrillation
Heart Failure Symptoms
Heart Failure Death

Camici et al. J Am Coll Cardiol 2009

ORIGINAL ARTICLE ARCHIVE

Decreased Coronary Reserve — A Mechanism for Angina Pectoris in Patients with Aortic Stenosis and Normal Coronary Arteries

Melvin L. Marcus, M.D., Donald B. Doty, M.D., Loren F. Hiratzka, M.D., Creighton B. Wright, M.D., and Charles L. Eastham

N Engl J Med 1982; 307:1362-1366 | November 25, 1982

The pathogenesis of angina pectoris in patients with aortic stenosis and normal coronary arteries remains uncertain.

We measured the maximal velocity of coronary blood flow in the left-anterior descending coronary artery at the time of elective open-heart surgery in 14 patients with aortic stenosis and LVH (13 had angina) and in 8 controls without LVH.

The ratio of peak velocity of coronary blood flow, after a 20-second occlusion, to resting velocity was decreased by more than 50 per cent ($P<0.05$) in the patients with aortic stenosis.

These data demostrate a selective and marked decrease in coronary reserve to the hypertrophied left ventricle in patients with severe aortic stenosis. The impairment in coronary reserve is probably an important contributor to the pathogenesis of angina pectoris in these patients.

Mechanisms of Coronary Microcirculatory Dysfunction in Patients With Aortic Stenosis and Angiographically Normal Coronary Arteries

Kim Rajappan, MA, MRCP*; Ornella E. Rimoldi, MD*; David P. Dutka, MD, MRCP;
Ben Ariff, MRCP; Dudley J. Pennell, MD, FESC, FRCP;
Desmond J. Sheridan, MD, PhD, FRCP; Paolo G. Camici, MD, FESC, FRCP

Demographic, Echocardiographic, and CMR Data

Patient Number	Age (y)/Sex	Symptoms	SWT, mm	LVID, mm	PWT, mm	Peak AVG, mm Hg	AVA, cm^2	LVMI (Echo), g/m^2	LVMI (CMR), g/m^2
1	74/F	CCS 1/NYHA I	18	45	18	101	0.76	242*	127*
2	69/F	NYHA II	13	43	14	106	0.72	140*	136*
3	41/M	CCS 1/NYHA I	12	43	13	64	1.06	128	112
4	80/M	CCS 1/NYHA I	14	46	13	85	0.96	162*	174*
5	54/M	CCS 1	16	45	15	100	0.43	171*	141*
6	60/M	Asymptomatic	15	48	14	67	1.29	200*	160*
7	67/M	Asymptomatic	13	47	14	110	0.65	168*	134*
8	57/M	CCS 1	15	40	16	52	1.09	174*	117*
9	58/F	CCS 1/NYHA I	16	36	16	90	0.69	178*	179*
10	77/M	Asymptomatic	18	53	15	85	0.77	250*	159*
11	79/M	CCS 1/NYHA II	16	42	17	112	0.41	191*	204*
12	63/M	Asymptomatic	14	43	16	58	0.96	148*	101
13	66/M	Asymptomatic	12	48	12	108	0.48	134*	97
14	70/M	Asymptomatic	16	50	16	71	0.84	240*	148*
15	67/M	Asymptomatic	12	42	12	108	0.65	103	120*
16	81/F	Asymptomatic	13	39	14	85	0.62	135*	132*
17	56/M	NYHA I	14	44	16	81	0.50	151*	102
18	60/M	Asymptomatic	15	55	15	92	0.54	216*	142*
19	74/M	CCS 2	16	49	17	104	0.59	220*	121*
20	73/M	Asymptomatic	16	43	13	105	0.46	164*	83
Mean	66.3	...	14.7	45.1	14.8	89.2	0.72	176	135
±SD	10.3	...	1.8	4.6	1.8	18.7	0.24	41	30

F indicates female; M, male; CCS, Canadian Chest pain Score; NYHA, New York Heart Association class of breathlessness; SWT, septal wall thickness at end diastole; LVID, left ventricular internal dimension at end diastole; PWT, posterior wall thickness at end diastole; Peak AVG, peak transvalvular Doppler gradient across aortic valve; AVA, aortic valve area; LVMI, left ventricular mass index; Echo, echocardiography.

*Denotes presence of LVH with that technique.

(*Circulation*. 2002;105:470-476.)

Total MBF as a function of LV mass in Ao stenosis

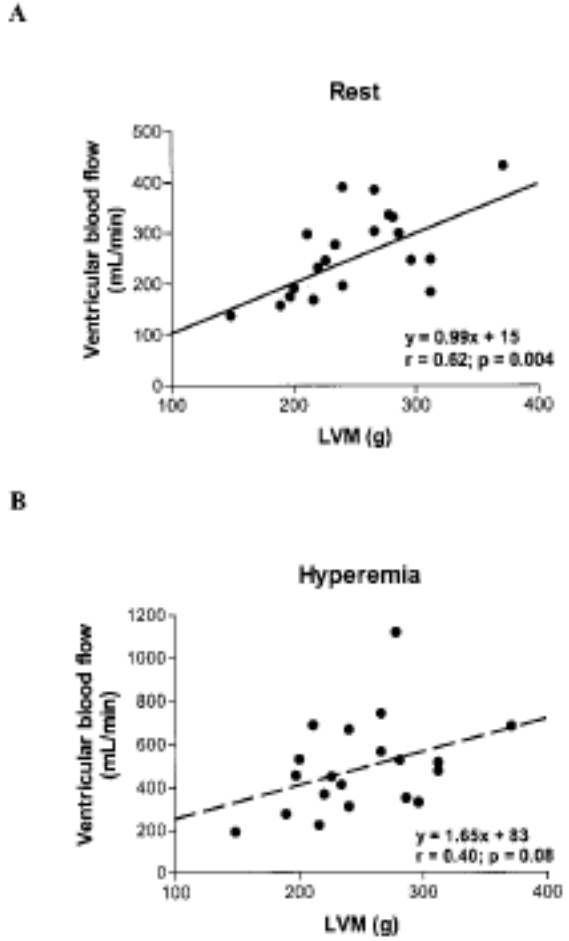


Figure 1. Relationship between LVM and total ventricular blood flow at rest (A) and during dipyridamole-induced hyperemia (B).

(*Circulation*. 2002;105:470-476.)

Total and transmural MBF in Ao stenosis: Effect of extravascular compressive (LVRPP) and trans-valvular gradient

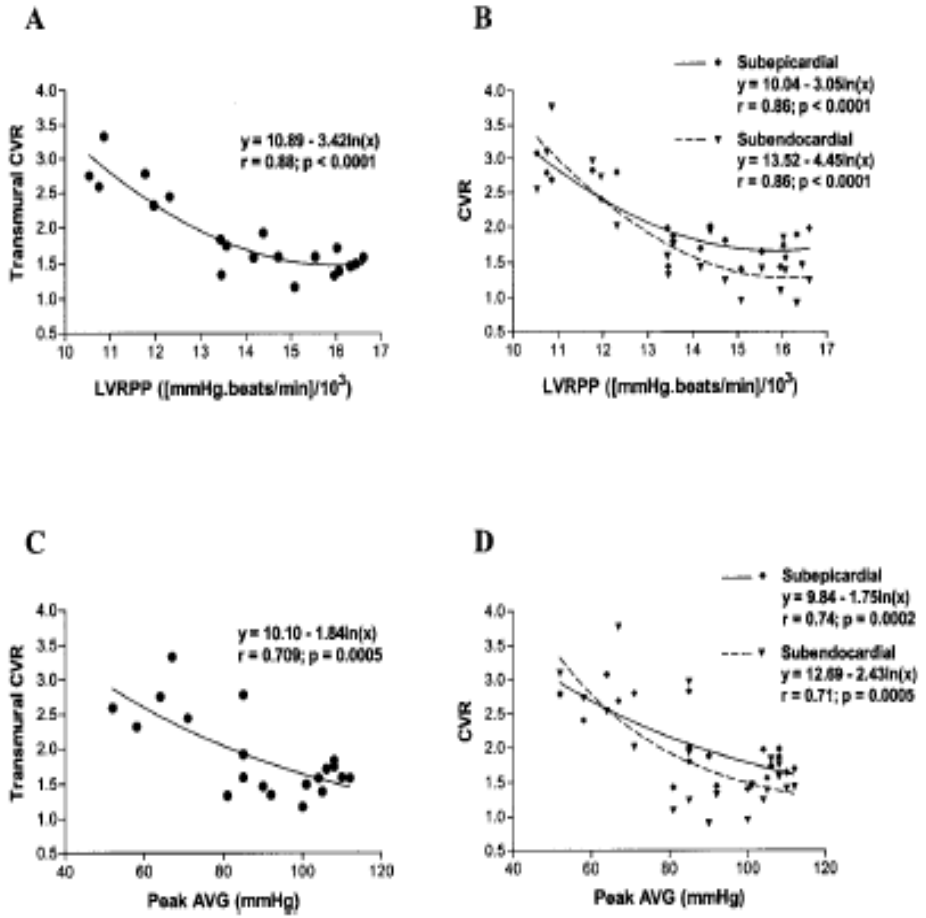


Figure 2. Relationship between LVRPP or peak AVG and CVR transmurally (A and C) and in the subendocardial and subepicardial layers (B and D).

(*Circulation*. 2002;105:470-476.)

Total and transmural MBF in Ao stenosis: relation to AVA

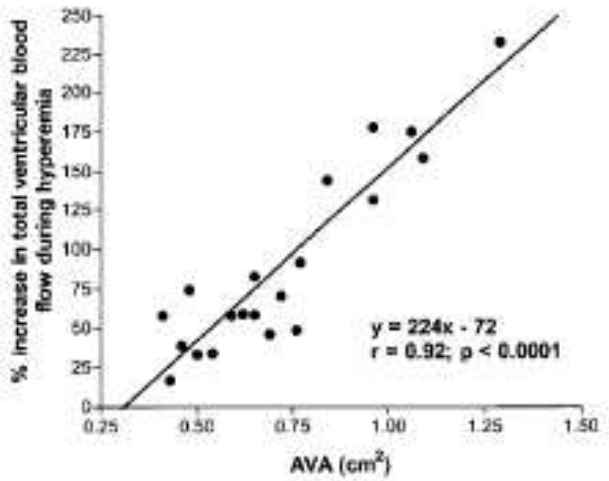


Figure 3. Relationship between percentage increase in total ventricular blood flow during hyperemia and AVA.

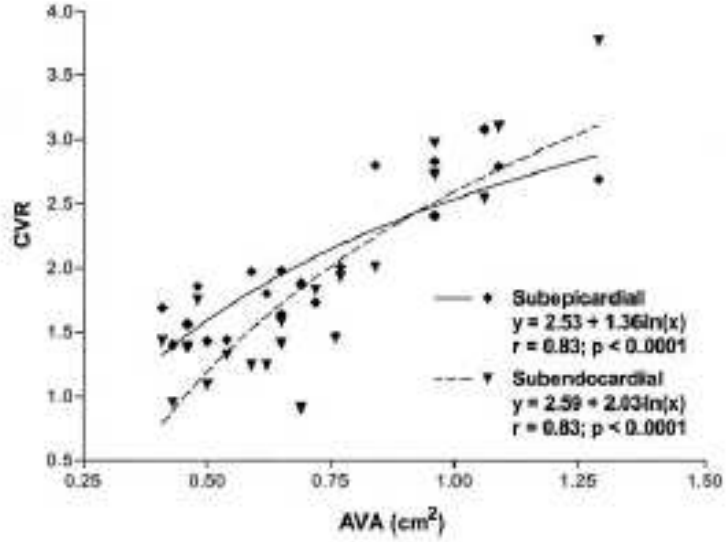


Figure 4. Relationship between CVR and AVA in the subepicardium and subendocardium. The lines intersect at 0.92 cm^2.

(*Circulation*. 2002;105:470-476.)

CFR vs. diastolic perfusion time

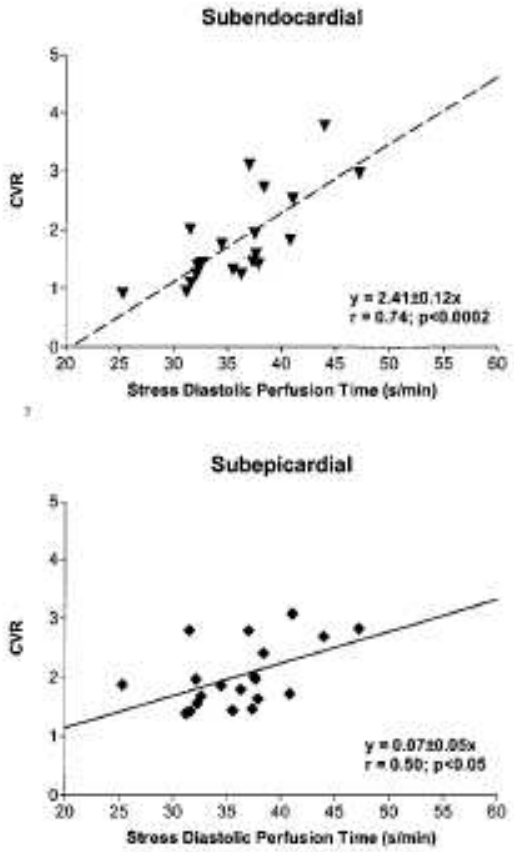


Figure 5. Relationship between CVR and DPT during dipyridamole stress in the subepicardium and subendocardium.

(*Circulation*. 2002;105:470-476.)

Table 2. Pathogenetic Mechanisms of Coronary Microvascular Dysfunction.

Alterations	Causes
Structural	
Luminal obstruction	Microembolization in acute coronary syndromes or after recanalization
Vascular-wall infiltration	Infiltrative heart disease (e.g., Anderson–Fabry cardiomyopathy)
Vascular remodeling	Hypertrophic cardiomyopathy, arterial hypertension
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Functional	
Endothelial dysfunction	Smoking, hyperlipidemia, diabetes
Dysfunction of smooth-muscle cell	Hypertrophic cardiomyopathy, arterial hypertension
Autonomic dysfunction	Coronary recanalization
Extravascular	
Extramural compression	Aortic stenosis, hypertrophic cardiomyopathy, arterial hypertension
Reduction in diastolic perfusion time	Aortic stenosis

N Engl J Med 2007;356:830-40.

Summary and conclusions

Microcirculatory dysfunction in patients with AS may explain ‘angina’ in absence of coronary artery stenosis

The severity of CFR reduction is related to indices of extravascular compressive forces such as external workload (LVRPP), transvalvular gradient, and mainly AVA as well as DPT;

This is consistent with the finding that defects on exercise thallium-201 scans are often observed in the patients with the most severe aortic stenoses despite the absence of significant coronary artery disease;

The subendocardial and subepicardial curves correlating CFR and AVA intersect at 0.92 cm^2, a figure that approximates closely to previously defined criteria of severe AS.

Functional Changes in Coronary Microcirculation After Valve Replacement in Patients With Aortic Stenosis

Kim Rajappan, MD; Ornella E. Rimoldi, MD; Paolo G. Camici, MD; Nicholas G. Bellenger, MD; Dudley J. Pennell, MD; Desmond J. Sheridan, MD, PhD

TABLE 1. Demographic, Echocardiographic, Cardiovascular Magnetic Resonance, and Microcirculatory Function Data

		Preoperative				1 Year Postoperative			
Patient No.	Age, y/Sex	BP	AVA, cm²	LVMI, g/m²	CVR	BP	AVA, cm²	LVMI, g/m²	CVR
1	74/M	109/53	0.59	121*	1.34	84/59	2.55	73	1.98
2	67/M	100/68	0.65	142*	1.17	120/61	3.59	93	2.15
3	79/M	106/69	0.41	199*	1.09	164/76	1.58	125*	1.90
4	54/M	101/69	0.43	158*	0.89	101/55	3.12	112	2.06
5	73/F	149/58	0.32	101*	1.71	132/44	1.16	66	1.70
6	77/M	172/74	0.77	170*	1.85	134/62	3.33	126*	2.57
7	66/M	148/70	0.48	110	1.37	136/64	2.10	80	1.60
8	67/M	132/75	0.65	128*	1.35	146/70	2.48	108	1.48
9	70/M	157/88	0.84	148*	2.07	145/68	2.74	115*	3.40
10	41/M	131/75	1.06	107	1.96	149/84	2.08	77	2.02
11	60/M	127/68	1.29	140*	2.37	116/81	3.67	84	3.47
12	80/M	108/65	0.96	153*	1.83	143/80	1.72	102	1.82
13	65/M	155/81	0.80	99	2.05	135/68	2.41	76	1.46
14	74/F	173/60	0.76	119*	1.54	143/75	2.13	86	2.61
15	69/F	161/84	0.72	128*	1.65	198/75	3.47	96*	3.34
16	73/M	101/67	0.46	83	1.09	88/62	2.65	66	2.02
17	56/M	147/85	0.50	104	1.37	146/72	2.30	92	1.30
18	58/F	161/93	0.69	183*	1.53	165/89	2.20	167*	1.56
19	57/M	116/73	1.09	125*	1.92	127/69	2.87	83	2.13
20	53/M	109/61	0.92	101	2.08	136/81	1.80	72	2.62
21	64/M	115/70	0.68	119*	1.50	111/66	1.57	87	1.89
22	63/M	138/90	0.96	103	1.95	135/77	1.66	87	1.66
Mean	65.5	133/73	0.73	129	1.62	134/67	2.42†	94†	2.12†
±SD	9.7	25/11	0.25	30	0.39	25/17	0.71	24	0.63

M indicates male; F, female; and BP, blood pressure.
*Presence of LVH.
†$P<0.001$ vs preoperative value.

(*Circulation*. 2003;107:3170-3175.)

Changes in CFR as a function of LV mass and AVA

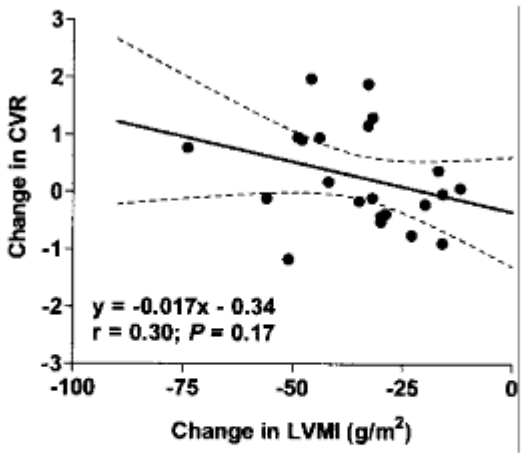

Figure 1. Relationship between absolute change in CVR and absolute change in LVMI after aortic valve replacement. Linear regression lines (solid line), 95% confidence intervals (dashed lines) with equations, and *r* and *P* values are shown.

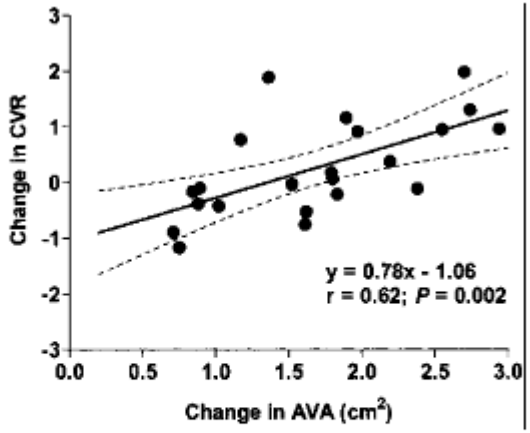

Figure 2. Relationship between absolute change in CVR and absolute change in AVA after aortic valve replacement. Linear regression lines (solid line), 95% confidence intervals (dashed lines) with equations, and *r* and *P* values are shown.

(*Circulation*. 2003;107:3170-3175.)

Changes in CFR as a function of DPT

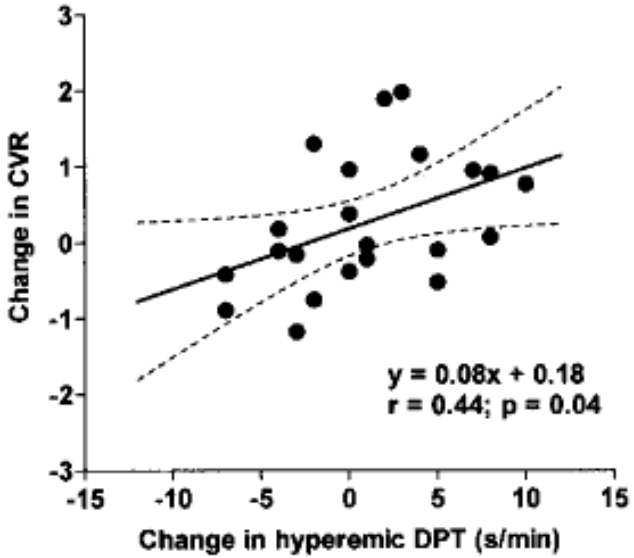

Figure 3. Relationship between absolute change in CVR and absolute change in hyperemic DPT after aortic valve replacement. Linear regression lines (solid line), 95% confidence intervals (dashed lines) with equations, and *r* and *P* values are shown.

(*Circulation*. 2003;107:3170-3175.)

Summary and conclusions

There was significant regression of LVM in all patients after AVR and a related reduction in total left ventricular blood flow;

There was a significant increase in CFR after AVR;

The changes in coronary microcirculatory function were not directly related to regression of LVM;

The improvement in CFR was more closely related to changes in hemodynamic variables, including AVA and DPT;

Whether these changes in microvascular function bear any prognostic significance remains to be determined.