Relation between symptoms and profiles of coronary artery blood flow velocities in patients with aortic valve stenosis: a study using transoesophageal Doppler echocardiography

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Abstract

Objective—To analyse profiles of coronary artery flow velocity at rest in patients with aortic stenosis and to determine whether changes of the coronary artery flow velocities are related to symptoms in patients with aortic stenosis.

Design—A prospective study investigating the significance of aortic valve area, pressure gradient across the aortic valve, systolic left ventricular wall stress index, ejection fraction, and left ventricular mass index in the coronary flow velocity profile of aortic stenosis; and comparing flow velocity profiles between symptomatic and asymptomatic patients with aortic stenosis using transoesophageal Doppler echocardiography to obtain coronary artery flow velocities of the left anterior descending coronary artery.

Setting—Tertiary referral cardiac centre.

Patients—Fifty eight patients with aortic stenosis and 15 controls with normal coronary arteries.

Results—Adequate recordings of the profile of coronary artery flow velocities were obtained in 46 patients (79%). Left ventricular wall stress was the only significant haemodynamic variable for determining peak systolic velocity ($r = -0.83$, $F = 88.5$, $P < 0.001$). The pressure gradient across the aortic valve was the only contributor for explaining peak diastolic velocity ($r = 0.56$, $F = 20.9$, $P < 0.001$). Controls and asymptomatic patients with aortic stenosis ($n = 12$) did not differ for peak systolic velocity [32.8 (SEM 9.7) v 27.0 (8.7) cm/s, NS] and peak diastolic velocity [58.3 (18.7) v 61.9 (13.5) cm/s, NS]. In contrast, patients with angina ($n = 12$) or syncope ($n = 8$) had lower peak systolic velocities and higher peak diastolic velocities than asymptomatic patients ($P < 0.01$). Peak systolic and diastolic velocities were -7.7 (22.5) cm/s and 81.7 (17.6) cm/s for patients with angina, and -19.5 (22.3) cm/s and 94.0 (20.9) cm/s for patients with syncope. Asymptomatic patients and patients with dyspnoea ($n = 14$) did not differ.

Conclusions—Increased pressure gradient across the aortic valve and enhanced systolic wall stress result in characteristic changes of the profile of coronary flow velocities in patients with aortic stenosis. Decreased or reversed systolic flow velocities

are compensated by enhanced diastolic flow velocities, particularly in patients with angina and syncope. This characteristic pattern of the profile of coronary artery flow velocities in patients with angina or syncope may be useful for differentiating those patients from asymptomatic patients.

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Keywords: aortic stenosis; coronary artery flow; Doppler echocardiography

Angina is a common symptom in patients with aortic stenosis.¹ In the absence of obstructive coronary artery lesions, angina has been attributed to the imbalance of oxygen supply and consumption.² In support of this assumption, abnormal coronary artery flow reserve has been reported in patients with aortic stenosis.³ Furthermore, changes of the coronary artery flow or flow velocity profile were described using angiography, Doppler catheters, epicardial Doppler echocardiography, and trans-thoracic Doppler.⁴⁻⁷ However, these changes in coronary artery flow have not yet been correlated to symptoms in patients with aortic stenosis. This paper draws on the hypothesis that patients with aortic stenosis have characteristic changes of the profiles of the coronary artery flow velocities at rest and that these changes are correlated with symptoms.

Methods

PATIENT POPULATION

Patients with a mean pressure gradient across the aortic valve of at least 25 mm Hg, determined by Doppler echocardiography, and stable clinical condition were selected for this prospective study. Exclusion criteria included: significant coronary artery disease ($> 50\%$ coronary artery stenosis), as determined by coronary angiography; combined aortic valve disease, with more than mild aortic regurgitation or disease of the other cardiac valves; a history of arterial hypertension; significant restrictive or obstructive lung disease; anaemia (< 12 g/dl Hb); clinical evidence of peripheral vascular disease; atrial fibrillation and bundle branch block; and inadequate transoesophageal Doppler studies. The study group consisted of 58 consecutive patients with aortic stenosis whom we were studying to determine the value

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of multiplane transoesophageal Doppler echocardiography for measuring aortic valve area. There were 27 men and 29 women (mean age 67.9, SEM 8.4, years). All patients were in sinus rhythm. Thirty six patients had no medication. In the other 22 patients all specific cardiac drugs were stopped. On enrolment to the study a history and physical examination was performed. Patients were questioned specifically about symptoms of angina, syncope, and dyspnoea on exercise. Fifteen asymptomatic patients without heart disease, who underwent transoesophageal echocardiography to exclude a cardiac source of embolism, served as a control group. There were eight men and seven women in this group (mean age 67.5, SEM 14.8, years).

CATHETERISATION

Informed consent was obtained from all patients, and routine cardiac catheterisation was carried out. Selective coronary angiography was performed using the Judkins technique. Aortic valve areas were calculated from the Gorlin formula⁸ and biplane angiography was used to determine left ventricular ejection fraction.⁹

ECHOCARDIOGRAPHY

All studies were performed using a Vingmed 800 C (Vingmed Sound). A 3.25 MHz mechanically driven annular array transducer was used for transthoracic echocardiography, and a 5 MHz multiplane transducer for transoesophageal echocardiography, respectively.

Left ventricular mass (LVM) was determined by M mode echocardiography using the Penn convention described by Devereux and Reichek¹⁰: $LVM (g) = 1.04 [(LVID_d + VST + PWT_d)^3 - (LVID_d)^3] - 13.6$, where $LVID_d$ is diastolic left ventricular internal diameter, VST is the diastolic left ventricular septal thickness, and PWT_d is the diastolic left ventricular posterior wall thickness. Left ventricular mass index, calculated by dividing the left ventricular mass by the body surface area,¹¹ was used in all statistical analyses.

Systolic left ventricular meridional wall stress (LVWS) was determined using the following formula¹²: $LVWS (dyn/cm^2) = 0.344 (P/LVID_s) / PWT_s [1 + (PWT_s/LVID_s)]$, where $LVID_s$ is systolic left ventricular internal diameter, PWT_s is the systolic left ventricular posterior wall thickness, and P is peak systolic left ventricular pressure. $LVID_s$ and PWT_s were derived by M mode echocardiography, P was determined by cardiac catheterisation.

The continuous wave Doppler transducer of the ultrasound probe was used to determine the pressure gradient across the aortic valve. Mean aortic gradients were calculated from five representative beats using the simplified Bernoulli equation, by averaging the peak gradients over the systolic ejection period.¹³

Transoesophageal echocardiography was performed to visualise the left anterior descending coronary artery and to obtain the flow velocity signal by pulsed Doppler echocardiography. The left coronary artery was imaged according to previously published guidelines.¹⁴ The sample volume of the pulsed Doppler was

positioned distal from the bifurcation of the left coronary artery in the left anterior descending artery and the flow velocity waveform was recorded. Care was taken to obtain both adequate systolic and diastolic flow velocities and to minimise the angle of the incidence of the Doppler beam and the flow. Velocity spectra were transferred as raw digital data to a Macintosh computer. After the original examination the data were assessed further by the evaluation software provided by the manufacturer (Echodisp, Vingmed Sound) by an investigator who was not aware of the results of the echocardiographic and catheterisation studies. Figure 1 shows a schematic illustration of the profile of the coronary artery flow velocities in a control subject and gives the variables which were measured. These variables included the duration of the heart cycle, systolic and diastolic velocity time integrals, the sum of systolic and diastolic velocity time integrals (net velocity time integral), peak systolic and diastolic velocities, the time from the beginning of the Q wave in the electrocardiogram to the onset of forward systolic flow, and the diastolic acceleration time. Both time intervals were corrected by the square root of the duration of the heart cycle. The results of five consecutive heart cycles were averaged in each patient. Figure 2 is an example of the profiles of the coronary artery flow velocities in patients with aortic stenosis. Reproducibility of measurements of coronary artery flow velocities was assessed in eight patients who underwent Doppler evaluations of the profile of coronary artery flow velocities twice, 10 minutes apart.

STATISTICS

Data are presented as means (SEM). Where normally distributed, group data were compared using the Student *t* test. Data showing non-normal distribution were compared using the Mann-Whitney U test. Relations between continuous variables were examined using the least squares method of linear regression. Aortic valve area, pressure gradient across the

Figure 1 Schematic illustration of the profile of coronary artery flow velocities in a control subject. Coronary artery flow is biphasic with both forward systolic and diastolic flow velocity. There is no reverse flow during systole. V_s , systolic velocity; V_d , diastolic velocity; $VTId$ diastolic velocity-time integral; $VTIs$, systolic velocity-time integral; TSF , time from the beginning of the Q wave in the ECG to the onset of forward systolic flow; ATd , diastolic acceleration time; ECG, electrocardiogram.

Figure 2 Original recording of the profile of coronary artery flow velocities in two patients with aortic stenosis. Example A shows the profile of coronary artery flow velocities of a patient with attenuated systolic flow velocities (Vs). However, there was no flow reversal during systole. Example B shows flow reversal during systole (white arrow). In this case diastolic acceleration time (ATd) is prolonged and peak diastolic flow velocity (Vd) is enhanced.

aortic valve, ejection fraction, left ventricular wall stress index, and left ventricular mass index were evaluated for their association with peak coronary artery flow velocities and velocity-time integrals by univariate analysis and stepwise multiple regression analysis. Only variables that were univariately significant at the $P < 0.05$ level were then taken for stepwise multi-

ple linear regression analysis (F to remove: 4.0) (StatView 4.0, Abacus Inc).

Results

PATIENT CHARACTERISTICS

Twelve patients were excluded because of inadequate transoesophageal Doppler studies of the coronary artery flow velocities (79%). There was no significant difference in age between the control subjects and the remaining 46 patients. The main symptom was angina in 12 patients, syncope in eight, and dyspnoea with exercise in 14; 12 patients were asymptomatic. The measurements of the haemodynamic variables and left ventricular mass index are given in table 1. Left ventricular mass index was higher in patients with aortic stenosis than in control subjects, at $131.5 (52.3) \text{ g/m}^2$ ($P < 0.01$). Symptomatic and asymptomatic patients with aortic stenosis reacted similarly in terms of ejection fraction and heart rate. Left ventricular mass index, pressure gradient across the aortic valve, and systolic left ventricular wall stress were higher in symptomatic than in asymptomatic patients with aortic stenosis. Patients with dyspnoea had lower pressure gradients across the aortic valve, lower systolic left ventricular wall stress indices, and higher aortic valve areas than patients symptomatic for angina or syncope.

CORONARY BLOOD FLOW VELOCITY PATTERN

Qualitative description

Control subjects had a biphasic coronary flow velocity profile with forward flow throughout both systole and diastole. Reverse flow was not observed. All patients with aortic stenosis had forward diastolic flow. Direction of systolic flow varied: 33 patients had continuous forward flow during systole, 13 patients had reverse flow in systole (fig 2). Seven of the latter patients had only reverse flow in early systole.

Table 1 Haemodynamic variables and left ventricular mass index in patients with aortic stenosis. Values are means (SEM)

	n	Age (years)	HR	AVA (cm ²)	ΔP (mm Hg)	EF (%)	LVWS (dyn/cm ² × 10 ³)	LVMI (g)
All patients with aortic stenosis	46	66.6 (8.6)	77.9 (6.7)	0.68 (0.3)	62.6 (20.9)	66.5 (10.7)	198.2 (37.3)	188.8 (57.2)
Asymptomatic patients								
with aortic stenosis	12	65.6 (10.9)	76.5 (11.4)	0.85 (0.2)	47.9 (10.9)	70.4 (5.8)	167.7 (30.9)	169.6 (68.8)
Patients with angina	12	66.7 (6.8)	80.1 (17.1)	0.53 (0.33)*	76.1 (19.5)†	66.0 (12.6)	251.2 (62.9)†	198.1 (50.7)*
Patients with dyspnoea	14	67.6 (7.5)	76.3 (17.4)	0.66 (0.34)*	59.5 (17.7)*	64.7 (13.0)	221.2 (63.1)*	193.5 (47.3)*
Patients with syncope	8	67.1 (8.6)	79.9 (14.0)	0.53 (0.21)†	80.4 (21.1)†	63.8 (12.9)	273.5 (37.1)†	210.8 (48.1)*

HR, heart rate; AVA, aortic valve area; ΔP, mean aortic gradient; EF, ejection fraction; LVWS, left ventricular wall stress; LVMI, left ventricular mass index.

* $P < 0.05$, † $P < 0.01$ symptomatic patients v asymptomatic patients.

Table 2 Coronary flow velocity profile. Values are means (SEM)

	Vs (cm/s)	Vd (cm/s)	VTId (cm)	VTIs (cm)	VTIs + d (cm)	TSF (ms)	ATd (ms)
Control subjects	32.8 (9.7)	58.3 (18.7)	18.5 (6.2)	6.2 (3.1)	24.6 (7.4)	35 (10)	29 (12)
All patients with AS	10.9 (24.5)†	71.6 (21.2)*	18.3 (5.8)	2.1 (3.9)†	20.4 (7.2)*	62 (37)†	46 (16)*
Asymptomatic patients with AS	27.0 (8.7)	61.9 (13.5)	18.0 (6.6)	4.5 (2.1)	22.5 (7.6)	53 (25)*	43 (12)†
Patients with angina	-7.7 (22.5)§	81.7 (17.6)‡	19.3 (5.6)	-1.5 (3.5)§	17.8 (6.7)§	77 (42)§	49 (17)‡
Patients with dyspnoea	24.6 (9.6)	61.9 (19.9)	18.4 (6.8)	4.7 (1.7)	23.1 (7.1)	42 (31)	41 (18)
Patients with syncope	-19.5 (22.3)§	94.0 (20.9)§	17.3 (3.0)	-2.2 (2.1)§	15.1 (2.7)§	93 (36)§	55 (14)§

Vs, systolic velocity; Vd, diastolic velocity; VTId, diastolic velocity time integral; VTIs, systolic velocity time integral; VTIs + d, VTIs + VTId; TSF, time from the beginning of the Q wave in the ECG to the onset of forward systolic flow; ATd, diastolic acceleration time.

* $P < 0.05$, † $P < 0.01$ patients with aortic stenosis v control subjects.

‡ $P < 0.05$, § $P < 0.01$ symptomatic patients v asymptomatic patients.

Figure 3 Correlation between peak systolic (V_s) and diastolic velocities (V_d) and mean aortic pressure gradient (ΔP).

Figure 4 Correlation between peak systolic (V_s) and diastolic velocities (V_d) and systolic left ventricular wall stress (LVWS).

Quantitative description

Coronary flow velocity data are given in table 2. Controls and asymptomatic patients with aortic stenosis did not differ significantly except for the diastolic acceleration time and the time from the beginning of the Q wave in the electrocardiogram to the onset of forward systolic flow, which were longer in the latter group. Patients with angina or a history of syncope had lower peak systolic velocities, higher peak diastolic velocities, smaller systolic velocity time integrals, a longer time from the beginning of the Q wave in the electrocardiogram to the onset of forward systolic flow, a longer diastolic acceleration time, and a smaller net velocity time integral than asymptomatic patients. However, patients with dyspnoea did not differ from asymptomatic patients with aortic stenosis. Reproducibility of measurements was good. The absolute difference of peak systolic and diastolic flow velocities were 3 (2) cm/s and 4 (3) cm/s, respectively.

RELATION BETWEEN LEFT VENTRICULAR MASS, HAEMODYNAMIC VARIABLES, AND PEAK SYSTOLIC AND DIASTOLIC CORONARY ARTERY FLOW VELOCITIES

Aortic valve area was positively correlated with peak systolic velocity ($r = 0.47$, $P < 0.05$) and peak diastolic velocity ($r = 0.30$, $P < 0.05$). Pressure gradient across the aortic valve was more closely correlated with peak systolic velocity ($r = -0.69$, $P < 0.01$) and peak diastolic velocity ($r = 0.56$, $P < 0.01$) than with aortic valve area (fig 3). Systolic left ventricular wall stress index was closely correlated with peak systolic velocity ($r = 0.83$; $P < 0.05$) and was positively correlated with peak diastolic velocity ($r = 0.47$; $P < 0.05$) (fig 4). Left ventricular

mass index correlated weakly with peak diastolic velocity ($r = 0.41$, $P < 0.05$). Ejection fraction did not correlate significantly with either peak systolic velocity or peak diastolic velocity. The systolic velocity-time integral was weakly correlated with systolic left ventricular wall stress index ($r = 0.43$, $P < 0.05$), while the diastolic velocity-time integral was weakly correlated with the pressure gradient across the aortic valve ($r = 0.4$; $P < 0.05$). Multivariate analysis showed that the systolic left ventricular wall stress index was the only significant factor for determining peak systolic velocity ($F = 88.5$, $P < 0.001$), while the pressure gradient across the aortic valve was the only factor that might explain peak diastolic velocity ($F = 20.9$, $P < 0.001$). A multivariate analysis could not be performed for systolic and diastolic velocity-time integrals, because these two variables were only univariately correlated with a single haemodynamic variable.

Discussion

CORONARY ARTERY FLOW CHANGES IN PATIENTS WITH AORTIC STENOSIS

Systolic flow changes

In patients with aortic stenosis, onset of systolic forward flow in the left coronary artery is delayed and peak systolic flow velocities and systolic velocity time integrals are reduced.⁵⁻⁷ These changes cause a reduced systolic flow. Flow reversal in the left coronary artery in early systole may even be demonstrated using angiography.⁴ The results of this study endorse these previous observations. An increase in extravascular compressing forces has been suggested as a mechanism for changes of the systolic flow.¹⁵ The finding of our study that the

systolic left ventricular wall stress index was the single most important determinant of peak systolic flow velocities supports this assumption. Furthermore, in agreement with previous studies the results of this study show that left ventricular mass on its own is not correlated with changes of the systolic flow.

Diastolic flow changes

Slow acceleration and rapid deceleration of diastolic coronary artery flow velocities have been reported in patients with aortic stenosis as compared to controls.⁵ The findings of the present study endorse these observations. However, in contrast to the previous study, higher peak diastolic velocities were found in patients with aortic stenosis than in controls. This may explain why there was no difference in diastolic velocity time integral between patients with aortic stenosis and controls. The mechanism for diastolic flow changes is not clear. Left ventricular hypertrophy may partly explain diastolic flow changes. In support of this hypothesis, slow diastolic flow acceleration was reported in patients with left ventricular hypertrophy due to arterial hypertension.¹⁶ A weak correlation between peak diastolic velocities and left ventricular mass was also found in this study. However, slow diastolic coronary artery flow acceleration and rapid deceleration disappears immediately after aortic valve replacement, despite unchanged left ventricular mass.⁶ Another possible mechanism of altered diastolic coronary artery flow is an attenuated capacitor effect of the epicardial coronary artery during systole. The results of this study support this assumption, as the increased pressure gradient across the aortic valve was the most important haemodynamic determinant of increased peak diastolic flow velocities, while at the same time the increased pressure gradient across the aortic valve was closely linked to decreased or even reversed systolic velocities.

CORRELATION BETWEEN SYMPTOMS AND PROFILE OF CORONARY ARTERY FLOW VELOCITIES

The three main symptoms in aortic stenosis are angina, dyspnoea, and syncope.²

Angina pectoris

In patients without coronary artery disease the incidence of angina was found to be 52%.¹ Angina in patients without coronary artery disease is attributed to an imbalance in myocardial oxygen supply and demand.² In support of this assumption histological findings suggestive of ischaemia were found in patients with aortic stenosis and normal coronary arteries.¹⁷ In addition, a decreased coronary blood flow reserve has been shown in patients with angina.³ However, despite a reduced coronary blood flow reserve, coronary blood flow at rest is adequately maintained as the cross sectional area of the left epicardial coronary artery is enlarged.^{18,19}

The results of our study show that patients with angina also have characteristic changes of the coronary artery flow velocity profile at rest. Increased systolic left ventricular wall stress

results in decreased systolic flow velocities, a delayed onset of systolic flow, and attenuated systolic velocity-time integral compared to asymptomatic patients. Despite increased diastolic flow velocities, the diastolic velocity-time integral is not higher in patients with angina than in asymptomatic patients, resulting in a lower net velocity time integral in patients with angina than in asymptomatic patients. As coronary artery flow is determined by the product of cross sectional area of the coronary artery and the net velocity-time integral, adequate coronary artery flow must be maintained by an increase in the cross sectional area of the coronary artery, which endorses the findings of the above mentioned study.

The prevalence of coronary artery stenosis was reported to be 39% in patients with aortic stenosis.²⁰ In patients with aortic stenosis and angina it is clinically important to distinguish between symptoms due to the valve disease and those due to concomitant obstructive coronary artery disease, since cardiac catheterisation is now performed in patients with aortic stenosis mainly to exclude anginal symptoms of coronary origin, at least in young patients without risk factors for coronary artery disease. The profile of coronary artery blood flow velocities in patients with significant stenosis of the left anterior descending coronary artery has been described in a previous study using transoesophageal Doppler echocardiography.²¹ In comparison to patients with normal left anterior descending coronary arteries, patients with significant stenosis had increased peak diastolic velocities. However, peak systolic velocities did not differ between the two groups, and reverse systolic flow was not observed in either group. The results of our study show that patients with aortic stenosis without concomitant coronary artery disease and angina have decreased peak systolic coronary artery flow velocities and that there may be reversed systolic flow. Thus the characteristics of systolic coronary flow velocities may be used to determine cut-off criteria to exclude anginal symptoms of coronary origin.

Syncope

Syncope as the first clinical manifestation of aortic stenosis was found in 15% of patients and it is well recognised that sudden death may be the first manifestation of severe aortic stenosis.¹ Different causes have been suggested as a mechanism for syncope: carotid sinus reflex hyperactivity, abrupt left ventricular failure, arrhythmias, and ischaemic myocardial depression.²²⁻²⁵ The most widely accepted theory is inappropriate left ventricular baroreceptor response.²⁶ However, in patients monitored during syncope, myocardial ischaemia was present before syncope developed. Hence it has been suggested that myocardial ischaemia accompanies syncope and may itself trigger an inappropriate left ventricular baroreceptor response.²⁷ The results of our study show that patients with a history of syncope have the same characteristic changes of the coronary artery flow velocity profile as patients with angina. Thus myocardial ischaemia may also play an important role in the syncope mechanism.

Dyspnoea

Dyspnoea as the initial manifestation of aortic stenosis was reported in 38.6% of patients.¹ Our study excluded patients in an unstable clinical state and with depressed left ventricular function. Nevertheless, 30.4% of our patient group were reported to have dyspnoea on exercise. No difference in coronary artery flow velocity profile was found between patients with dyspnoea on exercise and asymptomatic patients with aortic stenosis. This might be because in patients with dyspnoea the disease is less severe. On the other hand, changes in the coronary artery flow velocity profile may be less important to the mechanism of dyspnoea. In this respect, it is of interest that diastolic dysfunction has been suggested as the cause of dyspnoea in patients with aortic stenosis²⁸ and also that diastolic dysfunction has been found in 50% of patients with normal systolic left ventricular function and aortic stenosis.²⁹

METHODOLOGICAL CONSIDERATIONS AND LIMITATIONS

Transoesophageal echocardiography

In contrast to invasive Doppler echocardiography, the advantage of transoesophageal Doppler echocardiography is that it allows the dynamics of coronary artery blood flow velocities to be examined without altering the blood flow itself.³⁰ However, transoesophageal echocardiography also has its limitations. It is not feasible in all patients, is semi-invasive, and is technically difficult.³¹ The angle of the Doppler beam and the coronary artery flow may alter velocity measurements. In this study care was taken to keep the angle of the Doppler beam and the coronary artery flow below 30°. Only proximal velocity measurements can be obtained with transoesophageal Doppler; thus only extreme conditions of reversed flow are detected when measurements are taken close to the left main coronary artery. This may explain the differences in results obtained from other invasive studies. Doppler techniques measure velocities, and not flow itself, as blood flow calculation requires determination of the luminal cross sectional area. Flow velocities were only recorded in basal conditions. Determining coronary flow reserve using pharmacological hyperaemic stimuli could have revealed better discriminative values for identifying patients with myocardial ischaemia.

Symptoms

Categorising patients with aortic stenosis according to their main symptom has inherent limitations, in that patients with predominant dyspnoea on exercise may occasionally have angina, or patients with effort syncope may complain of angina before syncope.

SUMMARY AND CLINICAL IMPLICATIONS

Our study shows that systolic left ventricular wall stress index and increased pressure gradient across the aortic valve are the most important determinants of the coronary artery flow velocity profile in patients with aortic stenosis, resulting in decreased or reversed systolic coronary artery flow velocities and increased

diastolic flow velocities. In contrast to asymptomatic patients or patients with dyspnoea, patients with angina or syncope have attenuated systolic flow velocities and increased diastolic flow velocities. This characteristic pattern of the profile of coronary artery flow velocities in patients with angina or syncope may be useful for differentiating those patients from asymptomatic patients.

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SHORT CASES IN CARDIOLOGY

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Pulmonary oedema and pleural effusion in two patients with primary pulmonary hypertension treated with calcium channel blockers

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(A) Chest x ray on admission, showing pulmonary oedema and bilateral pleural effusion.
(B) Chest x ray after nifedipine treatment was stopped.

A 63 year old man who had had primary pulmonary hypertension (PPH) for 2 years was admitted in our department with right heart failure. This patient fulfilled all the diagnostic criteria for PPH.¹ Before treatment with calcium channel blockers was started his haemodynamic acute response to vasodilators was determined. Nifedipine (60 mg/day) was started. On admission to our department, this patient had severe dyspnoea at rest and was cyanosed. He showed marked signs of right heart failure, associated with signs of pulmonary oedema and pleural effusion which were confirmed by the chest radiography (fig 1A). Despite oxygen therapy and an intravenous infusion of frusemide, his haemodynamic and respiratory condition did not improve. A few hours later we decided to stop nifedipine. Subsequently, we saw a rapid decrease of dyspnoea, pulmonary oedema, and pleural effusion (fig 1B). This patient died 6 months later from a recurrence of right heart failure. Necropsy showed micro-thrombotic pulmonary arteriopathy. A 64 year old woman with PPH who was treated in our department with nifedipine (120 mg/day) has had the same medical history.

Because the clinical improvement occurred only after the wash-out time of nifedipine,² we concluded that nifedipine was the cause of this life-threatening state. The mechanism of these adverse effects seems to be either a negative cardiac inotropic effect or a modification of capillary blood flow, like that described in peripheral oedema caused by the dihydropyridines³ or a combination of both mechanisms. A modification of capillary blood flow may increase pulmonary capillary hydrostatic pressure and may cause fluid to cross from blood to tissue.

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3 Gustafsson D. Microvascular mechanisms involved in calcium antagonist edema formation. *J Cardiovasc Pharmacol* 1987;suppl 1:S121-31.