Changes in coronary sinus pH during dipyridamole stress in patients with hypertrophic cardiomyopathy

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Abstract

***Objectives*—The presence of angina pectoris and myocardial scarring in patients with hypertrophic cardiomyopathy (HCM) suggests that myocardial ischaemia is a factor in the pathophysiology of the disease. The clinical evaluation of ischaemia is problematic in HCM as baseline electrocardiographic abnormalities are frequent and thallium-201 perfusion abnormalities correlate poorly with anginal symptoms. Coronary sinus pH measurement using a catheter mounted pH electrode is a validated sensitive technique for the detection of myocardial ischaemia.**

***Methods and results*—11 patients with HCM and chest pain (eight men; mean (SD) (range) age 36 (11) (19–53) years) and six controls (two men; mean (SD) (range) age 49 (11) (31–62) years) with atypical pain and normal coronary angiograms were studied. Eight patients with HCM had baseline ST segment depression of $\geqslant$ 1 mm and four had reversible perfusion defects during stress ^{201}TI scintigraphy. A catheter mounted hydrogen ion sensitive electrode was introduced into the coronary sinus and pH monitored continuously during dipyridamole infusion (0·56 mg/kg over four min).**

The maximal change in coronary sinus pH during dipyridamole stress was greater in patients with HCM than in controls (0·082 (0·083) (0 to − 0·275) *v* 0·005 (0·006) (0 to − 0·012), P = 0·02). In six patients (four men; mean (SD) (range) age 29 (9) (19–40) years) the development of chest pain was associated with a gradual decline in coronary sinus pH (mean 0·123 (0·089)), peaking at 442 (106) s. There were no relations among left ventricular dimensions, maximal wall thickness, and maximum pH change. In patients with HCM there was a correlation between maximum pH change and maximum heart rate during dipyridamole infusion (r = 0·70, P = 0·02).

***Conclusion*—This study provides further evidence that chest pain in patients with HCM is caused by myocardial ischaemia. The role of myocardial ischaemia in the pathophysiology of the disease remains to be determined but coronary sinus pH monitoring provides a method for quantifying and prospectively assessing its effects on clinical presentation and prognosis.**

(*Heart* 1996;75:179–183)

Keywords: hypertrophic cardiomyopathy; ischaemia; pH

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Accepted for publication 28 September 1995

Patients with hypertrophic cardiomyopathy (HCM) frequently complain of typical angina despite normal coronary arteriograms.[1] Clinical evidence, including the presence of ST segment depression[2–4] and reversible thallium-201 perfusion defects[3 5–8] suggests that myocardial ischaemia may be responsible, but the evaluation of ischaemic symptoms in patients with the disease remains problematic. The presence of baseline electrocardiographic abnormalities in many patients complicates the interpretation of ST segment changes at rest and during exercise. Similarly, the kinetics of ^{201}TI in hearts affected by HCM have not been studied in any detail and there is a poor correlation between symptomatic status and the presence of reversible ^{201}TI defects in patients with the disease.[3 5–8]

In an attempt to elucidate the cause of chest pain in patients with HCM several studies have used myocardial lactate extraction as a "gold standard" marker of ischaemia.[3 9] This technique, however, has a number of important limitations, including a susceptibility to sampling error and the inability to detect rapid changes in coronary venous metabolite concentration.[10 11] Coronary sinus pH measurement using a catheter mounted pH electrode overcomes many of these problems[12–14] and provides an alternative metabolic marker of ischaemia for use in the evaluation of patients with symptoms that may be of ischaemic origin.

The aim of this study was to investigate changes in coronary sinus venous pH during intravenous dipyridamole infusion in patients with HCM compared with that in controls, and to determine its relation to clinical, electrocardiographic, and ^{201}TI scintigraphic characteristics.

Patients and methods

PATIENTS

This study was approved by the local research ethics committee. Patients were required to

Table 1 Clinical characteristics in patients with hypertrophic cardiomyopathy (HCM)

Patient no	Age (years)	Sex	FHSD	NYHA	Syncope	SVT	VT	ExST	Vo_2 max (ml/min/kg)	Ex time (min)	ExBP
1	33	M	+	1	–	–	–	–	31·0	10·78	
2	39	M	–	1	–	–	–	+	26·6	9·15	Flat
3	29	F	–	2	–	–	–	–	39·8	9·97	
4	53	M	–	1	+	–	+	+	30·2	9·22	
5	45	M	–	2	–	+	–	–	32·8	7·2	Flat
6	46	M	–	1	–	–	+	+	24·3	7·62	
7	40	F	–	2	–	+	–	+	24·0	7·15	
8*	28	M	+	2	–	–	–	–	24·7	8·98	
9	19	M	+	2	–	+	–	+	24·0	5·15	Flat
10	19	F	–	2	–	–	–	+	17·4	4·47	Flat
11	43	M	–	1	–	–	+	–	24·2	13·33	
Mean SD	36 (11)								27·2 (6·0)	8·47 (2·52)	

*Patient taking amiodarone. FHSD, family history of premature sudden death and HCM; NYHA, New York Heart Association dyspnoea classification; SVT, history of supraventricular tachycardia; VT, non-sustained ventricular tachycardia during 48 h ambulatory electrocardiographic monitoring; ExST, ⩾ 1 mm ST segment depression during exercise testing; Vo_2 max, maximal oxygen capacity during exercist testing; Ex time, exercise duration; ExBP, exercise blood pressure response (see text).

give written, informed consent before entry into the study.

HCM

Eleven patients (eight men, three women; mean (SD) (range) age 36 (11) (19–53) years) with HCM were studied (table 1). HCM was defined by characteristic clinical, echocardiographic, and haemodynamic features.[15 16] All patients had left ventricular hypertrophy ⩾ 1·5 cm on cross sectional echocardiography, in the absence of any other cardiac or systemic cause. Patients with a blood pressure of ⩾ 165/95 mm Hg or a history of systemic hypertension, or both, were excluded. Nine patients had a history of typical angina pectoris on exertion. The remaining two patients (numbers 6 and 11) had occasional episodes of typical exertional angina, but their chest pain was more usually atypical—that is, occurred at rest or lasted for more than 30 min duration without evidence of infarction. Coronary arteriography showed no evidence of large vessel coronary disease in the five patients aged ⩾ 40. Younger patients did not undergo coronary arteriography.

Cross sectional and M mode echocardiography were performed using conventional techniques.[17 18] All patients had a resting peak systolic left ventricular outflow gradient < 30 mm Hg (table 2). Left ventricular thickness was recorded in the anterior and posterior septum and the free and posterior left ventricular wall at the mitral valve and papillary muscle level. Accurate posterior wall measurements could not be obtained at the mitral level in patient number 7. Poor visualisation and a fibromuscular band precluded determination of all left ventricular dimensions at the mitral valve level in patient number 11.

Seven patients fulfilled electrocardiographic criteria for left ventricular hypertrophy—that is, Romhilt score of ⩾ 5,[19] and had ST segment depression of ⩾ 1 mm present in one or more leads of the baseline electrocardiogram. One of the remaining four patients had ⩾ 1 mm ST segment depression in one or more leads.

All patients underwent symptom limited exercise testing using the Bruce protocol. Six patients had at least 1 mm ST segment depression from baseline at peak exercise. Four patients had a "flat" exercise blood pressure response—that is, a systolic blood pressure rise of less than 20 mm Hg above the resting value.[20]

Controls

Six control patients (two men, four women; mean (SD) (range) age 49 (11) (31–62) years) were studied. They were selected from patients consecutively referred for coronary angiography as part of the investigation of atypical chest pain. Symptom limited exercise tests were normal in all patients. No patient had valvular heart disease or left ventricular hypertrophy on cross sectional echocardiography. Two patients had borderline hypertension—that is, systolic blood pressure 160–165 mm Hg and diastolic 90–95 mm Hg. Three patients had a family history of coronary artery disease, three were active smokers, and one

Table 2 Baseline echocardiographic data in patients with hypertrophic cardiomyopathy

Patient no	Mitral valve				Papillary muscle				Grad (mm Hg)	LA size	LVED	LVES
	Ant septum	Post septum	Free wall	Post wall	Ant septum	Post septum	Free wall	Post wall				
1	10	12	9	12	19	13	7	12	6	37	49	29
2	12	12	19	11	17	19	22	18	0	56	52	30
3	11	9	8	12	16	11	8	11	0	28	36	16
4	35	17	10	10	27	20	10	12	12	40	35	22
5	27	13	13	10	21	28	12	10	26	50	49	26
6	18	10	11	18	20	15	21	23	0	52	50	30
7*	16	16	14	—	14	23	11	12	0	49	45	31
8	21	16	10	13	16	15	10	9	16	41	38	23
9	15	17	12	11	16	17	14	14	0	46	45	24
10	17	11	11	12	19	16	14	19	6	47	40	24
11*	22	—	—	—	18	18	11	13	0	34	40	20
Mean (SD)	19 (7)	13 (3)	12 (2)	12 (3)	19 (4)	18 (5)	14 (4)	13 (5)	6 (9)	44 (8)	44 (6)	25 (4)

All measurements in millimetres. *See text. Ant, anterior; Post, posterior; Grad, peak resting outflow gradient; LA, left atrium; LVED, left ventricular end diastolic cavity dimensions; LVES, end systolic cavity dimensions.

Table 3 Results of dipyridamole pH study and thallium-201 scintigraphy in patients with hypertrophic cardiomyopathy

Patient no	*Max pH change*	*Time max pH change (s)*	*ST dep*	*SBP base*	*SBP dip*	*DBP base*	*DBP dip*	*HR base*	*HR dip*	*RPP base*	*RPP dip*	*^{201}TI defects*	
												Reversible	*Fixed*
1	0·025	50	−	114	114	70	69	77	89	8778	10 146	—	—
2	0·086	410	+	147	147	76	85	75	98	11 025	14 406	—	—
3	0·275	610	−	112	125	66	75	82	110	9184	13 750	—	—
4	0·015	270	−	138	147	74	75	72	85	9936	12 495	A,L	—
5	0·11	210	−	110	130	70	85	86	110	9460	14 300	A,I	—
6	0·015	140	−	107	158	57	80	55	80	5885	12 640	—	Ap
7	0·026	310	−	128	137	76	87	70	90	8968	12 330	—	A
8	0·114	360	−	129	135	74	71	75	90	9675	12 150	—	—
9	0·169	470	+	144	165	70	87	100	115	14 400	18 975	A	—
10	0·066	490	+	107	110	57	58	70	88	7490	9680	A,S	—
11	0·000	-	−	148	153	83	87	72	102	10 656	15 606	—	—
Mean (SD)	0·082 (0·083)	332 (171·2)		126 (17)	138 (18)	70 (8)	78 (10)	76 (11)	96 (12)	9586 (2141)	13 316 (2576)		

A, anterior; Ap, apical; I, inferior; S, septal; L, lateral; ST dep, ⩾ 1 mm ST segment depression (from baseline) during dipyridamole infusion; DBP/DBP base/dip, maximum systolic and diastolic blood pressure at baseline and during dipyridamole infusion (mm Hg); HR base/dip, maximum heart rate at baseline and during dipyridamole infusion (beats/min); RPP base/dip, heart rate systolic pressure product at baseline and during dipyridamole infusion.

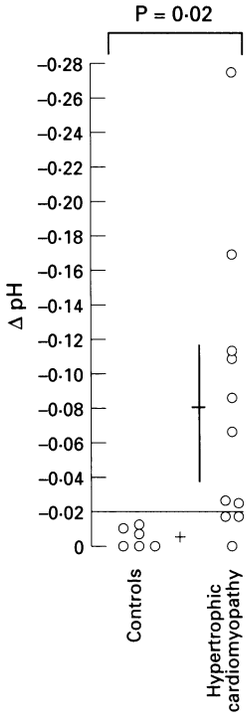

Figure 1 Maximum change in coronary sinus pH during dipyridamole infusion in controls and patients with hypertrophic cardiomyopathy. Means (SD) are shown.

had a cholesterol of > 250 mg/dl (> 6·5 mmol/l). Coronary arteriography was normal in all patients.

CORONARY SINUS pH MEASUREMENT

Cardioactive medication was discontinued for at least five half lives before evaluation. One patient with HCM was receiving amiodarone 200 mg daily (serum levels 0·4 mg/l); the drug was not discontinued because of its long half life. Substances containing theophylline or caffeine were avoided for at least 48 h before study.

Electrodes were constructed according to a previously published protocol.[13] A fine Trimel (Johnson Matthey, London) coated silver wire was threaded through medical grade polyethylene tubing (0·9 mm external diameter, 125 cm long). The terminal 1 cm of insulation was removed from the silver wire and a silver chloride coating applied electrolytically. The silver chloride electrode was withdrawn into the polyethylene tubing, and an internal buffer solution (citrate buffered saline) introduced. A gap of 1 cm was left at the end of the tubing, into which a porous ceramic plug was inserted. A membrane of a pH sensitive ligand (tridodecyclamine; Fluka AG, Switzerland) was then applied by dip coating four or five times. Once dry, the end of the electrode was gently shaken to make contact between the internal electrolyte solution and the ceramic plug.

The electrode was insensitive to oxygen and ions other than hydrogen with an output equal to the theoretical Nernst equation. All electrodes were calibrated and tested before each study. Only electrodes that demonstrated a linear reproducible response to pH in the range of 6–8 units were used. Electrodes were sterilised before each study in aqueous glutaraldehyde. A 7 French gauge Cournand catheter (Cordis, Miami) was introduced under fluoroscopic control into the coronary sinus through the left subclavian vein. The tip was positioned just before the great cardiac vein (confirmed by contrast injection). The pH electrode was passed through the catheter, so that its tip protruded 1 cm from the end. A reference electrode (K4112; Radiometer, Copenhagen) was positioned at the proximal end of the coronary sinus catheter through a Y adapter. The electrode was then allowed to stabilise for 10 min before each study. Dipyridamole (0·56 mg/kg) was administered over 4 min by a peripheral cannula. Changes in coronary sinus pH, heart rate, and blood pressure were monitored continuously for 10 min after dipyridamole infusion. Changes in pH were calculated from the change in millivolts using the Nernst equation.

Electrocardiograms were performed before and after the study and every 2 min after dipyridamole injection using a Marquette system (Marquette Electronics, Diagnostic Division, Milwaukee, WI).

^{201}TI SINGLE PHOTON EMISSION TOMOGRAPHY

Dipyridamole ^{201}TI single photon emission computed tomography was performed in all patients with HCM (on a separate occasion) according to a previously published protocol[21] using a wide field gammacamera (400T; General Electric). Regional perfusion was visually assessed from a bull's-eye polar coordinate map.

Redistribution of TI tracer was determined by comparing the immediate with the delayed image at 3 h. ^{201}TI perfusion defects were classified as "transient" or "fixed".

STATISTICAL ANALYSIS

All values are expressed as mean (one SD). Statistical analysis was performed using Student's *t* test for paired and unpaired observations (two tailed). A p value of ⩽ 0·05 was considered significant.

Results

ELECTROCARDIOGRAPHIC CHANGES

All patients with HCM experienced chest pain during dipyridamole infusion. Chest pain was associated with ⩾ 1 mm ST segment depression from baseline at 80 ms after the J point in one or more leads in three patients (table 3). Of these, only one had a maximal heart rate of > 100 beats/min.

CORONARY SINUS pH

The maximal change in coronary sinus pH was significantly greater in patients with HCM than in controls (0·082 (0·083) units (range 0 to − 0·275) *v* 0·005 (0·006) (range 0 to − 0·012) in controls, P = 0·02) (fig 1).

In six patients with HCM (four men; mean age (SD) (range) 29 (9) (19–40) years) chest

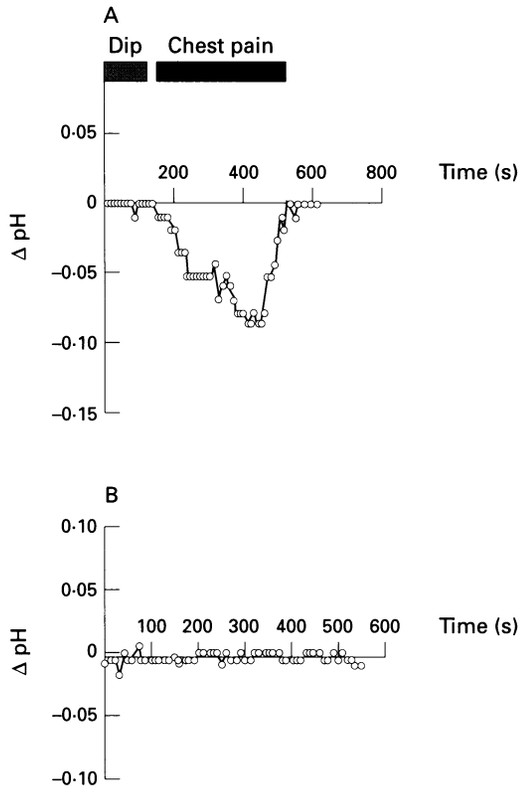

Figure 2 (A) Change in coronary sinus pH after dipyridamole infusion in a 39 year old patient with hypertrophic cardiomyopathy, showing relation between coronary sinus pH and chest pain. Dip, dipyridamole infusion. (B) Coronary sinus pH during dipyridamole infusion in 55 year control patient with atypical chest pain illustrating a "flat" response.

pain was associated with a gradual decline in coronary sinus pH of $\geq$ 0·02 pH units from baseline (mean (SD) 0·123 (0·089), peaking at 442 (106) s (fig 2(A)). With the resolution of symptoms coronary sinus pH returned rapidly to baseline. The maximum pH change (0·11 units) was of short duration (< 10 s) in patient number 5. In the remaining four patients with HCM (including the two individuals with atypical chest pain) and all the controls the response of coronary sinus pH during dipyridamole stress was flat, with only brief deviations ($\leq$ 10 s) of $\leq$ 0·025 units from the baseline value (fig 2(B)).

Dipyridamole produced a significant increase in rate pressure product in the HCM group (9586 (2141) to 13 316 (2576); P < 0·0001) due to an increase in heart rate (76 (11) to 96 (12) beats/min; P < 0·0001) and systolic blood pressure (126 (17) to 138 (18) mm Hg, P < 0·02). In patients with HCM there was a correlation between maximum pH change and peak heart rate during dipyridamole infusion (r = 0·70, P = 0·02) but not with rate pressure product at rest or during dipyridamole infusion.

RELATION TO ECHOCARDIOGRAPHY, EXERCISE TESTING AND ^{201}TI SCINTIGRAPHY

Maximum pH change correlated with neither left ventricular cavity dimensions nor left ventricular wall thickness at the mitral or papillary muscle level in patients with HCM.

The mean (SD) maximal pH change in patients with $\geq$ 1 mm ST segment depression during exercise testing was 0·095 (0·109) versus 0·051 (0·046) in patients without ST segment depression (P = not significant). Three of the six patients with a gradual decline in pH had a flat blood pressure response during exercise testing. There was no relation between maximum pH change and maximal oxygen consumption during exercise (r = 0·53, P = 0·09) or total exercise time (r = 0·57, P = 0·19).

Four patients had one or more reversible ^{201}TI perfusion abnormalities. The maximum pH change in this group was 0·090 (0·065) versus 0·077 (0·096) in patients without reversible defects (P = not significant). Two of the six patients with a gradual decline in coronary sinus pH had reversible defects.

Two of the three patients with ST segment depression ($\geq$ 1 mm from baseline) during dipyridamole infusion had reversible defects.

Discussion

The presence of angina pectoris in patients with HCM[1] and normal coronary arteriograms suggests that myocardial ischaemia is a factor in the pathophysiology of the disease. Clinical evaluation of ischaemia in HCM by conventional techniques is problematic as baseline electrocardiographic abnormalities are common and reversible ^{201}TI defects correlate poorly with anginal symptoms.[3 5-8] There are also conflicting data on the association between ^{201}TI perfusion abnormalities and "metabolic" markers of ischaemia.[3 22] The present study shows that dipyridamole infusion causes a decline in coronary sinus pH in patients with HCM and chest pain, indicating that myocardial ischaemia is important in the pathophysiology of this disease. The poor correlation between "ischaemic" ^{201}TI perfusion defects and pH changes is entirely consistent with previously published reports, although the small size of the patient cohort precludes any definitive conclusions.

Previous studies in patients with HCM have used myocardial lactate extraction as a surrogate metabolic marker of myocardial ischaemia. In a study of 20 patients with HCM, Cannon *et al*[9] investigated changes in great cardiac vein blood flow and lactate consumption during rapid atrial pacing and found that coronary blood flow fell in 18 patients when the pacing rate was increased to 150 beats/min. This fall was associated with a rise in left ventricular end diastolic pressure, chest pain, and a reduction in mean lactate consumption at the peak pacing rate. Net lactate production, however, was shown in only six patients, demonstrating the now widely recognised limitations of conventional coronary sinus lactate studies. The technique is subject to sampling errors, particularly when the myocardial lactate arteriovenous difference is small—that is, approaches the limits of sensitivity of most methods for lactate determination,[10 11] and the determination of absolute rates of lactate uptake or release require the use of labelled substrate.[23]

Coronary sinus pH measurement using an ion selective electrode has several potential advantages over venous sampling methods, including continuous monitoring, a rapid response, and independence from changes in coronary sinus blood flow.[12-14] It does, how-

ever, share the disadvantage of being unable to detect ischaemia in that part of the myocardium not drained by the coronary sinus. In 1982, Cobbe and Poole-Wilson[12] used the technique to study 20 patients with effort angina during incremental atrial pacing. They showed that patients with chest pain or ST segment depression, or both, during pacing ("ischaemic group") had a significantly greater decline in coronary sinus pH compared with those individuals without symptoms or electrocardiographic changes ("non-ischaemic group"). In a later study of eight patients undergoing percutaneous transluminal angioplasty, Crake *et al*[14] showed a decline in coronary sinus pH of between 0·01 and 0·12 units after balloon inflations of $\geqslant$ 15 s. In both studies the maximal change in coronary sinus pH occurred immediately after withdrawal of the ischaemic stimulus, suggesting that it was caused by the "washout" of ischaemic metabolic byproducts after restoration of flow to the relevant myocardial segment(s). In the present study, many patients with HCM demonstrated a characteristic slow decline in pH in parallel with symptoms peaking at a time approximating with the predicted maximal effect of dipyridamole.[24] Dipyridamole produces microvascular vasodilatation that, in patients with clinically significant coronary atheroma, induces ischaemia by producing a "steal" phenomenon in myocardium supplied by diseased vessels.[24] In patients with HCM and normal epicardial vessels the mechanism of dipyridamole induced ischaemia is probably multifactorial, but the "small vessel" disease described by Maron *et al*[25] and other workers[26] may result in a similar redistribution of blood away from myocardium subtended by narrowed and thick walled arterioles. Under different physiological conditions other factors, such as an increase in the extravascular component of coronary resistance,[27] inadequate microvascular blood flow in relation to increased myocardial mass,[28] septal perforator artery compression, and raised intracavity diastolic pressures,[9] may also contribute. In the present study there was a correlation between maximal heart rate and pH change. This may be explained simply by the associated increase in cardiac workload, but it is also possible that the increase in heart rate indirectly reflected the degree of dipyridamole induced coronary vasodilatation and, therefore, the magnitude of "coronary steal".[24]

The present study provides further evidence that chest pain in patients with HCM is caused by myocardial ischaemia. Continuous coronary sinus pH monitoring may help in the evaluation of patients with HCM as it provides a method for prospectively assessing the presence and effects of myocardial ischaemia in patients with the disease.

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