

Cardiac hypertrophy, hypertrophic cardiomyopathy, and hyperparathyroidism—an association

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SUMMARY Left ventricular hypertrophy (symmetric, asymmetric, or hypertrophic cardiomyopathy) is an almost invariable accompaniment of primary hyperparathyroidism. Five of 18 patients with hypertrophic cardiomyopathy had raised serum concentrations of parathyroid hormone with normal serum calcium concentrations. Left ventricular hypertrophy did not occur in any of the six patients with hypercalcaemia alone. These relations suggest that parathyroid hormone rather than a rise in the extracellular calcium concentration is associated with a spectrum of left ventricular hypertrophy.

All patients with increased circulating parathyroid hormone concentrations should have echocardiographic examination of the left ventricle. Conversely, parathyroid hormone concentrations should be measured in all patients with left ventricular hypertrophy from an unknown cause, especially those with hypertrophic cardiomyopathy.

Calcium has powerful positive inotropic and chronotropic effects on cardiac muscle.¹ Any factor that promotes transmembrane calcium flux could be involved in the pathogenesis of cardiac hypertrophy.² Prompted by the discovery that left ventricular hypertrophy (symmetric, asymmetric, or hypertrophic cardiomyopathy) is often found in our patients with primary hyperparathyroidism, we have attempted to identify further cases of primary hyperparathyroidism and also to determine whether hormone and calcium concentrations were altered in patients with hypertrophic cardiomyopathy. We also studied patients with hypercalcaemia due to causes other than hyperparathyroidism.

Patients and methods

Forty patients were studied (aged 24-80, mean 63; 15 men, 25 women). Twenty two had been fully investigated because of hypercalcaemia in the metabolic and general medical wards of this hospital at some time during the past two years. (No patient with a blood pressure >150/90 mm Hg was

included.) Sixteen of these patients were found to have primary hyperparathyroidism and six of these had had operations to remove either a parathyroid adenoma or a hyperplastic gland. The remaining six of the 22 patients were hypercalcaemic from causes other than hyperparathyroidism. In all six patients the concentration of serum calcium had been raised on several occasions for at least two years and no associated malignancy had been disclosed. We also studied 18 patients with hypertrophic cardiomyopathy diagnosed by echocardiography and, in some cases, angiography.

ECHOCARDIOGRAPHY

M mode echocardiograms were recorded with an Irex IIIB ultrasonoscope (frequency 2.25 MHz, repetition rate 1000/s). The output was displayed on a strip recorder at a paper speed of 100 mm/s with a simultaneous electrocardiogram. Records were taken with the patient in the left lateral position. Echocardiograms were recorded just above the level of the tips of the mitral valve cusps so that movement of the cusps could be observed. Care was taken to produce clear continuous endocardial echoes. Additional views were recorded to show the aortic and mitral valves. All procedures were performed by one observer (RAG) without knowledge of the patient's biochemical status. The following measurements

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Table 1 Echocardiographic data (mean (1SD)) for 40 study patients

Variable	Hypercalcaemia				Normal* (n=6)	Hypertrophic cardiomyopathy (n=18)
	Hyperparathyroidism (n=16)					
	NLV (n=1)	SLVH (n=6)	ASH (n=4)	HCM (n=5)		
LV posterior wall (mm)	10	17 (4)	9 (1)	15 (4)	10 (2)	14 (5)
LV septal thickness (mm)	10	17 (5)	19 (4)	22 (7)	11 (1)	20 (6)
LV septal:PW thickness ratio	1	1 (0.2)	2.2 (0.2)	1.5 (0.2)	1.2 (0.3)	1.5 (0.4)
LV End systolic dimension (mm)	28	24 (4)	25 (7)	21 (6)	30 (5)	23 (5)
Septum to mitral valve (mm) at onset of systole	28	23 (4)	26 (5)	21 (2)	26 (3)	22 (7)
SAM (%)	0	0	0	20	0	56
Premature AV closure (%)	0	0	0	20	0	11

*Normal parathyroid functions. NLV, normal left ventricular dimensions; SLVH, symmetric left ventricular hypertrophy; ASH, asymmetric septal hypertrophy; HCM, hypertrophic cardiomyopathy; LV, left ventricle; AV, aortic valve; SAM, systolic anterior motion of the mitral valve; PW, posterior wall.

were obtained over five cycles and a mean value was calculated: (a) End diastolic posterior wall thickness and septal thickness were estimated at the onset of the Q wave. A posterior wall thickness of > 10.5 mm and a septal thickness of > 11 mm at end diastole were regarded as abnormal as was a septal to posterior wall ratio of $> 1.3:1$. (b) Left ventricular cavity dimension was estimated at end systole—that is the minimum dimension. (c) The distance from the endocardial surface of the septum to the mitral valve at the onset of systole was estimated. (d) The presence or absence of systolic anterior motion of the mitral valve and mid-systolic closure of the aortic valve were noted.

Echocardiograms were classified as normal, symmetric left ventricular hypertrophy, asymmetric hypertrophy, or hypertrophic cardiomyopathy according to the criteria of Gibson *et al*³ and Doi *et al*.⁴

None of the patients had clinical or echocardiographic evidence of valvar heart disease.

OTHER INVESTIGATIONS

Plasma calcium, phosphate, alkaline phosphatase, urea, electrolytes, and creatinine were measured on a SMAC Technician AutoAnalyzer. Serum parathyroid hormone concentration was measured by a

radioimmunoassay (Immunonuclear Co-operative Corporation, Stillwater, Minnesota, USA) with an antibody specific for the mid-molecular peptide of parathyroid hormone. In our hands the sensitivity of this assay is 10 pmol/l and intra-assay variation is less than 10%. This assay method is based on that described by Roos *et al*.⁵ The normal reference range for parathyroid hormone in our laboratory is 20–85 pmol/l. The biochemical results for this study were those recorded at the time of the diagnosis of each patient.

Results

In all patients with hypertrophic cardiomyopathy the posterior wall was ≥ 8 mm thick and the septum was ≥ 15 mm. Patients with symmetric left ventricular hypertrophy also had posterior wall and septal thickness greater than 13 mm. Patients with asymmetric septal hypertrophy had a posterior wall thickness greater than 7 mm but a septal thickness of greater than 12 mm. Table 1 gives details of all measurements.

Table 2 shows biochemical data for all 22 patients presenting with hypercalcaemia. There were two groups of patients: those in whom parathyroid hormone concentration was raised and those in whom it

Table 2 Biochemical data (mean (1SD)) in 22 patients presenting with hypercalcaemia

	Calcium (mmol/l)	Phosphate (mmol/l)	AP (IU/l)	PTH* (pmol/l)
Hypercalcaemic with raised PTH (n=16):				
Normal LV dimensions (n=1)	2.94	0.88	160	260
Hypertrophic cardiomyopathy (n=5)	2.96 (0.35)	0.89 (0.13)	110 (41)	220 (100–1000)
Asymmetric septal hypertrophy (n=4)	2.98 (0.15)	0.8 (0.25)	170 (110)	300 (160–420)
Symmetric LV hypertrophy (n=6)	2.97 (0.33)	0.79 (0.14)	110 (80)	320 (140–1000)
Hypercalcaemic with normal PTH concentration (n=6)	2.73 (0.09)	0.83 (0.08)	77 (26)	55 (40–70)

*Median (range). AP, alkaline phosphatase; LV, left ventricle; PTH, parathyroid hormone.

Table 3 Biochemical data (mean (1SD)) in 18 patients presenting with hypertrophic cardiomyopathy

	Calcium (mmol/l)	Phosphate (mmol/l)	AP (IU/l)	PTH* (pmol/l)
Patients with normal PTH concentration (n=13)	2.43 (0.12)	1.07 (0.12)	74 (18)	50 (25–77)
Patients with raised PTH concentration (n=5)	2.37 (0.08)	1.14 (0.13)	94 (52)	135 (89–350)

*Median (range). AP, alkaline phosphatase; PTH, serum parathyroid hormone.

was normal.

Of 16 patients with primary hyperparathyroidism, five had hypertrophic cardiomyopathy, six had symmetric left ventricular hypertrophy, and four had asymmetric septal hypertrophy. One patient had no echocardiographic abnormalities. No echocardiographic abnormality was seen in any of the six hypercalcaemic patients without hyperparathyroidism.

Parathyroid hormone concentration was raised in five of the 18 patients with hypertrophic cardiomyopathy. None of the patients had hypercalcaemic, hyperphosphataemic, or renal failure to explain the increase in parathyroid hormone concentration (Table 3).

In patients with primary hyperparathyroidism, serum concentrations of calcium, phosphate, alkaline phosphatase, and parathyroid hormone were similar in those with hypertrophic cardiomyopathy, symmetric left ventricular hypertrophy, or asymmetric septal hypertrophy.

Discussion

Our data show that primary hyperparathyroidism is almost invariably associated with left ventricular hypertrophy in its various forms. Five of sixteen patients with hyperparathyroidism had hypertrophic cardiomyopathy. We found no echocardiographic evidence of myocardial hypertrophy in patients with hypercalcaemia due to causes other than primary hyperparathyroidism; all patients in this group had low or non-detectable serum concentrations of parathyroid hormone. McFarland *et al* have suggested that hypertrophic cardiomyopathy may be related to the prolonged stimulus provided by hypercalcaemia.⁶ From our study, it seems that myocardial hypertrophy (including hypertrophic cardiomyopathy) is primarily associated with parathyroid hormone itself and not with a raised concentration of extracellular calcium.

The high frequency of increased parathyroid hormone concentrations in patients who presented with clinical and echocardiographic features of hypertrophic cardiomyopathy, suggests an association between raised concentrations of this hormone and

hypertrophic disease. Five of 18 patients with hypertrophic cardiomyopathy had increased serum concentrations of parathyroid hormone with normal serum concentrations of calcium and phosphate and no renal failure. As far as is known, the mid-molecular assay is specific for parathyroid hormone but we cannot exclude the possibility that the immunoassay was detecting some similar but distinct peptide with a direct effect on cardiac muscle calcium flux. The high frequency of raised serum concentrations of parathyroid hormone in our patients with hypertrophic cardiomyopathy contrasts with the results of McFarland *et al* who found raised hormone concentrations in only two of 32 cases of hypertrophic cardiomyopathy.⁶ This difference may have been due to the different assays used in the two studies.

Parathyroid hormone has a positive chronotropic effect on myocardial cells in culture and its action is mimicked by calcium ionophore and blocked by verapamil.⁷ In hamsters with congenital myopathy there was an increase in intracellular calcium concentrations in skeletal muscle; after parathyroidectomy the intracellular calcium concentration fell and myopathy improved.⁸ Parathyroid hormone has also been shown to have a positive inotropic effect on the rat heart at physiological concentrations.⁹ Since this action is also blocked by verapamil, it must be directly related to the movement of calcium into the myocardial cell. These experimental data indicate that parathyroid hormone has a direct effect on the myocardium which is mediated by an influx of calcium. Such positive chronotropic and inotropic effects are consistent with the possibility that in the long term the maintenance of high concentrations of parathyroid hormone may result in cardiac hypertrophy. Hypertrophy and disarray of the cardiac muscle fibril, identical to that seen in hypertrophic cardiomyopathy, has been produced experimentally by substances which disturb membrane stability, such as triac and calcium ionophore,^{2,10} and parathyroid hormone could act in a similar way. The time that has elapsed since some of our patients had parathyroidectomy is not sufficient to assess whether myocardial hypertrophy has regressed. Clinical evidence suggests that

improvement will occur.¹¹ Experiments aimed at investigating the structure and function of the myocardium using a parathyroid hormone stimulus are underway in our laboratory and are designed to define both the mode of action of the hormone and to build a model of increasing ventricular hypertrophy.

Our data indicate that all patients with hyperparathyroidism should be examined by echocardiography so that the presence of myocardial hypertrophy will not be missed. Conversely, serum concentrations of parathyroid hormone should be measured in all patients with left ventricular hypertrophy from an unknown cause, (especially those with hypertrophic cardiomyopathy) so that any parathyroid abnormality can be treated. Most of our patients with raised serum parathyroid hormone concentrations had normal electrocardiograms and none was hypertensive. Females predominated in the present series and this may be because of the small numbers of patients studied.

In conclusion, an association between cardiac hypertrophy (symmetric, asymmetric, and hypertrophic cardiomyopathy) and an increased concentration of parathyroid hormone has been demonstrated that is independent of hypercalcaemia. For the first time a pattern of cardiac muscle hypertrophy clearly related to an hormonal abnormality has been shown to occur. This adds another dimension to the understanding of a possible cause of idiopathic ventricular hypertrophy and even suggests that hypertrophic cardiomyopathy could be one form of end stage exuberant cardiac muscle hypertrophy. Further elucidation of the role and nature of parathyroid hormone in relation to ventricular hypertrophy and of a causal link between hyperparathyroidism and all forms of ventricular hypertrophy, including hypertrophic cardiomyopathy, is awaited.

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