EXEMPLAR

Reversible ischaemia in hypertrophic cardiomyopathy

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Abstract

Atypical and typical chest pains are common symptoms in patients with hypertrophic cardiomyopathy. Some of these chest pains seem to be caused by ischaemia. It is difficult to objectively demonstrate ischaemia in hypertrophic cardiomyopathy. The first line treatment for chest pain considered to be ischaemic in patients with hypertrophic cardiomyopathy is the use of either a β blocker or calcium blocker. Septal myectomy can be effective in patients with symptoms refractory to conventional treatment but is associated with significant morbidity and mortality. Recently dual chamber pacing has been advocated in such patients. In some cases dual chamber pacing alleviates chest pain in hypertrophic cardiomyopathy by an anti-ischaemic action, presumably by reducing the left ventricular outflow tract gradient and perhaps by causing an associated decrease in left ventricular outflow tract gradient and perhaps by causing an associated decrease in left ventricular end diastolic pressure.

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Hypertrophic cardiomyopathy is an autosomal dominant heart muscle disease that seems to be the phenotypic expression of at least several genotypic abnormalities. Prevalence of hypertrophic cardiomyopathy is 20 in 100 000 individuals—that is 0.02%.¹ The major importance of the condition lies in its propensity to cause sudden death but there is also associated morbidity. The clinical picture varies; some patients are entirely free of symptoms, while others are severely incapacitated. Common symptoms include breathlessness, palpitations, syncope, and chest pain.

Chest pain is a common symptom²⁻⁴ (occurring in 22 of 64 patients in the original series of Braunwald *et al.*²). A history of typical exertional angina is suggestive of hypertrophic cardiomyopathy in many patients but in others the history does not suggest classical

angina and in some there is a mixture of typical and atypical chest pains. In a substantial proportion of patients the chest pains probably reflect underlying myocardial ischaemia.

Multiple evidence points to the importance of myocardial ischaemia in patients with hypertrophic cardiomyopathy. Maron *et al.*^{5,6} described small vessel disease in patients with hypertrophic cardiomyopathy which was characterised by thickening of the vessel wall with proliferation of medial and intimal components and a decrease in luminal size. These vascular abnormalities were located adjacent to areas of myocardial fibrosis suggesting that they may result in ischaemic myocardial damage.^{5,6} The presence of abnormal small vessels in some infants who died of hypertrophic cardiomyopathy implies that the abnormality may be present from birth as part of the developmental abnormality in hypertrophic cardiomyopathy.^{5,6} In one study coronary blood flow was increased at rest in patients with hypertrophic cardiomyopathy and during incremental pacing initially rose normally but at higher pacing rates decreased in association with metabolic evidence of cardiac ischaemia and a rise in left ventricular end diastolic pressure.⁷ Positron emission tomography has demonstrated resting regional disparity of myocardial perfusion and metabolism with depressed perfusion and decreased accumulation of palmitate and deoxyglucose labelled with fluorine-18 in the interventricular septum.⁸ In another study positron emission tomography demonstrated reduced regional myocardial blood flow in the presence of maintained glucose uptake suggesting discordance between flow and glucose metabolism.⁹

Factors believed to be involved include increased myocardial oxygen demand due to hypertrophy and reduced coronary perfusion especially in subendocardial muscle.¹⁰ The latter is partly caused by left ventricular end diastolic pressure but thickening of the intramural small vessels may be contributory.^{6,11} Systolic compression of the septal perforating arteries is well documented in patients with hypertrophic cardiomyopathy but the pathophysiological significance is unclear.¹² In older patients with hypertrophic cardiomyopathy obstructive atheromatous disease of the epicardial coronary arteries may also be present.¹³

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It is difficult to demonstrate objectively ischaemia in patients with hypertrophic cardiomyopathy in clinical practice. The resting electrocardiogram frequently shows repolarisation abnormalities and interpretation of thallium scans is difficult, in part because of differences in regional myocardial mass. One report demonstrated an association between reversible thallium abnormalities and chest pain¹⁴ but others have not found this relation.¹⁵ A recent report demonstrated that while reversible perfusion defects were not associated with chest pain, there was an association with reduced global and regional thallium washout.¹⁶ While the association with chest pain is poor, Cannon *et al*¹⁷ demonstrated convincingly that reversible thallium defects are associated with cardiac ischaemia in patients with hypertrophic cardiomyopathy. A recent study demonstrated that thallium evidence of ischaemia was more common in young patients with hypertrophic cardiomyopathy who had suffered a previous cardiac arrest or syncope compared with that in similar patients without a history of these features suggesting that ischaemia may contribute to the mechanism of sudden death.¹⁸ Ischaemia may contribute to late systolic failure seen in some patients with hypertrophic cardiomyopathy¹⁹ given the finding reported by Maron *et al*^{5,6} of fibrosis in areas of small vessel disease in patients with this condition.

The first line treatment for chest pain and breathlessness in patients with hypertrophic cardiomyopathy is the use of either a β blocker or non-dihydropyridine calcium channel blocker. In the series of Kaltenbach and Hopf²⁰ 85% of patients demonstrated an improvement in symptoms of breathlessness and chest pain following the introduction of

high dose verapamil 320–720 mg and in the series of Rosing *et al*²¹ 54% were improved over long term follow up. Other studies have demonstrated symptomatic improvement with propranolol.²²

A minority of patients are severely incapacitated by chest pain or breathlessness despite maximum medical treatment. Septal myectomy and myotomy has been performed in those with obstruction. Septal myectomy can be very effective in severely symptomatic patients with outflow tract gradients but there is significant mortality and morbidity and this operation does not seem to improve prognosis.^{23,24}

Recently dual chamber (DDD) pacing has been advocated by several groups as a treatment for symptoms in hypertrophic cardiomyopathy. Some reports have demonstrated relief of chest pain and shortness of breath in such patients, particularly those with outflow tract gradients.^{25,26} The mechanism of this effect is unclear. Complete ventricular capture during DDD pacing seems important, often necessitating relatively short atrioventricular delays. Most groups have used atrioventricular blocking drugs such as verapamil to maximise the atrioventricular delay at which complete atrioventricular capture is obtained and therefore retaining as much atrial contribution to ventricular filling as possible.^{25,26} It has been proposed that the haemodynamic benefit is a consequence of paradoxical septal motion with an associated reduction in the left ventricular outflow tract gradient.^{25,26} A recent study has suggested that diastolic function may be worsened by DDD pacing in patients with hypertrophic cardiomyopathy.²⁷ The conflicting effects of reduction in left ventricular outflow tract gradients and worsening of diastolic function may explain the variable clinical responses to DDD pacing reported in the literature.

While dual chamber pacing often improves symptoms of chest pain and breathlessness in patients with hypertrophic cardiomyopathy, chest pain may not necessarily reflect ischaemia.^{15,16} To our knowledge there have been no previous studies of objective documentation of relief of ischaemia by DDD pacing reported in the literature. We report a severely symptomatic patient with hypertrophic cardiomyopathy in whom DDD pacing effected relief of chest pain and breathlessness in association with near abolition of an extensive reversible thallium defect.

Case report

A 32 year old man with known hypertrophic cardiomyopathy presented in February 1994 complaining of increasing chest pain despite treatment with propranolol which was ceased because of unacceptable fatigue. Sustained release verapamil 240 mg daily was also ineffective. He experienced typical angina pectoris at low work loads and atypical chest pain at rest. He had a jerky pulse, a double apical impulse, and a mid-systolic murmur. His

Figure 1 Stress (rows labelled 1) and rest (rows labelled 2) tomographic thallium scans before pacing. There is severely reduced thallium uptake in the interventricular septum (solid arrows), inferior wall (open arrow), and apex. Thallium uptake by the right ventricular myocardium (arrow head) is increased. Except for a small residual apical defect, left ventricular thallium uptake returns to normal at rest. Corresponding transverse (A), vertical long axis (VL), and horizontal long axis (HL) slices after dipyridamole and exercise (1) and at rest (2). Orientation is as shown in the margin. Reading from the left slices are taken from apex to base (A), septum to lateral wall (VL), and inferior to anterior (HL).

Figure 2 Repeat stress (1) and rest (2) thallium scans after pacing. There is now only a minimal reversible septal perfusion defect (arrow). Orientation and legend are as for figure 1.

electrocardiogram showed left ventricular hypertrophy with repolarisation changes and his chest radiograph was normal. The echocardiogram showed severe asymmetric left ventricular hypertrophy, the basal septum measuring 2.4 cm. There was complete systolic anterior motion of the mitral valve and a peak instantaneous left ventricular outflow tract gradient of 102 mm Hg. There was grade II mitral regurgitation. A dipyridamole and exercise stress thallium scan (fig 1) showed severe reduction in thallium uptake in the interventricular septum, inferior wall, and apex of the left ventricle associated with marked left ventricular dilatation. Repeat scan after reinjection of thallium at rest showed a reduction in left ventricular dimensions and virtually complete normalisation of thallium uptake in the hypertrophied interventricular septum and the inferior wall of the left ventricle. Cardiac catheterisation confirmed the presence of a left ventricular outflow tract peak to peak gradient of 78 mm Hg, a left ventricular end diastolic pressure of 34 mm Hg, and the absence of obstructive epicardial coronary artery disease.

Verapamil was increased progressively to 720 mg each day without significant relief of angina pectoris and was discontinued because of significant symptomatic hypotension. A Teletronics Meta DDDR 1254 DDD pacemaker (Teletronics Pacing Systems, Denver, Colorado, USA) was implanted via the right cephalic vein because of the disabling symptoms. The pacemaker was subsequently reprogrammed so that the ventricular complexes during atrioventricular sequential paced rhythm were identical to those in ventricular demand mode implying complete ventricular capture. This was achieved with an atrioventricular interval of 40 ms combined with verapamil 240 mg.

When reviewed 1 month after the procedure the patient had attained virtual complete relief of chest pain and breathlessness. He

was able to walk up hills and indefinitely on the flat. Repeat echocardiography demonstrated a 40% reduction in peak left ventricular outflow tract gradient to 64 mm Hg. During a repeat dipyridamole and exercise thallium study he achieved a high workload and experienced only mild breathlessness and fatigue with no chest pain. The stress thallium scan showed a small reversible perfusion defect involving the basal portion of the septum, but no evidence of any fixed or reversible perfusion defect in the apical or inferior segments of the left ventricle which had previously been ischaemic (fig 2). The symptomatic benefit has been maintained at 4 months follow up.

Conclusions

Myocardial ischaemia commonly occurs in patients with hypertrophic cardiomyopathy, although clinical recognition of ischaemia can be difficult. Ischaemia may be of importance in the mechanism of sudden death in young patients with the disease and may contribute to late systolic failure seen in some patients. Chest pains in patients with hypertrophic cardiomyopathy are probably often caused by ischaemia. Ischaemia may sometimes be silent. In this study we have reported a severely symptomatic patient in whom DDD pacing resulted in almost complete relief of breathlessness and chest pain, and previous extensive reversible cardiac ischaemia on thallium scans. To our knowledge there is no previous report of objective documentation of relief of ischaemia by DDD pacing. The presumptive anti-ischaemic action is achieved by reducing the left ventricular outflow tract gradient and perhaps by causing an associated decrease in left ventricular end diastolic pressure. The effects of these changes would be to depress myocardial oxygen demand and increase the transcoronary perfusion gradient.

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