BETA-ADRENERGIC BLOCKING AGENTS IN HYPERTROPHIC CARDIOMYOPATHY (HOCM)

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The aims of treatment in hypertrophic cardiomyopathy (HOCM) are to relieve symptoms, slow down the rate of progression and to reduce the risk of sudden death.

The most common symptoms in HOCM are angina and shortness of breath and fatigue on exertion (Braunwald *et al*, 1964). Angina of effort in the hugely hypertrophied heart, results from the reduced coronary flow time caused by a disproportionate rise in pulse rate on exercise and possibly also from the somewhat increased left ventricular internal stroke work. Angina is not confined, however, to those with outflow tract obstruction nor can its incidence or severity be correlated in any way with this, so that of the three contributory components the last seems to be the least important. Shortness of breath is related to a rise in left atrial pressure on exercise caused by reduction in filling rate of the incompliant left ventricle and probably inability of the left atrium to empty completely during exercise despite enhanced left atrial activity. Fatigue no doubt results from the greatly impoverished cardiac response to exercise when it can be shown that the stroke volume, instead of rising, falls in patients with HOCM and the minute output may barely rise. This results in a very poor measurable maximum work capacity. The fall in stroke volume with tachycardia again results from inability of the left ventricle to fill properly.

When spontaneous loss of obstruction occurs in patients with HOCM who have not been treated surgically this is accompanied by a rise in left ventricular end-diastolic pressure and by deterioration in symptoms rather than improvement (Goodwin and Oakley 1972, Oakley 1971). Surgical treatment carries an appreciable mortality and has not yet been shown to be followed by any definite improvement in the long term natural history.

Beta-adrenergic blocking drugs have been used in HOCM for more than five years without any hard facts emerging. Although they alleviate angina (Cohen and Braunwald, 1967), outflow tract obstruction is influenced only to a variable extent (Flamm *et al*, 1968). At the Royal Postgraduate Medical School, London, the effects of beta-adrenergic blockade on left ventricular end-diastolic pressure and stroke volume in HOCM has been examined, both acutely and also by non-invasive means during chronic oral administration. The effect of these drugs on exercise capacity has also been measured. Studies have been made of maximum work capacity with indirect cardiac output measurements before and after beta-blocking drugs have been given. The effects of chronic oral administration of beta blocking drugs was examined by a double blind trial.

The early interest in beta-adrenergic antagonists derived from suggestions that the left ventricle was hyperkinetic and that excess endogenous catecholamine activity was present, neither of which has been confirmed. The left ventricle in HOCM is by no means hyperkinetic, its function is impaired, although more so in diastole (compliance failure) than in systole. The suggestion of hyperkinesia arose because of the sudden systolic fall-off in the pulse resulting from late onset of outflow tract obstruction. This fall-off gives the pulse its jerky quality. Ejection from the left ventricle is not excessively rapid and the pulses are normal in HOCM when obstruction is mild or absent. There is, nevertheless, one aspect of the response of the HOCM heart to sympathetic stimulation which does appear to be abnormal. Isoprenaline causes a rise rather than a fall in left ventricular end-diastolic pressure and this is an almost specific feature of this disorder and one which contrasts with the fall or lack of change in pressure which is seen after isoprenaline, given both in the normal heart and in other forms of left ventricular disease. It also contrasts sharply with the fall in end-diastolic pressure which occurs in HOCM when the heart rate is increased by pacing. It is because the beta-adrenergic blocking group of drugs block these cardiac actions of adrenaline that they may be particularly helpful in the treatment of this disorder. In addition prevention of excessive tachycardia on exercise may allow the stroke volume to rise more normally, or at least not to fall, during exercise and thus combat a rise in left atrial pressure and a fall in stroke output, which together are responsible for dyspnoea, angina and sometimes for syncope and sudden death.

Practolol was chosen for the acute haemodynamic studies because of the cardioselective action without peripheral effect. A small dose was chosen in order to avoid a drop in the resting heart rate. Between 20 and 30 milligrams of practolol were given (0·3 mg. per Kg.) to six patients with HOCM during the course of diagnostic cardiac catheterization. Heart rates, cardiac output (indocyanine green dye dilution) left ventricular pressure and aortic pressure were measured at rest, during mild supine leg exercise, during atrial pacing and after intravenous injection of isoprenaline. The measurements were repeated before and after practolol was given. Before practolol all patients had abnormally high left ventricular end-diastolic pressures, and these pressures rose further on exercise (LVEDP rose from average 21 to 33 mm.Hg.). After practolol the resting LVEDP averaged 19 and rose to 24 mm.Hg. on exercise. In nearly every case the exercise was achieved at a lower LVEDP but without a fall in left ventricular stroke work. These studies which were carried out by Dr. Michael Webb-Peploe (Webb-Peploe *et al*, 1971) and Dr. John Graber (Graber *et al*, 1971) gave the first direct evidence of benefit from a beta-adrenergic blocking drug in HOCM since following acute administration of practolol, the same cardiac work was achieved at a lower LVEDP. Further studies, when left ventricular volume was also measured, showed that after practolol the same left ventricular stroke work was achieved not only at a lower LVEDP, but also at the same or higher end-diastolic volume. This observation suggested the possibility that beta-adrenergic blocking drugs may have some beneficial effect on left ventricular distensibility in HOCM.

Studies on the effect of beta-adrenergic blockade on the cardiac response to exercise in HOCM were carried out by Drs. Richard Edwards, Richard Croxson and Arni Kristinsson at the Royal Postgraduate Medical School. It was found that beta-adrenergic blockade with propranolol reduced the excessive tachycardia of exercise and permitted a rise in stroke volume, although in most cases this was achieved with a further decrease in cardiac output per minute. Nevertheless, the mechanism of improvement in angina achieved by beta-blocking agents in HOCM almost certainly occurs as in ischaemic heart disease by this limitation of exercise induced tachycardia and reduction of oxygen consumption by the heart. Nevertheless the poor circulatory response to exercise is not improved by beta-blockade in HOCM.

As a result of the acute haemodynamic studies and of the exercise studies, a double blind trial on the effects of long term oral beta-blocking agents was carried out by Drs. Peter Hubner, Galal Ziady and Geoffrey Lane at the Royal Postgraduate Medical School (Hubner *et al*, 1972). In this study propranolol was compared with practolol against a placebo tablet and the effects were judged by recording symptoms and by apex cardiography and mitral echocardiography as well as by conventional auscultatory criteria. A reduction, or even total abolition of the atrial beat of the impulse cardiogram was observed in the patients taking either practolol (800 mgm. daily) or propranolol (320 mgm. daily) but this was not found to occur in patients while they were on the placebo tablet. The ultrasound record showed evidence of an improvement in left ventricular filling with

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an increase in the speed of the diastolic closure slope, suggesting an improved rate of filling but in most cases there was no material change in the systolic pre-opening movement of the mitral valve. This is in accord with the lack of change in outflow tract obstruction seen in most patients after beta-blockade.

The reduction in left ventricular end-diastolic pressure observed in the acute haemodynamic studies (and indirectly by the loss of the atrial beat of the impulse cardiogram in the double blind study) could be attributed to a fall in left atrial contractile force caused by the beta-blocking drug. The LVEDP also showed a fall in the pre *a* wave diastolic pressure in the ventricle and the atrial re-opening movement seen on the mitral echocardiogram was not diminished. It seems likely that there is a true change in the filling characteristics of the left ventricle. Furthermore, the effect of the beta-blocking drugs is the opposite to the effect of the beta-stimulating drugs, although the effect of these could be attributed to enhancement of the force of left atrial contraction.

As a result of these studies we recommend that beta-adrenergic blocking drugs should be prescribed to all patients with HOCM after confirmation of a diagnosis and regardless of the presence and admitted extent of incapacity or of outflow tract obstruction. Since symptomatic patients without outflow tract obstruction seem to have a more severe form of the disorder and a higher chance of sudden death than patients with outflow tract obstruction, they are most likely to benefit from therapy. Syncope and sudden death, which probably follow episodes of tachycardia which have caused even greater curtailment of left ventricular filling with reduction in coronary blood flow may also be prevented by these drugs. But as yet we have no evidence on the effect on prognosis.

The dose should be a relatively high one and children tolerate beta-blocking agents well, so the dose in children should be relatively higher than for adults. 800 mg. t.d.s. of propranolol, or 800 mg. b.d. of practolol are average doses, although more can be prescribed in individual cases, depending on tolerance.

Atrial fibrillation is seen in the minority of patients with HOCM and is more common in severe cases and in older age groups. The dysrhythmia often marks the onset of serious deterioration and sometimes of congestive heart failure. Deterioration is probably related to the uncontrolled tachycardia, the irregular rate and the loss of atrial transport. Control of ventricular rate and anticoagulants to prevent embolism are important. Beta-blocking drugs alone very often adequately control the rate, but in these patients there is no contraindication to adding digoxin when the rate remains too high on beta-blocking agents alone.

Pregnancy seems to be well tolerated in HOCM in most instances, perhaps because the patients, being relatively young, are at an earlier stage of their disease. Propranolol or practolol have been given throughout pregnancy to 20 patients. All the pregnancies were successful and all the patients are still living. No undue slowing of the foetal heart rate has been noted at any stage, and neither has there been any adverse effect on uterine contraction. Caesarian section has only been implemented for obstetric indications.

SUMMARY

Diminished compliance of the left ventricle in HOCM is associated with slow diastolic filling and a marked rise in its end-diastolic pressure on effort. This accounts for the poor circulatory response to exercise when, despite excessive tachycardia, cardiac output fails to rise, stroke volume may fall and so may the blood pressure. Angina, dyspnoea and syncope are thereby explained.

It has been shown in patients with HOCM that beta-adrenergic blockade with practolol controls the exercise tachycardia and enables stroke output to be increased on effort even though minute output may show a further fall. The resulting prolongation of coronary flow time in the reduction in the metabolic cost of exercise could relieve angina as well as reduce the incidence of exercise induced syncope or dysrhythmia.

Neither propranolol nor practolol reduce the resting LV outflow tract gradient in HOCM and it is no longer believed that enhanced sympathetic control of the heart plays any part in the disease. Both propranolol and practolol prevent rises in gradient provoked by exercise or isopranaline. Both drugs reduce the resting LVEDP and diminish the rise in LVEDP induced by exercise or isopranaline.

In a double blind trial of long term oral practolol and propranolol against a placebo it was shown that the incidence of angina was reduced and that dyspnoea was improved in the treated patients. Apex cardiography revealed diminution or loss of the atrial beat suggestive of a fall in LVEDP and mitral echocardiography showed improvement in the diastolic closure rate suggestive of more normal left ventricular filling. Propranolol was slightly better than practolol.

Haemodynamic improvement has been shown to result from beta-adrenergic blockade in HOCM and this has been confirmed in clinical usage by a double blind trial. It is suggested that long germ therapy should be started on diagnosis of the disease and that this offers more hope of benefit than surgical resection of the outflow tract.

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