CASE REPORT

Reversal of severe pulmonary hypertension with β blockade in a patient with end stage left ventricular failure

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Abstract

A 52 year old man with severe chronic left ventricular failure (New York Heart Association class IV) was considered unsuitable for cardiac transplantation because of high and irreversible pulmonary vascular resistance (PVR). In an attempt to produce symptomatic improvement, metoprolol was cautiously introduced, initially at 6.25 mg twice daily. This was slowly increased to 50 mg twice daily over a two month period and continued thereafter. After four months of treatment the patient's symptoms had improved dramatically. His exercise tolerance had increased and diuretic requirements reduced to frusemide 160 mg/day only. Assessment of right heart pressures was repeated and, other than a drop in resting heart rate, there was little change in his pulmonary artery pressure or PVR. His right heart pressures were reassessed showing a pronounced reduction in pulmonary artery pressure and a significant reduction in PVR, which fell further with inhaled oxygen and sublingual nitrates. He was then accepted onto the active waiting list for cardiac transplantation. A possible mechanism of action was investigated by assessing responses to β agonists during treatment. Not only was there pronounced improvement in PVR but it was also demonstrated that β receptor subtype cross-regulation may have contributed to the mechanism of benefit.

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We report the response to β blockade in a patient with chronic left ventricular failure who was considered unsuitable for cardiac transplantation because of high irreversible pulmonary vascular resistance (PVR). After eight months of β blockade, reinvestigation showed that his PVR had fallen and had become reversible such that he is now suitable for and awaiting cardiac transplantation. This beneficial effect of β blockade on the pulmonary hypertension of left ventricular failure has not previously been described and widens further the growing indications for the use of β blockers in heart failure. In addition, we investigated a possible mechanism of benefit by measuring the patient's haemodynamic responses to β agonists before and during treatment.

Case report

The patient was a 52 year old man who presented to us in May 1993. He had had myocardial infarctions in 1986 and 1988. Significant left ventricular impairment had been documented by echocardiography in 1988. He had been taking an ACE inhibitor since 1991. He was in New York Heart Association (NYHA) heart failure class I and had no angina. Echocardiography demonstrated a dilated poorly contracting left ventricle. He was able to exercise on a treadmill for seven minutes of a standard Bruce protocol, being limited by exhaustion, without chest pain or ischaemic ECG changes. Treatment with aspirin and lisinopril (10 mg/day) were continued.

In November 1994 he was referred again because of progressive symptomatic deterioration in breathlessness. He did not have chest pain. He now had NYHA class IV heart failure. Coronary angiography demonstrated diffuse triple vessel coronary artery disease. Left ventriculography showed an ejection fraction of 10%. It was thought that surgical revascularisation would not be of benefit in the presence of such diffuse disease and in the absence of chest pain. Stress echocardiography and thallium scanning to reveal the presence of hibernating myocardium were therefore not performed. Right heart pressures revealed severe pulmonary hypertension (pulmonary artery pressure of 70/35 mm Hg) and a PVR of 440 dyn.s.cm^{-5} (table 1), which was not reversible with inhaled oxygen or sublingual nitrates. The patient's symptoms of breathlessness and peripheral oedema were barely controlled with frusemide 240 mg/day and metolazone 2.5 mg/alternate day in addition to digoxin 250 μg/day, lisinopril 10 mg/day, and warfarin. He was referred for cardiac transplantation but was not considered suitable because of his high and irreversible PVR.

Previous studies have suggested haemodynamic benefit from dobutamine[1] and salbutamol[2] infusions in patients with heart failure. However, investigations using graded

Table 1 Pressures, measured using Swan-Ganz catheter, and cardiac output, measured via thermodilution method

	November '94	*August '95*	*December '95*	*July '96*
Heart rate (beats/min)	100	78	70	72
Aortic pressure (mm Hg)	100/60	101/50	108/75	135/85
Mean pulmonary artery pressure (mm Hg)	45	42	34	34
Mean pulmonary capillary wedge pressure (mm Hg)	30	27	21	19
Pulmonary vascular resistance (dyn.s.cm^{-5})	440	307	257→157*	227→145*
Cardiac output (l/min)	3.2	3.9	3.9	4.6

*Before and after inhaled oxygen and sublingual nitrates.

infusions of dobutamine (0–16 μg/kg/min) and salbutamol (0–4 mg/kg/min) over 15 minutes each with continuous pulmonary artery pressure monitoring suggested that they would be ineffective in reducing the patient's PVR to levels suitable for cardiac transplantation. In an attempt to produce symptomatic improvement, metoprolol was cautiously introduced, initially at 6.25 mg twice daily. This was slowly increased to 50 mg twice daily over a two month period and continued thereafter. After four months of treatment the patient's symptoms had improved dramatically. His exercise tolerance had increased and diuretic requirements reduced to frusemide 160 mg/day only. Assessment of right heart pressures was repeated and, other than a drop in resting heart rate, there was little change in his pulmonary artery pressure or PVR (table 1).

In December 1995 his right heart pressures were reassessed (table 1); there was a pronounced reduction in pulmonary artery pressure (48/24 mm Hg) and a significant reduction in PVR to 257 dyn.s.cm^{-5}, falling to 145 dyn.s.cm^{-5} with inhaled oxygen and sublingual nitrates. He was accepted onto the active waiting list for cardiac transplantation.

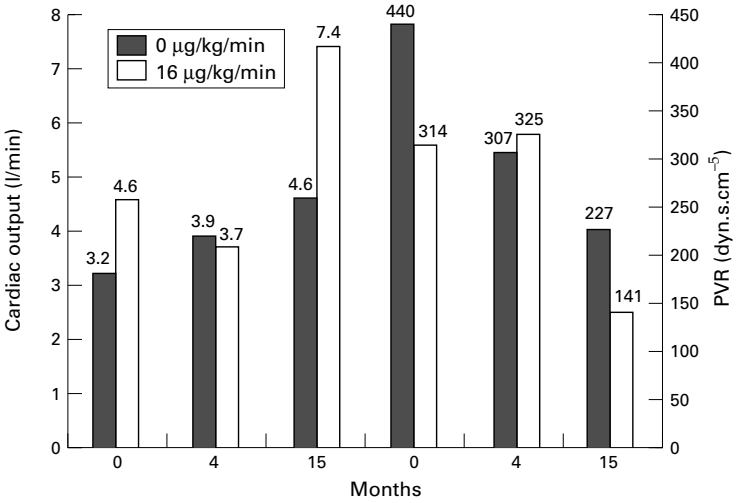

Figure 1 Cardiac output and pulmonary vascular resistance (PVR) with infusion of dobutamine at 0, 4, and 15 months after metoprolol.

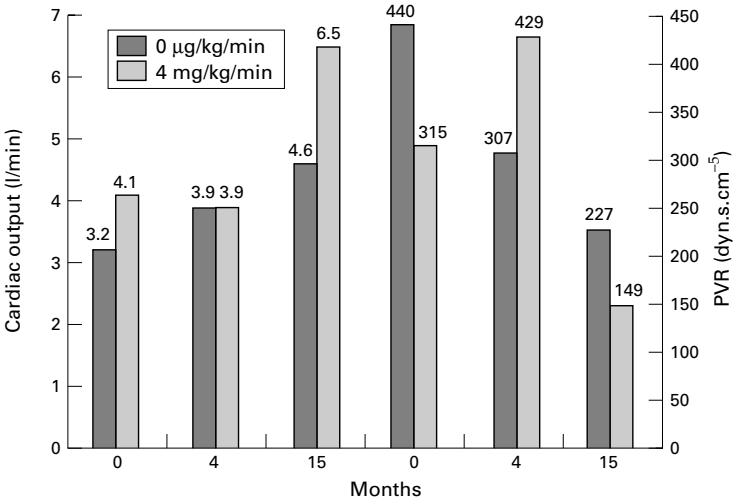

Figure 2 Cardiac output and pulmonary vascular resistance (PVR) with infusion of salbutamol at 0, 4, and 15 months after metoprolol.

Discussion

Attention has focused in recent years on the contribution of neurohormonal mechanisms to the development and progression of heart failure. Both activation of the renin–angiotensin system and the sympathetic adrenergic system occur in response to left ventricular dysfunction, and chronic activation of these systems may be further detrimental to myocardial function.[3] Not only do catecholamine concentrations correlate with the severity of left ventricular dysfunction but they are independent risk factors of poor prognosis.[4]

Several studies—CONSENSUS (cooperative north Scandinavian enalapril survival study),[5] SOLVD (studies of left ventricular dysfunction),[6] VeHFT-II (verapamil in heart failure)[7]—have demonstrated both symptomatic improvement and mortality benefits from inhibition of the renin–angiotensin system in patients with heart failure. The effects of inhibition of the adrenergic system are less clear. A number of studies have shown β blockers to have beneficial effects on morbidity.[8 9] However, only one recent trial involving carvedilol has demonstrated any mortality benefits.[10] The mechanism by which β blockers exert their beneficial effects in heart failure is unclear. Differential modulation of β receptor subtypes may be important. Cardiac β1 receptor density is decreased in the failing heart, which renders it insensitive to β1 stimulants both in vivo[11] and in vitro.[12] This downregulation of β1 receptors has been attributed to high circulating concentrations of noradrenaline.[13 14] Cardiac β2 receptor function in the failing heart is also altered and appears to be due to uncoupling of the β2 receptor to the G protein–adenylate cyclase complex.[15] A decreased heart rate response to β2 agonism in heart failure has been observed.[16] Having assessed our patient's haemodynamic responses to dobutamine (a β1 agonist) and salbutamol (a highly selective β2 agonist) before metoprolol treatment, we were able to repeat these studies after β blockade to investigate its effect on β1 and β2 responsiveness.

Before metoprolol, a graded infusion of dobutamine produced a modest rise in cardiac output and a modest fall in PVR (fig 1). After four months the response to dobutamine was blunted, there being no significant change during the infusion (fig 1). After 15 months, there was a profound increase in the sensitivity of the heart to the dobutamine infusion with a more pronounced rise in cardiac output and fall in

PVR (fig 1). Responses to salbutamol showed a similar pattern (fig 2). Early clinical improvement at four months was associated with blunted responses to β agonists and the persistence of high pulmonary artery pressures. It was only after sustained β blockade that increased sensitivity to β agonists was found with a concomitant improvement in pulmonary hypertension.

The enhanced response to β agonists at 15 months could be explained by β adrenoceptor subtype crossregulation by β1 blockade with metoprolol. Previous studies have shown an increase in β2 responsiveness after β1 blockade in vitro[17] and in vivo.[18] This appears to be selective for cardiac β2 receptors.[19] The increase in dobutamine sensitivity might be due to the relatively poor selectivity of dobutamine for β1 receptors in man[20]—that is, dobutamine acting through β2 receptors in a patient whose β2 receptors have been sensitised by β1 blockade. Heilbrunn *et al* demonstrated a similar increase in sensitivity to dobutamine after six months of metoprolol treatment in patients with idiopathic dilated cardiomyopathy.[21] An intermediate stage of blunted responses has not previously been described.

The improvement in PVR is unlikely to result from any direct effect on pulmonary vascular β1 receptors as there are no significant populations of β1 receptors in the pulmonary arteries. It could be mediated via an alteration in pulmonary vascular β2 receptor function caused by β1 blockade. It is more likely that the fall in PVR was secondary to a long term lowering of pulmonary capillary wedge pressure. This possibility is supported by our finding of an improvement in pulmonary pressures coinciding with a fall in pulmonary capillary wedge pressure.

CONCLUSION

This case demonstrates that β adrenoreceptor subtype crossregulation may be part of the beneficial effects of long term β blockade in heart failure. It is clearly not the sole mechanism as clinical benefit was obvious at a time when the responses to β agonists were blunted. At this stage the benefits could be due to preventing cytotoxic effects of catecholamines, anti-ischaemic effects or changes in myocardial metabolism. However, it is intriguing to find pronounced improvements in PVR coinciding with increased responses to β agonists in the presence of continuing β blockade. Further studies are needed to unravel the molecular mechanisms of β blockade in heart failure but our case indicates a role for β blocker treatment in patients with heart failure and severe "fixed" pulmonary hypertension.

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