

Failure of balloon dilatation of the pulmonary valve in carcinoid pulmonary stenosis

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Abstract

Background—Carcinoid heart disease typically results in pulmonary stenosis and tricuspid incompetence. Percutaneous balloon dilatation is an effective treatment for congenital pulmonary stenosis and has been applied successfully to tricuspid stenosis caused by carcinoid heart disease. The value of balloon dilatation of the pulmonary valve in carcinoid pulmonary stenosis was assessed.

Methods—Two patients with severe congestive heart failure secondary to carcinoid heart disease and with documented pulmonary stenosis had balloon dilatation of the pulmonary valve. In both cases tricuspid regurgitation was also present together with reduced cardiac output.

Results—The procedure was technically successful in both patients. One patient experienced symptomatic benefit for two months and the other experienced no improvement. Both patients subsequently required combined tricuspid and pulmonary valve replacement from which good results and symptomatic improvement were obtained.

Conclusion—Though balloon dilatation of the pulmonary valve is technically feasible it is unlikely to provide useful palliation in carcinoid heart disease. Valve surgery should be considered in patients in whom the malignancy is controlled but carcinoid heart disease is producing drug resistant congestive heart failure.

Pulmonary and tricuspid valve disease caused by the carcinoid syndrome is a rare cause of congestive heart failure. The usual pattern, of predominantly pulmonary stenosis and tricuspid incompetence, results in a considerable reduction in cardiac output. We describe two patients with carcinoid heart disease who were treated with balloon dilatation of the pulmonary valve.

Case reports

CASE 1

A 51 year old man was referred with a four month history of severe exertional dyspnoea (New York Heart Association grade III) and ankle swelling which had been resistant to diuretic therapy (frusemide 80 mg daily and amiloride 10 mg daily). He had presented four years earlier with diarrhoea, flushing, and palpitation and had been diagnosed as having metastatic carcinoid disease. He had undergone

hepatic artery ligation and was receiving subcutaneous α interferon three times a week.

Examination showed a raised jugular venous pressure with a prominent V wave, parasternal lift, ejection murmur in the pulmonary area with a single second sound, ankle oedema, pulsatile hepatomegaly, and ascites. Echo and Doppler cardiography showed severe dilatation of the right side of the heart with tricuspid incompetence and pulmonary stenosis. The instantaneous pulmonary gradient estimated from the Doppler examination was 16 mm Hg.

Cardiac catheterisation showed a stenotic pulmonary valve with a simultaneous peak to peak right ventricular to pulmonary artery gradient of 20 mm Hg, tricuspid incompetence, and a reduced cardiac output as reflected by a pulmonary artery oxygen saturation of 60% (giving a cardiac output of 3.1 l/min calculated by the Fick formula, using assumed oxygen uptake of 117 ml/min⁻¹m⁻²). There was minimal tricuspid stenosis with a gradient (of 2 mm Hg) only during the "a" wave.

Percutaneous balloon dilatation of the pulmonary valve was performed. The valve was easily dilated with two inflations of a 19 mm balloon. No deformity of the balloon was seen during inflation. The gradient was abolished but right ventricular angiography showed persistent thickening and deformity in the region of the valve and there was no change in the pulmonary artery oxygen saturation, suggesting that no immediate improvement in cardiac output had occurred.

The patient experienced no benefit from the procedure and was subsequently referred for surgery without further haemodynamic assessment. At operation the pulmonary valve was found to be stenosed with fibrosed rolled back cusps and the tricuspid valve was stenosed and incompetent with fibrotic leaflets and shortened chordae adherent to the ventricular walls. Pulmonary and tricuspid valve replacement was performed without incident and with resolution of the congestive cardiac failure. The patient's treatment was subsequently changed to octreotide (a somatostatin analogue) and he was well at the time of his last assessment 18 months later.

CASE 2

A 46 year old man was referred with a six month history of severe exertional dyspnoea. He had presented three years previously with abdominal pain and had been diagnosed as suffering from carcinoid syndrome with hepatic metastases. He had been treated

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initially with α interferon and subsequently with octreotide.

On examination he had a raised jugular venous pressure with a prominent V wave, soft pulmonary component of the second heart sound, and ejection murmur in the pulmonary area with a quiet early diastolic murmur at the left sternal edge. Abdominal examination showed tender hepatomegaly.

Echocardiography showed tricuspid incompetence and pulmonary stenosis with incompetence and mild aortic incompetence. Cardiac catheterisation showed a simultaneous peak to peak gradient of 40 mm Hg across the right ventricular outflow tract. There was mild tricuspid stenosis (reflected by an "a" wave gradient of 5 mm Hg), gross tricuspid incompetence on right ventricular angiography, and a cardiac output of 3.2 l/min, calculated by the Fick formula with an assumed oxygen consumption of 118 ml/min⁻¹m⁻²).

Percutaneous dilatation of the pulmonary valve was undertaken with a 20 mm balloon followed by a 23 mm balloon. As in case 1 no nipping of the balloon was observed during inflation. The gradient across the valve was reduced to 15 mm Hg though the angiogram showed persistent thickening and there was no improvement in the pulmonary artery oxygen saturation. The procedure produced immediate symptomatic improvement and the clinical signs of tricuspid regurgitation disappeared.

Unfortunately the improvement was maintained for only two months, when he relapsed. Repeat catheterisation showed recurrence of the pulmonary gradient with a withdrawal gradient of 38 mm Hg and right ventricular pressure of 55/5 mm Hg. In view of these findings and the clinical deterioration he was referred for surgery. At operation the pulmonary valve cusps were heavily thickened and rolled up against the valve ring. The tricuspid valve was grossly disorganised with the posterior cusp heavily thickened and rolled backwards. The tricuspid and pulmonary valves were replaced and he was comparatively well 14 months later.

Discussion

CARCINOID SYNDROME

The carcinoid syndrome is produced by the metabolic products, as yet incompletely identified, of a slowly progressive malignancy usually originating in the small bowel (although occasionally from other sites such as ovary or lung). The syndrome is produced only when the tumour has metastasised to liver, presumably because before this the metabolites are produced in small quantities and are detoxified by the liver. Lesions of the heart valves are reported to occur in about 20% of cases clinically,¹ but if echocardiography is used they are detected in up to 70%.^{2,3} There is conflicting evidence about the overall importance of cardiac disease as a cause of death in the carcinoid syndrome: Moertel stated that only 10% of patients with the carcinoid syndrome developed cardiac symptoms and of these half died a cardiac death (about 5% of patients with

the syndrome),¹ Thorson *et al* reported that 50% of patients have cardiac failure causing death in 30% of patients,⁴ Lundin *et al* that "right ventricular failure is one of the major causes of death in patients with the carcinoid syndrome resulting from midgut tumours,"⁵ and Ross and Roberts that "carcinoid heart disease frequently is the cause of death in patients with the carcinoid syndrome".⁶ The explanation for this divergence of opinion is not clear, though there may have been differences in the patient populations and, as discussed below, with improved control of the malignancy heart failure may have become an increasingly common problem.

The disease typically affects the right side of the heart: plaques are occasionally found in the left heart but they are rarely of haemodynamic significance.

PATHOLOGY

The anatomical consequences of involvement of the tricuspid and pulmonary valves are narrowing of the valve orifices together with tethering and immobility of the leaflets. Possibly because the two valves are of different sizes this produces principally incompetence with a much lesser degree of stenosis in the tricuspid valve and principally stenosis with a minor degree of incompetence in the pulmonary valve.^{6,7} The combination of outflow tract obstruction with atrioventricular valvar incompetence is liable to have a profound effect on cardiac output with the pulmonary stenosis exacerbating the tricuspid regurgitation.

Pathological studies have looked at the distribution and nature of the plaques and there has been speculation about the pathogenesis.⁶⁻⁹ In a necropsy study of 21 cases the plaques were found to affect the valve structures and also the endocardial surfaces of the right atrium and the right ventricle, though right ventricular plaques were smaller (both in thickness and area). Plaques were also sometimes seen in the great veins and coronary sinus.⁶ Histology showed that the atrial and ventricular surfaces of the anterior leaflet of the tricuspid valve were involved in the fibrotic process, but only the ventricular surface of the posterior and septal leaflets of the tricuspid valve and the pulmonary arterial surface of the pulmonary valve.

Ultrastructural studies of the carcinoid plaques have proved interesting.^{8,10} It was initially thought that the plaques were of collagen and fibrin but it has been shown by light and electron microscopical studies that they are composed of smooth muscle cells (thought to be derived from primitive mesenchymal cells present normally in the sub-endocardial layer) in a stroma of acid mucopolysaccharide, collagen, and microfibrils. No elastic fibres are present.^{8,10} The lesions are often predominantly superficial and well circumscribed and they were described in the earlier work⁸ as being entirely limited to the endocardium and subendocardial layer. However, the more recent study¹⁰ suggested a more infiltrative nature and showed lesions extending into the myocardium.

AETIOLOGY OF PLAQUES

The aetiology of the plaques is unknown. The clinical features of the carcinoid syndrome (flushing, diarrhoea, and bronchospasm), are thought to be produced by the effects of the circulating vasoactive products of the malignancy, including serotonin and its metabolites, tachykinins (neuropeptide K and substance P), prostaglandins, kallikrein and bradykinin.^{8,11} There are, however, probably numerous other unidentified compounds at work. It has been postulated that the plaques are a result of the action of these substances on the endocardium and that a resulting increase in endothelial permeability allows migration of primitive mesenchymal cells which then differentiate into the smooth muscle cells seen in the carcinoid lesions. It has been further speculated that this process of endothelial injury is exacerbated by hydrodynamic factors such as turbulence, which might explain the localisation of plaques.⁸

Several studies have attempted to correlate factors such as length of symptoms and concentrations of circulating substances with the presence of heart disease in the carcinoid syndrome. Most have found that the presence of carcinoid heart disease is not associated with a longer duration of symptoms^{6,12} but that it is associated with raised concentrations of circulating vasoactive compounds (serotonin-*reflected* in the urinary concentrations of its metabolite 5-hydroxyindole acetic acid^{11,12} and tachykinins¹¹), but there have been conflicting findings.^{13,14} Though raised concentrations have not been shown to be associated with carcinoid heart disease, bradykinin has also been proposed as an aetiological factor, because it is produced in large amounts, is capable of producing endothelial injury, and its inactivation in the lung might explain the predominance of lesions in the right side of the heart.^{8,9}

Evidence also suggests a link between serotonin rich diets and endomyocardial fibrosis in Uganda.¹⁵ Finally methysergide (a serotonin antagonist) can produce retroperitoneal and occasionally valvar and endocardial lesions,¹⁶ both of which point indirectly to the role of serotonin in the aetiology of the plaques.

PROGNOSIS AND THE NEED FOR INTERVENTION

By the time carcinoid heart disease has developed the prognosis is poor with a median survival time of 14 months. In the past most patients died of their malignancy or other complications rather than heart disease.¹ In general, therefore, carcinoid heart disease has been treated conservatively, surgery being reserved for patients thought likely to have an unusually good prognosis. Recently introduced medical treatments have greatly improved the quality of life for many with the carcinoid syndrome. Both α interferon and octreotide (a long acting somatostatin analogue) reduce flushing and diarrhoea in 60–70% of patients, and there is some evidence of improved survival with α interferon.^{17,18} If patients survive longer with a better quality of life the

relative impact of the cardiac lesions is likely to be greater and it can be expected that the number of patients in good general condition referred for cardiological intervention will increase in the next few years.

We argued that although the pulmonary valve gradients were not great in our two patients, relief of the outflow tract obstruction would reduce the degree of tricuspid regurgitation and improve cardiac output. The dramatic resolution of the tricuspid incompetence in case 2—albeit for only a few weeks—provides some support for this proposition.

Balloon dilatation of the pulmonary valve is a safe technique, with excellent immediate and long-term results in patients with congenital pulmonary valve stenosis. It is the recommended treatment for patients with this condition.¹⁹

Successful balloon dilatation of carcinoid tricuspid stenosis has been reported in one patient and the authors speculated that balloon dilatation of carcinoid pulmonary stenosis was also likely to be effective.²⁰ The likely efficacy of balloon dilatation applied to the carcinoid pulmonary valve has also been speculated upon by Cheng.²¹ Combined balloon dilatation of the tricuspid and pulmonary valves has also been reported as successful in a patient with combined tricuspid and pulmonary stenosis in the carcinoid heart,²² not the typical pattern of valve lesions in this disease.

The results in our two patients, however, were disappointing; whereas double valve replacement produced good results. The rapid recurrence of the right ventricular outflow tract obstruction is perhaps not surprising in view of the pathology. Presumably the balloon merely compressed the fibrous plaques, which subsequently recoiled or continued to grow, in contrast to the splitting of fused commissures that is caused by balloon dilatation for pulmonary valve stenosis. The smaller pulmonary valve gradient in case 1 may indicate that in this case the tricuspid regurgitation was a more important cause of congestive cardiac failure than in case 2.

Reported cases of valve surgery for carcinoid heart disease include a series of 13 patients collected from published reports and reviewed by Strickman⁹ and a series of 32 reported cases collected more recently by Lundin *et al.*⁵ Further cases have also recently been described by Bilinska *et al.*²³ and by Fetherston and Davis.²⁴ Patients undergoing surgery (usually tricuspid valve replacement with either pulmonary valvotomy, valvectomy or valve replacement⁵) have in general done well, with the median survival from Strickman's series being in excess of two years, which is excellent given the natural cause of the disease by the time cardiac symptoms develop.

The two cases described here accord with the view that valve surgery can be expected to produce good symptomatic relief in advanced carcinoid heart disease and is superior to balloon dilatation of the pulmonary valve, which we found to be ineffective.

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