The CREST syndrome—successful reduction of pulmonary hypertension by captopril

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Summary

A patient with severe pulmonary hypertension due to pulmonary arteriolar obliteration complicating a long standing CREST variant of systemic sclerosis showed improvement in cardiac output and exercise tolerance during treatment with captopril, which was discontinued because of persistent systemic hypotension.

It is suggested that captopril would have a useful and possible prophylactic effect early in pulmonary hypertension in systemic sclerosis.

KEY WORDS: CREST, pulmonary hypertension, captopril.

Introduction

Pulmonary hypertension is a potentially fatal manifestation of progressive systemic sclerosis and may occur in the CREST (calcinosis, Raynaud's phenomenon, oesophageal dysfunction, sclerodactyly, telangiectasia) variant of systemic sclerosis. Interstitial pulmonary fibrosis is generally absent in the latter and pulmonary arterial obliteration is suggested as the cause rather than the result of the pulmonary hypertension (Salerni *et al.*, 1977). When pulmonary hypertension is established, death from rapidly progressive cardiac failure becomes inevitable. Captopril is known to reduce ventricular pre- and after-load and has the potential to reduce pulmonary hypertension (Vrobel and Cohn, 1980). We have assessed the efficacy of captopril in a patient with pulmonary hypertension complicating the CREST syndrome.

Case report

Our patient, a 49-year-old woman, developed Raynaud's phenomenon aged 13 years, a sicca syndrome with telangiectases aged 33 years, calcino-

sis aged 39 years, and sclerodermatous involvement of the large bowel aged 48 years. Her mother had progressive systemic sclerosis and Sjögren's syndrome. She first complained of dyspnoea in July 1980 and was found to be in right ventricular failure without pulmonary fibrosis. Rapid progression of pulmonary hypertension over the next few months led to her re-admission in February 1981 in gross right heart failure, a very enlarged liver with jaundice, ascites and generalised oedema. Her weight was 65 kg, blood pressure 130/80 mmHg, right bundle branch block on electrocardiogram (ECG), the chest X-ray showed cardiomegaly, the cardio-thoracic ratio being 19/27 with markedly enlarged pulmonary arterial shadows and no suggestion of pulmonary fibrosis. Lung function tests demonstrated a mild restrictive pattern with no deterioration from previous records over 3 years and an echocardiogram showed right ventricular enlargement. Right heart catheter studies were performed: the pulmonary artery pressure was recorded at 115/50 mmHg and the pulmonary wedge pressure was 15 mmHg. The pulmonary hypertension and secondary right ventricular failure was attributed to pulmonary artery obliterative disease as described in the CREST syndrome. Her symptoms were partially controlled with reduction of oedema and ascites using frusemide 80 mg b.d. and spironolactone 200 mg b.d. with a weight reduction of 9 kg. However, the jugular venous pressure and cardiomegaly were unchanged. As the patient continued to deteriorate, it was decided to attempt to improve her cardiac function and possibly reduce pulmonary artery pressure by using captopril.

While the patient was stable on the diuretic regime, cardiac function was monitored serially using multiple gated radionuclide angiography. The left and right ventricular ejection fractions (LVEF and RVEF) were calculated using a method previously

FIG. 1. Gated radionuclide in the modified right anterior oblique view. (a) before captopril therapy; (b) after captopril therapy.

FIG. 2. Corresponding line drawing to Fig. 1. RV=right ventricle; LV=left ventricle; ED=end diastolic frame; ES=end systolic frame.

described (Lahiri *et al.*, 1982). The heart was imaged in the best septal view, allowing for its abnormal rotation. Before captopril therapy the right ventricle was virtually non-contractile (RVEF=5%) associ-

ated with impaired left ventricular function (LVEF=41%, Figs 1 and 2). Following 1 month's treatment with captopril, her clinical condition improved and repeat radionuclide angiogram demonstrated improvement in cardiac function (RVEF=20%, LVEF=62%). Due to the severity of her condition, the dose of captopril was gradually increased to 400 mg over the next 6 weeks. During this period, systemic hypotension and fluid retention were marked but she was well enough to be discharged home on the same diuretic regime without weight gain (56 kg) with subjective improvement, improved exercise capacity and cardiac function. Following discharge the patient maintained her improvement for one month until systemic hypotension and fluid retention recurred requiring readmission when captopril was stopped due to systemic hypotension. Symptoms were initially controlled with increased doses of diuretic but the patient continued to deteriorate. After 8 weeks, a repeat radionuclide angiogram showed deterioration in cardiac function to pretreatment levels (RVEF=4%, LVEF=37%). At this time, the patient was moribund, failed to respond to treatment and shortly after developed bronchopneumonia and died.

Post-mortem findings demonstrated pulmonary oedema with patchy bronchopneumonia. There was intimal hyperplasia and mucoid degeneration of the small and medium sized pulmonary arteries without evidence of pulmonary fibrosis.

Discussion

The underlying mechanisms of systemic sclerosis remain unknown. A vascular basis has been proposed by Fries (1979) with a failure of vasoregulatory control allowing arterial pressures to be transmitted to more fragile distal vessels and subsequent endothelial damage followed by leakage of protein and fluid causing irreversible changes. The initial arteriolar changes of systemic sclerosis are very similar to those found in essential, malignant and primary pulmonary hypertension, and it is suggested that microvascular hypertension may be a cause rather than the result of the disease process in systemic sclerosis.

The renin-angiotensin-aldosterone system may be active in systemic hypertension and in chronic heart failure. Reduction in angiotensin production by converting enzyme inhibitors has been reported to lower systemic blood pressure and improve chronic heart failure by balanced preload and afterload reduction. Angiotensin II is a pulmonary vasoconstrictor, producing vasoconstriction when infused into the human circulation at a dose level low enough to minimise its systemic pressor effect (Bergofsky, 1980). In angiotensin II excess, a reduction in its level may induce pulmonary arterial vasodilatation allowing a subsequent increase in right ventricular output. In a group of patients with systemic hypertension, infusion of a converting enzyme inhibitor reduced pulmonary vascular resistance although pulmonary arterial pressures were not markedly elevated (Niarchos, Roberts and Laragh, 1979). In resistant congestive cardiac failure, patients treated with captopril had equivalent reduction in systemic arterial pressure, systemic vascular resistance, pulmonary wedge pressure, pulmonary arterial resistance, right atrial pressure, and it was concluded that pulmonary arterial vasodilatation occurred in these patients (Vrobel and Cohn, 1980). Treatment with captopril in one patient with primary pulmonary hypertension produced improvement in ventricular function with reduction in systemic and pulmonary vascular resistance, but without a fall in pulmonary arterial pressure (Horowitz *et al.*, 1981). The mode of action of angiotensin II converting enzyme inhibitors on the

pulmonary circulation remains unknown and may not just be due to a reduction of angiotensin II production, as an increase in kinin levels due to their reduced breakdown is a possible alternative.

In our patient, the rapid and progressive onset of pulmonary hypertension was similar to the malignant systemic hypertension described with renal involvement in systemic sclerosis. The pulmonary arteriolar wall changes described in the CREST variant of systemic sclerosis are comparable to those seen in the kidney, gut and digital vessels in systemic sclerosis (Young and Mark, 1978). Studies reporting the successful management of renal hypertension in systemic sclerosis (Zawada *et al.*, 1981) along with the proposed pulmonary vasodilator effect of converting enzyme inhibitors led us to use captopril in our patient. Even though moribund at the onset of therapy, a definite improvement occurred in dyspnoea, exercise tolerance and in cardiac function measured by radionuclide angiography.

Our results suggest that converting enzyme inhibitors may be of use in pulmonary hypertension associated with this disease, especially if used at an earlier stage in its development.

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