with 1.9% in the placebo arm. These results suggest that significant early reperfusion arrhythmias are less common than expected from cursory analysis of the major thrombolytic trials.

The importance of the 'door to needle' time from when the patient reaches medical assistance until he/she receives thrombolysis is well established. Pooled results from five published trials of pre-hospital thrombolysis suggest a 17% reduction in short-term mortality with pre-hospital thrombolysis. Dr Hansen speculates that pre-hospital thrombolysis may increase the incidence of reperfusion arrhythmias. There is in fact good evidence that this is the case. The European Myocardial Infarction Project (EMIP) group study of pre-hospital versus in-hospital thrombolysis for acute myocardial infarction demonstrated an increased incidence of ventricular fibrillation in patients receiving thrombolysis prior to reaching hospital (2.5%), compared with an incidence of 1-6% in patients not receiving treatment until they arrived later in the hospital. This has obvious implications for the training of general practitioners and paramedics and the availability of monitoring and defibrillation equipment. Many general practitioners, although recognizing the benefits of early treatment, are unwilling to give thrombolysis out of hospital, and yet it is here that two thirds of deaths from myocardial infarction occur.

Experimentally the incidence of reperfusion arrhythmias is greater the more rapid the reperfusion process. When the concept of thrombolysis for acute myocardial infarction was in its infancy and thrombolytics were given directly into the occluded coronary artery it was noted that restoration of coronary blood flow frequently induced ventricular arrhythmias. Primary angioplasty, which might be expected to produce very rapid reperfusion, has recently been tested as a first-line treatment for myocardial infarction. The PAMI study demonstrated a much higher incidence of ventricular fibrillation in the angioplasty group compared with those patients receiving tPa (6.7% vs 2.0% respectively, P=0.02), suggesting that rapid reperfusion in man is associated with an increased incidence of ventricular fibrillation, similar to animal models. The argument that these patients are in hospital and therefore the development of ventricular fibrillation is less of a concern is neither intellectually appealing nor practically comforting. Finally, at the cellular level we would consider that mechanisms other than oxygen free radical injury may be implicated in the development of reperfusion arrhythmias. These would include potassium undershoot i.e. temporary local extracellular hypokalaemia, or adrenergic mechanisms.

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References


Myocardial fibrosis and hyperaldosteronism

The important role of the renin-angiotensin-aldosterone system in the regulation of myocardial fibroblast function in the extracellular matrix in hypertension and heart failure has been emphasized in a supplement of this Journal. However, the separate role of aldosterone is frequently
overlooked\textsuperscript{12} although aldosterone can directly stimulate collagen synthesis by cardiac fibroblasts\textsuperscript{13}, and recent work has demonstrated that mineralocorticoid receptors are present and coexpressed with 11\(\beta\)-hydroxysteroid dehydrogenase in the human heart, which thus has the necessary cellular machinery required for a direct action by aldosterone\textsuperscript{13}.

We describe a patient with hyperaldosteronism due to Conn’s syndrome who illustrates the potential effect of elevated aldosterone levels on the myocardial fibroblast.

A 35-year-old Chinese male presented with a 2-month history of breathlessness on exertion and cough. Mild hypertension had been recorded 2 years previously, but no medication was prescribed. Examination revealed uncontrolled atrial fibrillation and signs of biventricular congestive heart failure. An ECG confirmed atrial fibrillation and showed left ventricular hypertrophy. An echocardiogram showed concentric left ventricular hypertrophy, moderate dilatation of the left ventricle, moderate reduction of LV systolic function (fractional shortening (FS) of 24%), mild mitral regurgitation and a small pericardial effusion. Serum potassium was 1.8 mmol\(\cdot\)l\(^{-1}\). Following an episode of pulmonary infarction, repeat 2D echocardiography showed worsening left ventricular function. In order to exclude an active myocarditis, cardiac catheterization with coronary angiography and right ventricular endomyocardial biopsy was performed.

Left ventricular angiography showed global hypokinesia and coronary angiography normal coronary arteries. Routine histology of the right ventricular endomyocardial biopsy did not reveal any evidence of lymphocyte infiltration or myocarditis. Staining with collagen specific picrosirius red stain demonstrated endocardial and interstitial fibrosis (Fig. 1). Repeat echocardiography showed persistent left ventricular enlargement (LVEDD = 7.0 cm), FS of 25% and estimated ejection fraction of 48%. Doppler assessment of left ventricular diastolic function revealed a restrictive filling pattern with a very short E-wave deceleration time of 75 ms (normal 200 ± 40 ms) with a large ratio of peak E/peak A velocities of 5.83 (normal 1.44 ± 0.4). Isovolumic relaxation time was within normal limits at 80 ms; estimated right ventricular systolic pressure was 32 mmHg. Subsequent investigations confirmed the diagnosis of Conn’s syndrome with serum aldosterone level >3300 pmol\(\cdot\)l\(^{-1}\), and plasma renin supine 0.35 mg\(\cdot\)l\(^{-1}\)\(\cdot\)h\(^{-1}\) (while receiving treatment for symptomatic heart failure). A CT abdominal scan pre- and post-contrast confirmed a right adrenal mass sized 2 × 2 × 1.5 cm; the left adrenal was normal. The patient is awaiting laparoscopic adrenalectomy.

This patient illustrates the possible role of aldosterone upon the development of myocardial fibrosis and LV diastolic dysfunction. Considerable experimental animal work has demonstrated that aldosterone can stimulate an abnormal accumulation of type I collagen which can be reversed by spironolactone\textsuperscript{1,2}. Hypokalaemia is also a major component of Conn’s syndrome and thus can produce myocardial damage by itself and may cause some degree of reparative or replacement fibrosis. However, in a rat model with primary hyperaldosteronism, treatment with the potassium sparing diuretic amiloride, which has no aldosterone receptor antagonist activity, prevented reparative myocardial scarring (presumably by preventing hypokalaemia), but did not affect the pathological reactive fibrosis\textsuperscript{3}. Thus, hypokalaemia per se is not a sufficient explanation for the degree of fibrosis found in patients with hyperaldosteronism. Furthermore, hypertension alone would not directly stimulate collagen synthesis by cardiac fibroblasts\textsuperscript{13}.

This effect of aldosterone on the development of myocardial fibrosis may be particularly important in congestive heart failure when angiotensin II and aldosterone levels are elevated and perhaps aldosterone inhibitors combined with angiotensin converting enzyme inhibitors may provide an additional benefit in heart failure.

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