Galactose Tolerance Test of Liver Function in Pulmonary Heart Disease

A. J. THOMAS AND R. A. SAUNDERS

From Departments of Medicine and Pathology, Llandough Hospital (United Cardiff Hospitals), Cardiff

A study of the liver function in pulmonary heart disease (Thomas, Rees, and Saunders, 1965) suggested that galactose was not metabolized normally by the liver, and so the galactose tolerance test was frequently abnormal. The results suggested that the galactose tolerance test could be abnormal before signs of clinical heart failure appeared. It seemed either that hypoxia was a factor causing disordered liver function or that hepatic congestion was present in advance of the other signs of cardiac failure. The earlier work further suggested that the galactose tolerance test was abnormal in chronic bronchitis without clinical heart failure. There was some support for this latter suggestion in an earlier observation that a palpable tender liver margin could be present in chronic pulmonary disease without other signs of congestive heart failure (Thomas, 1948). To study this problem further the galactose tolerance has been measured in 50 patients with chronic bronchitis and 25 patients with asthma. Lung function tests and electrocardiograms were recorded in all, oxygen and carbon dioxide levels in most, and right heart pressures in 19 patients. Galactose enzyme studies have been made in 38 patients.

Subjects and Methods

The oral galactose tolerance test, as described by Maclagan and Rundle (1940) and used in the previous work, was used in this study, but a galactose oxidase method for estimating galactose has been used (Hjelm, 1967). The result of the peroral test is expressed as the galactose index and is the sum in mg./100 ml. of the increases in galactose in the 4 half-hourly blood samples over the fasting level. A galactose index of 140 or over is abnormal. Malabsorption as indicated by the xylose tolerance test is uncommon in these patients, but 14 intravenous galactose tolerance tests have been carried out to ensure that malabsorption was not affecting any doubtful result in an oral test. In most cases of chronic bronchitis the galactose tolerance test was done when the patients had improved from their exacerbations. In certain cases the test was done when heart failure was present and again after recovery. In asthma the test was done as soon as possible after the acute exacerbation, in some patients three days after admission. In many patients the test has been repeated a number of times.

Galactose uridylic transferase was measured in the red cells by a modification of the method of Bretthauer et al. (1959). The range of normal of the galactose uridylic transferase was taken as 12–30 units per g. Hb. In order to check the presence of this enzyme galactose-1-phosphate was estimated in the red cells of some of the patients using the method described by O’Brien and Ibbott (1962). Galactokinase has been measured biochemically by the method of Cardini and Leloir (1953). In 6 cases measurements of galactokinase and galactose uridylic transferase were made by the method of Robinson (1963), incubating galactose-1-C14 with intact red cells and studying the products by chromatography.

Results

On repeated testing, 38 patients with severe chronic bronchitis had a forced expiratory volume in one second (FEV1.0) of less than 1.2 litres, 32 having FEV1.0 of less than 1 litre. Of these, 34 had galactose tolerance indices well above 140 units. In 18 of the 34 the test was repeated on two or more occasions at intervals varying from weeks to months and the results were still abnormal in 31 instances. Of 12 patients with chronic bronchitis and FEV1.0 between 1.2 and 1.5 litres at that time, there was more variation, 8 having abnormal galactose indices and 4 having normal indices between 80 and 140 units. These results suggest that severe chronic bronchitis (FEV1.0 of less than 1.2 litres) gives rise to a disturbance of liver function comparable to that seen in heart failure.
when the condition had improved and the oedema cleared but a palpable though less tender liver was present. The galactose index was still abnormal. In 3 of these patients the index was abnormal months later with no evidence of clinical heart failure.

Pulmonary Heart Disease. The electrocardiographic pattern of pulmonary heart disease was present in 30 of the 50 cases of chronic bronchitis, and all 30 had an abnormal galactose index at some time. Twelve patients had normal electrocardiograms with abnormal galactose indices. These patients also had severe chronic bronchitis. Two patients had electrocardiographic evidence of pulmonary heart disease and normal galactose indices.

The electrocardiographic pattern was normal in 20 of the 25 patients with asthma. It was of interest that 4 of those with abnormal galactose indices also had some abnormality in the electrocardiogram.

Pulmonary Hypertension. In 19 patients with chronic bronchitis, pulmonary artery pressures were recorded at rest when recovery from an exacerbation was satisfactory. The mean pulmonary artery pressures of all were above 15 mm. Hg. The galactose tolerance test was abnormal in 16 of these (Fig. 1). Two patients had high mean resting pulmonary artery pressures with normal galactose indices. Most subjects with pulmonary hypertension also have an abnormal galactose index, but there is no statistical correlation. Of the patients with abnormal galactose indices, 14 had resting right atrial pressures below 10 mm. Hg and right ventricular end-diastolic pressures below 8 mm. Hg and so were not in heart failure (Fig. 2). This suggests that patients with chronic bronchitis without heart failure can have abnormal galactose tolerance tests indicative of some disorder of liver function.

Hypoxia. All of the cases of chronic bronchitis had hypoxia at some time and the majority were still hypoxic according to their oxygen saturation at the time of the galactose tolerance test (Fig. 3). However, the finding of 3 patients with oxygen saturations above 90 per cent and abnormal galactose indices at that time suggested that hypoxia was not the full explanation. Many of the cases of asthma had only recovered in the previous day or so from severe transient hypoxia and yet had normal galactose indices.

Pco₂. Pco₂ was above normal at some time in the patients with chronic bronchitis and was still high at the time of the test in a number of them (Fig. 4). There were 6 examples of a Pco₂ of 40

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**Fig. 1.**—The galactose index and the mean pulmonary artery pressure in mm. Hg. Though all the readings are outside the accepted range of normality, shown by the rectangle, there is no evidence of a relation between the indices (r=0·20; p>0·2).

**Fig. 2.**—The mean right atrial pressure (mm. Hg) is not raised to a degree sufficient to cause hepatic congestion in many of the patients with abnormal galactose tolerance.
mm. Hg or below with an abnormal galactose index. There was one instance of a PCO₂ of 51 mm. Hg and a normal galactose index. Though for both indices most of the subjects are outside the usually accepted ranges of normality, there is no definite evidence of any relation (r = 0.18; p > 0.2).

Galactose Enzymes. Galactose uridyl transferase was measured in the red cells in 38 patients, 8 with asthma and 30 with severe chronic bronchitis. The results were normal in 32 and only moderately reduced in 6. It seems that a deficiency of this enzyme is not responsible for the abnormality if the results in the red cells can be interpreted as representing the level in the liver. This deduction is further supported by the estimation of galactose-l-phosphate which gave normal values. The abnormal galactose index must be due to the presence of galactose itself. Tests for the presence of galactokinase were also done, and this enzyme was present in normal quantity in the red cells. In 6 samples the radiochromatograms of the products of incubation of C-14 labelled galactose with red cells were recorded and these qualitatively supported the previous results showing peaks for galactose, galactose-l-phosphate, and UDP galactose. These results are interpreted as indicating that these enzymes are present in adequate amount, and that further search must be made for the deficiency in the liver responsible for the disturbance of the galactose mechanism. It seems likely that the disturbance is in one of the co-enzyme systems.

DISCUSSION

We have shown that in severe chronic bronchitis there is an abnormality of the galactose metabolism resulting in abnormal galactose tolerance tests. These tests are understandably abnormal in the presence of heart failure due to pulmonary disease, and the accepted cause is hepatic congestion. Evidence put forward here suggests that galactose metabolism is abnormal in severe chronic bronchitis without obvious clinical heart failure. These patients have hypoxia, hypercapnia, and pulmonary hypertension, and it is difficult to separate these factors. The surprising normality of the galactose tolerance test in most cases of severe asthma, even after a few days after episodes of severe hypoxia, suggests that at least temporary hypoxia is not the main cause of the abnormality. This deduction is supported by the occasional case of chronic bronchitis with persisting abnormality of galactose tolerance and oxygen saturation of 90 per cent. In asthma the PCO₂ level is usually within normal limits at the time of the test, but in many cases of chronic bronchitis the PCO₂ is raised and this could explain the difference in the galactose index of the two conditions. However, even in some cases of chronic bronchitis the galactose index test has remained abnormal when the PCO₂ has come down to 40 mm. Hg and there is no statistically significant relation. Pulmonary hypertension is present in severe chronic bronchitis, but in the small series analysed here there was no statistical relation.

The most constant finding in these cases, as recorded in an earlier paper (Thomas et al., 1965) and confirmed now, is the relation between the abnormal galactose tolerance and the persistently reduced ventilatory capacity in chronic bronchitis. Walker and Pickard (1962) described some of the effects of respiration on the inferior vena cava, and
indicated that breath holding could raise the pressure in the inferior vena cava. Nakjavan, Palmer, and McGregor (1966) have shown the influence of respiration on venous return in “pulmonary emphysema”. They showed that, in some patients characterized by gross hyperinflation of the lungs, the pattern of flow in the inferior vena cava at the level of the diaphragm was quite different from the normal, being maximal in expiration and much reduced or completely arrested in inspiration. They point out that if upward flow occurs only in expiration when intrathoracic pressure is high, then inferior vena caval pressure must be high.

The changed intrathoracic pressure relations are evident in this series in the greatly increased respiratory variation of the pulmonary arterial pressure, a variation of three times the normal. The resultant effect on the liver is a reduction of hepatic blood flow and production of hepatic congestion. These give the same result with the galactose tolerance test as clinical heart failure. Temporary hyperinflation as seen in acute asthma is insufficient to produce this effect on the liver, but persisting reduction of ventilatory capacity with hyperinflation, even in chronic asthma, will produce the same effect.

We suggest that the liver in chronic bronchitis has reduced hepatic blood flow and hepatic congestion before there is clinical heart failure and that the galactose tolerance test is one method of demonstrating this effect. The abnormal galactose metabolism is thought to be due to a disturbance of the co-enzyme system, but further study is needed to confirm this suggestion.

**Summary**

The galactose tolerance test of liver function has been done in 50 patients with chronic bronchitis and 25 patients with asthma. The test is abnormal in most patients with severe chronic bronchitis \((\text{FEV}_{1.0} < 1.2 \text{ L})\) but normal in most patients with asthma. It is suggested that the abnormality is related to the persistently low ventilatory capacity. The galactose index is abnormal in heart failure due to a congested liver. It remains abnormal in chronic bronchitis when heart failure has cleared. These cases have raised pulmonary arterial pressures and raised \(\text{PO}_{2}\) but no direct relation is found. Hypoxia is not the complete explanation. The suggested mechanism is a reduction in hepatic blood flow and production of hepatic congestion, without heart failure, by the changed intrathoracic pressures affecting venous return in the inferior vena cava and causing an increase in inferior caval pressure.

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**References**


