The possible role of endogenous digitalis-like substance in the causation of pre-eclampsia

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Summary

Digoxin levels have been reported in neonatal blood when neither the mother nor the baby had received digoxin. An endogenous digoxin-like substance (DLS) that may be causally related to hypertension has been described. Using a commercially available radio-immunoassay kit, we investigated the presence of an immunoreactive DLS in 21 pre-eclamptic mothers, 36 mothers with normal blood pressure (the control group) and their infants. We found mean DLS levels to be higher in cord blood from infants born to the pre-eclamptic mothers than in cord blood from those born to mothers in the control group. Levels were also higher in cord blood than in maternal blood in both the pre-eclamptic and the control groups. DLS seems to be associated with pre-eclampsia. Although further work is needed for verification, a hypothesis on the possible role of DLS in the causation of pre-eclampsia is presented.

Pre-eclampsia is known as the disease of theories, because so many possible causes have been mentioned in the literature. In a recent study at Tygerberg Hospital, Parowvallei, CP, an endogenous substance which cross-reacts with radio-immunoassays for digoxin was detected in the cord blood of newborn infants. Higher levels of this substance were found in maternal and cord blood when the mothers had had pre-eclampsia. This pilot study was carried out to establish whether higher levels of the immunoreactive digitalis-like substance (DLS) are to be found in patients with pre-eclampsia.

Patients and methods

Thirty-six patients with normal blood pressure (the control group) and 21 with pre-eclampsia were studied. All these patients were selected at random and none had ever received digoxin. For the diagnosis of pre-eclampsia, a sustained blood pressure of at least 140/90 mmHg when measured on two occasions at least 6 hours apart together with proteinuria or general oedema had to be present.

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A specimen of venous blood was taken from the cord immediately after delivery of each infant, and a blood specimen was subsequently taken from the mothers.

Digoxin levels were determined with a commercially available radio-immunoassay kit (Gammacoat; Clinical Assays, Cambridge, Mass., USA). A Packard Autogamma counter was used to determine the radioactivity of the 125I-labelled digoxin. (A paper on the radio-immunoassay, a comparison of three different available commercial kits, gel chromatography and other laboratory studies on DLS appears on p. 878 of this issue of the SAMJ).

Since the assay of DLS was not accurate for minute quantities of this substance all values below 0.5 ng/ml were regarded as 0.5 ng/ml for the purposes of statistical calculations. The two groups of patients were then compared to determine whether DLS levels in maternal and cord blood were higher when the mother had pre-eclampsia than when the blood pressure was normal.

Results

The two groups of patients were comparable as regards maternal age, duration of pregnancy, 5-minute Apgar score, and birth weight (Table I). All but 2 patients with pre-eclampsia had proteinuria; 2 patients had a trace of protein in the urine, 7 patients +, 7 patients ++ and 3 patients +++. Diastolic blood pressures varied between 90 and 95 mmHg in 3 patients, between 100 and 105 mmHg in 4, and between 105 and 120 mmHg in 8; 6 patients had diastolic blood pressures of over 120 mmHg. Fourteen patients were primiparous and the parity of the remaining 7 ranged between 2 and 5. Only 1 patient had not attended the antenatal clinic, while 5 patients had made 1 - 5 visits, 6 patients 6 - 10 visits and 7 patients more than 10 visits. One patient may have had underlying hypertension (diastolic blood pressure > 90 mmHg before 20 weeks); 14 patients had no underlying hypertension and 6 patients definitely had underlying hypertension.

<table>
<thead>
<tr>
<th>TABLE I. COMPARISON BETWEEN NORMAL AND PRE-ECLAMPTIC PATIENTS</th>
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<tbody>
<tr>
<td>Normal patients</td>
</tr>
<tr>
<td>(N = 36)</td>
</tr>
<tr>
<td>Maternal age (yrs)</td>
</tr>
<tr>
<td>Duration of pregnancy (wks)</td>
</tr>
<tr>
<td>5-minute Apgar score</td>
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<td>Birth weight (g)</td>
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</table>

NS = not significant
In the presence of normal blood pressure maternal DLS levels ranged from 0.5 to 0.85 ng/ml with a mean of 0.52 ± 0.06 ng/ml, while in the presence of pre-eclampsia they ranged from 0.5 to 1.48 ng/ml (mean 0.68 ± 0.3 ng/ml). Values of DLS in cord blood of infants born to mothers with normal blood pressure ranged from 0.5 to 1.5 ng/ml (mean 1.06 ± 0.34 ng/ml). In both groups the umbilical cord DLS levels were higher than the levels in maternal blood. The values reported here are also summarized in Fig. 1.

Discussion

In 1969 Dahl et al. proposed that a circulating saluretic substance might cause a sustained rise in arterial pressure in salt-sensitive hypertensive rats. Elaborating on this theory, de Wardener and MacGregor suggested that in man essential hypertension was due to an inherited deficiency in the ability of the kidney to eliminate sodium, a deficiency which became more marked as sodium intake increased. The decreased ability to eliminate sodium causes a small increase in the extracellular fluid volume. The concentration of a circulating inhibitor of sodium transport is then increased. Since this substance inhibits the transport of sodium across the cell membrane the intracellular calcium concentration increases vascular reactivity and thereby induce vasoconstriction. This increases vascular reactivity and ultimately leads to increased arterial blood pressure. The possibility that an 'endogenous digitalis' exists was strongly suggested by La Bella on the basis of cross-reaction with digitalis in radio-immunoassays and radioreceptor assays and inhibition of Na-K-ATPase.

An exciting observation was made by Kuhnert et al. when they found that infants born to pre-eclamptic mothers had fetal erythrocytes which contained significantly less Na-K-ATPase than those of infants born to mothers with normal blood pressure. These results indicate that some inhibition of sodium transport in fetal erythrocytes is associated with pre-eclampsia. An endogenous substance in neonates which causes false-positive digoxin measurements was also noted in a recent report. The apparently higher concentrations in the amniotic fluid suggested that the substance may also be produced by the infant before birth.

Conclusion

In this study we found higher levels of DLS in the presence of pre-eclampsia than in the presence of normal blood pressure. This is an interesting finding, and when the earlier part of the discussion is considered it seems likely that this substance could be associated with pre-eclampsia. One should keep in mind that this is a limited study and that more data are needed before definite conclusions can be reached. It is exciting to consider DLS as a possible aetiological factor in pre-eclampsia, however, and we propose the following hypothesis:

The underlying lesion is inadequate excretion of sodium by the kidney. This leads to accumulation of extracellular sodium and fluid, triggering the release of DLS. DLS inhibits Na-K-ATPase, causing the well-established increased vascular reactivity of pre-eclampsia and hypertension (Fig. 2). DLS may also have a positive inotropic effect on the heart, increasing cardiac output and raising the blood pressure further, but increased cardiac output in pre-eclampsia is not well established.

DLS can probably be considered a natriuretic hormone, because Na-K-ATPase inhibition in the kidney causes natriuresis which would tend to correct the underlying salt imbalance but not the increased arterial blood pressure. Thus, DLS could be considered a possible mechanism for the development of pre-eclampsia.
retention by the kidney. Thus the price to pay for adjusting sodium retention is hypertension. This hypothesis is in agreement with that of Dahl et al.4

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REFERENCES


First-pass determination of the right ventricular ejection fraction using two regions of interest and the right anterior oblique view

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Summary

The right ventricular ejection fraction (RVEF) was determined on the right anterior oblique view in 9 patients during the first pass of a bolus of technetium-99m employing a gamma camera with high count-rate capability. The RVEF was calculated by using: (i) a fixed end-diastolic region of interest (ROI); and (ii) an end-diastolic and end-systolic ROI. Because of the movement of the tricuspid plane the first of these methods often gave low values, and agreement between the first two peaks was not as good as that when the second method was used. The mean for the second method was in agreement with that in a previous study using a gated first-pass technique and two ROIs but was somewhat higher than those reported by workers using either one ROI or the anterior view.

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Evaluation of right ventricular performance in clinical medicine is often difficult. The clinical signs of lung disease characterized by hyperinflation overlap with those of failure and hypertrophy of the right ventricle. The presence of air between the heart and the thoracic wall makes echocardiographic evaluation of the heart impossible. The ECG changes due to right ventricular overload are frequently subtle in chronic obstructive pulmonary disease, and the patterns of systolic overload or right ventricular hypertrophy are rarely seen. The estimation of chamber size from chest radiographs is difficult in the presence of overinflation of the lungs.

In view of this, radionuclide determination of the right ventricular ejection fraction (RVEF) has been examined and found useful. Marshall et al.4 studied 34 patients with chronic obstructive airway disease and found 17 with a reduced RVEF (38 ± 2%). In addition they found a clinical application, namely a significant increase in the RVEF in the presence of therapeutic blood levels of the bronchodilator aminophylline. Winzelberg1 has discussed the conditions in which a decreased RVEF may be observed.

Although the ejection fraction is a well-accepted measure of ventricular function, right ventricular performance has been difficult to quantitate by conventional means.6 Calculation of right ventricular stroke volume on cine angiography depends on a geometrical approach and is difficult because of the complex geometry of this chamber.1 Since radionuclide techniques are much less dependent on geometrical factors, they represent an attractive way of determining the RVEF.1,6

Although the RVEF could be obtained from a gated blood pool study at equilibrium, first-pass radionuclide cardioangiography is preferred by many because of temporal and...