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

A. D. BEYERS, H. J. ODENDAAL, L. L. SPRUYT, D. P. PARKIN

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.

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Pre-eclampsia is known as the disease of theories, because so many possible causes have been mentioned in the literature.[1] 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.[2] 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.

Departments of Medicine, Obstetrics and Gynaecology and Pharmacology, Tygerberg Hospital and University of Stellenbosch, Parowvallei, CP
A. D. BEYERS, M.B. CH.B.
H. J. ODENDAAL, M.D., F.C.O.G. (S.A.), F.R.C.O.G.
L. L. SPRUYT, B.SC. (PHARM.) HONS, M.B. CH.B.
D. P. PARKIN, B.SC. (FARMAKOL.) HONS, M.B. CH.B.

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 ^{125}I-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 I. COMPARISON BETWEEN NORMAL AND PRE-ECLAMPTIC PATIENTS

	Normal patients ($N = 36$)	Pre-eclamptic patients ($N = 21$)	t	P
Maternal age (yrs)	**24,8 ± 7,63**	**23,5 ± 5,76**	**0,66**	**NS**
Duration of pregnancy (wks)	**38,24 ± 2,58**	**38,30 ± 1,78**	**0,10**	**NS**
5-minute Apgar score	**9,23 ± 1,29**	**9,05 ± 1,54**	**0,46**	**NS**
Birth weight (g)	**2 952 ± 790**	**2 990 ± 582**	**0,19**	**NS**

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 0,82 ± 0,28 ng/ml); infants born to mothers with pre-eclampsia had values ranging from 0,5 to 2,0 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.

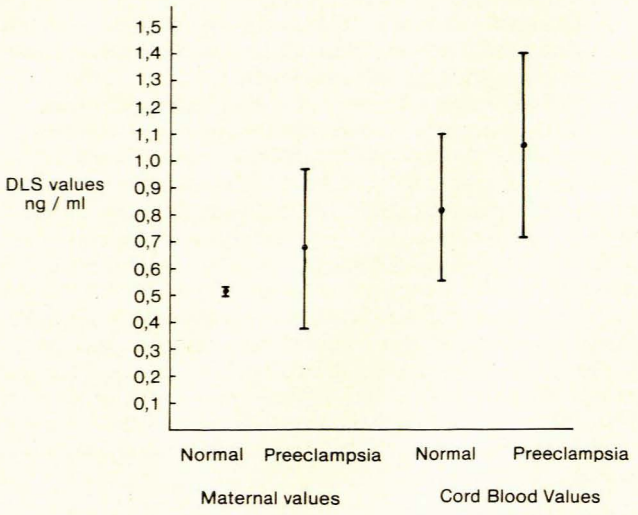

Fig. 1. DLS values in maternal and cord blood samples from pre-eclamptic mothers and mothers with normal blood pressure and their infants.

Discussion

In 1969 Dahl *et al.*[3] 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[4] 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 sodium concentration is raised, which in turn raises the intracellular calcium concentration. This increases vascular reactivity with a subsequent gradual rise in arterial blood pressure. In a later report MacGregor *et al.*[5] found evidence for a raised concentration of a circulating sodium transport inhibitor in patients with essential hypertension.

At this stage it is also necessary to stress the important concept that Na^+-K^+-adenosine triphosphatase (Na^+K^+-ATPase) is directly related to the status of sodium transport and therefore also to sodium balance. The presence of a circulating inhibitor of Na^+-K^+-ATPase activity was noted by Kramer,[6] who found that the inhibitor isolated from human urine binds to specific antibodies to digoxin. He also postulated that this inhibitor could influence various Na^+-K^+-ATPase-dependent transport systems. Depression of the Na^+-K^+ pump will raise intercellular concentrations of sodium and calcium and thereby induce vasoconstriction. Haddy[7] came to a similar conclusion, namely that inhibition of Na^+-K^+-ATPase causes increased contractile activity and therefore increased arterial blood pressure. The possibility that an 'endogenous digitalis' exists was strongly suggested by La Bella[8] 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.*[9] 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.[10] 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[11] 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.[12]

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

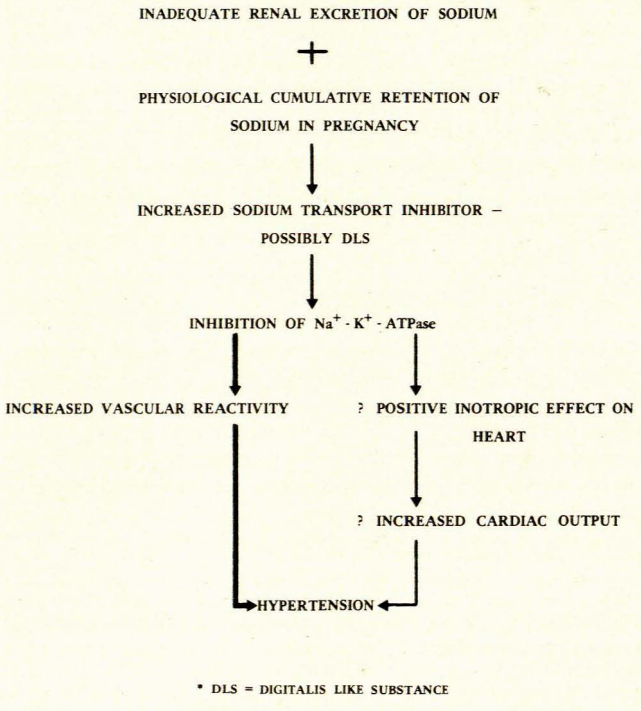

Fig. 2. The possible role of endogenous DLS in the development of pre-eclampsia.

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

1. Zaaiman J du T. Pre-eklampsie, die siekte van teorieë. *S Afr Med J* 1979; **56:** 121-122.
2. Beyers AD, Spruyt LL, Seifart HI, Kriegler A, Parkin DP, Van Jaarsveld PP. Digoxin immunoreactive substance in cord blood, neonates and placental extract of mothers not on digoxin therapy. *S Afr Med J* 1983; **64:** 42.
3. Dahl LK, Knudsen KD, Iwai J. Humoral transmission of hypertension: evidence from parabiosis. *Circ Res* 1969; suppl 1, 21-33.
4. De Wardener HE, MacGregor GA. Dahl's hypothesis that a saluretic substance may be responsible for a sustained rise in arterial pressure: its possible role in essential hypertension. *Kidney Int* 1980; **18:** 1-9.
5. MacGregor GA, Fenton S, Alaghband-Zadeh J, Markandu N, Roulson JE, De Wardener HE. Evidence for a raised concentration of a circulating sodium transport inhibitor in essential hypertension. *Br Med J* 1981; **283:** 1355-1357.
6. Kramer HJ. Natriuretic hormone — a circulating inhibitor of sodium- and potassium-activated adenosine triphosphate. *Klin Wochenschr* 1981; **59:** 1225-1230.
7. Haddy FJ. Humoral factors and the sodium-potassium pump in low renin hypertension. *Klin Wochenschr* 1982; **60:** 1254-1257.
8. La Bella FS. Is there an endogenous digitalis? *Trends Pharmacol Sci* 1982; **3:** 354-355.
9. Kuhnert BR, Kuhnert PM, Murray BA, Sokol RJ. Na/K- and Mg-ATPase activity in the placenta and in maternal and cord erythrocytes of pre-eclamptic patients. *Am J Obstet Gynecol* 1977; **127:** 56-60.
10. Valdes R, Brown BA. Endogenous substance in newborn infants causing false positive digoxin measurements. *J Pediatr* 1983; **102:** 947-950.
11. Gant NF, Worley RJ. *Hypertension in Pregnancy - Concepts and Management.* New York: Appleton-Century-Crofts, 1980.
12. Assali NS, Holm LW, Parker HR. Systemic and regional hemodynamic alterations in toxemia. *Circulation* 1964; **30:** suppl 2, 53-57.

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

H. J. WASSERMAN, A. OTTO

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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Department of Nuclear Medicine, Tygerberg Hospital, Parowvallei, CP
H. J. WASSERMAN, M.SC., PH.D.
A. OTTO, M.MED. (INT.) (Present address: Department of Nuclear Medicine, Universitas Hospital, Bloemfontein)

Reprint requests to: Dr H. J. Wasserman, Dept of Nuclear Medicine, Tygerberg Hospital, Tygerberg, 7505 RSA.

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.[1] 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.[2] The estimation of chamber size from chest radiographs is difficult in the presence of overinflation of the lungs.[3]

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 ($38 \pm 2\%$). 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. Winzelberg[5] 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.[7] Since radionuclide techniques are much less dependent on geometrical factors, they represent an attractive way of determining the RVEF.[5,8]

Although the RVEF could be obtained from a gated blood pool study at equilibrium,[9] first-pass radionuclide cardioangiography is preferred by many because of temporal and