Do high fetal catecholamine levels affect heart rate variability and meconium passage during labour?

G. J. HOFMEYR, J. ESSER, V. CHERYL NIKODEM, MARIE LAWSON, T. KRAMER, A. M. GÜLMEZOGLU

Abstract *Objectives.* **To determine the relationship between umbilical arterial catecholamine levels and fetal heart rate variability and meconium passage.**

Study design. **A prospective descriptive study was performed. Umbilical artery catecholamine levels were measured in 55 newborns and correlated with fetal heart rate before delivery, umbilical arterial pH, base excess and the presence of meconium-stained liquor.**

Results and conclusion. **The range of catecholamine levels was enormous, with very high epinephrine or norepinephrine levels in several fetuses. We were unable to demonstrate an association between high catecholamine levels and the presence of normal fetal heart rate variability despite acidaemia. We postulate that high catecholamine levels may inhibit fetal meconium passage.**

S Afr Med J 1993; **83:** 739-742.

The use of fetal heart rate (FHR) patterns during labour to evaluate fetal well-being is imprecise.[1,2] Baseline variability is considered to be one of the most important indicators of fetal well-being,[3] yet false-positive results are common. False-negative results (good variability despite fetal compromise) are less common but potentially more serious. A possible explanation for the presence of normal variability despite fetal compromise is the effect of high catecholamine levels in the asphyxiated fetus.

Induced hypoxaemia in healthy fetal lambs produces increased FHR variability[4,5] and catecholamine secretion.[6-8] Catecholamine infusion to simulate the levels occurring during hypoxaemia also causes an increase in variability.[6] The increased FHR variability that occurs during hypoxaemia in fetal lambs may therefore be a catecholamine effect.[9] The possibility that this mechanism may operate in human fetuses is supported by the finding of raised levels of fetal scalp plasma norepinephrine in association with increased FHR variability during labour.[10]

We undertook a prospective study to assess the relationship between FHR variability, meconium excretion, acidaemia and catecholamine secretion in human fetuses.

Department of Obstetrics and Gynaecology, Coronation Hospital and University of the Witwatersrand, Johannesburg
G. J. HOFMEYR, M.B. B.CH., M.R.C.O.G.
V. CHERYL NIKODEM, B.A. CUR.
T. KRAMER, M.B. B.CH.
A. M. GÜLMEZOGLU, M.D.
Department of Nuclear Medicine, Johannesburg Hospital and University of the Witwatersrand, Johannesburg
J. ESSER, M.B. B.CH., M.MED.
MARIE LAWSON, B.SC.

Accepted 24 Nov 1992.
Reprint requests to: Prof. G. J. Hofmeyr, Dept of Obstetrics and Gynaecology, Coronation Hospital and University of the Witwatersrand, York Road, Parktown, 2193 RSA.

Subjects and methods

Fifty-five women in established labour were asked to participate in this study. In all cases continuous external cardiotocography (CTG) was in progress. After delivery the umbilical cord was clamped at two points about 20 cm apart, and cord arterial blood collected. One sample was collected into a heparinised syringe and blood gases were measured immediately by means of an automated analyser (Protea Instrumentation 1312 Blood Gas Manager). The other sample was collected into a cooled syringe, transferred to a cooled ethylenediamine tetra-acetic acid (EDTA) tube, and immediately centrifuged at 5 000 revolutions per minute; the plasma was frozen in liquid nitrogen within 4 minutes of collection for catecholamine assays. Norepinephrine, epinephrine and dopamine levels were measured by high-performance liquid chromatography.[11] Dopamine levels were measured in only 30 of the 55 samples because of inadequate volumes of plasma.

Clinical data were obtained from the hospital notes. The abdominal cardiotocographic tracings were saved and later evaluated blind to the clinical and other details of each case. Long-term FHR variability was defined as the range of spontaneous baseline heart rate fluctuations with a cyclicity of 3 - 6 per minute,[12] excluding episodes of acceleration or deceleration. Long-term variability was evaluated over the last 10 minutes of good-quality recording before delivery. Variability below 10 beats per minute was taken as reduced.

Statistical comparisons were done using the Mann-Whitney *U*-test for continuous variables and Fisher's exact probability test for proportions.

Results

The mean age of the 55 subjects was 23 years (range 16 - 38 years) and the mean gestational age 39 weeks (range 34 - 42 weeks); 3 deliveries were preterm (< 37 weeks). One delivery was by caesarean section during labour, 3 were assisted, and the remainder were spontaneous.

There was no correlation between the presence of reduced FHR variability or meconium staining of the amniotic fluid, and fetal acidaemia, defined as cord arterial base excess (BE) less than –10 mmol/l (Table I).

TABLE I.
Relationship of neonatal acidaemia to long-term variability and the presence of meconium staining of the amniotic fluid (*N* = 55)

	Umbilical arterial BE	
	< –10	⩾ –10
No.	13	41
FHR variability < 10/min	5 (38%)	12 (29%)
Meconium present	2 (15%)	6 (15%)

There were no statistically significant differences. One sample had no BE result.

The ranges of catecholamine levels measured were enormous (Table II and Figs 1 and 2). The number of dopamine measurements is too small for meaningful

comment and will not be referred to further, but the results are included for completeness. None of the differences between the groups compared was statistically significant. Among the acidaemic fetuses, those with normal FHR variability tended to have lower rather than higher norepinephrine and epinephrine levels (Table II).

Discussion

The accurate evaluation of fetal well-being during labour remains an unsolved problem. As confirmed in this study, meconium staining of the amniotic fluid is a very unreliable indicator of fetal acidaemia. This is not surprising, since many other factors such as fetal age and maternal ingestion of herbal remedies or aperients[13] may be associated with meconium passage *in utero*. The presence of meconium calls for careful evaluation of fetal well-being[14] and vigilance at the time of delivery to avoid meconium aspiration, but not in itself for expedited delivery. Similarly, reduced FHR variability alone was not predictive of fetal acidaemia. The failure of electronic FHR monitoring to identify fetal distress with accuracy is reflected in the failure of several large randomised trials to demonstrate any clear benefit from the routine use of electronic FHR monitoring in uncomplicated labours that are neither prolonged nor augmented with oxytocin.[14]

Fetal norepinephrine and epinephrine levels increase considerably during labour, and exceed maternal levels at delivery.[15,16] High catecholamine levels are thought to be of importance for various adaptations to extra-uterine life,[17] including non-shivering thermogenesis,[18] lung

TABLE II.
Comparisons of cord catecholamine levels (pg/ml) according to FHR and neonatal variables

	Epinephrine			Norepinephrine			Dopamine		
	N	Median	Range	*N*	Median	Range	*N*	Median	Range
Liquor									
Clear	45	193	U - 3 000	46	1 432	188 - 26 108	25	59	28 - 281
Meconium	9	92	U - 1 048	9	970	98 - 13 952	5	55	49 - 376
Cord arterial BE									
⩾ –10	41	132	U - 1 406	41	1 333	98 - 26 108	20	57	28 - 376
< –10	12	203	U - 3 000	13	1 507	515 - 23 727	18	55	28 - 376
FHR variability									
⩾ 10/min	37	178	U - 1 624	37	1 401	188 - 23 727	18	55	28 - 376
< 10/min	17	119	U - 3 000	18	1 583	98 - 26 108	12	64	36 - 281
Subgroup BE									
< –10 FHR variability									
⩾ 10/min	8	203	U - 1 624	8	1 226	515 - 3 839	6	57	35 - 122
< 10/min	4	595	U - 2 985	5	6 532	620 - 21 855	5	108	36 - 119

U = unrecordable; lower limit of assay 15 pg/ml.
There were no statistically significant differences.

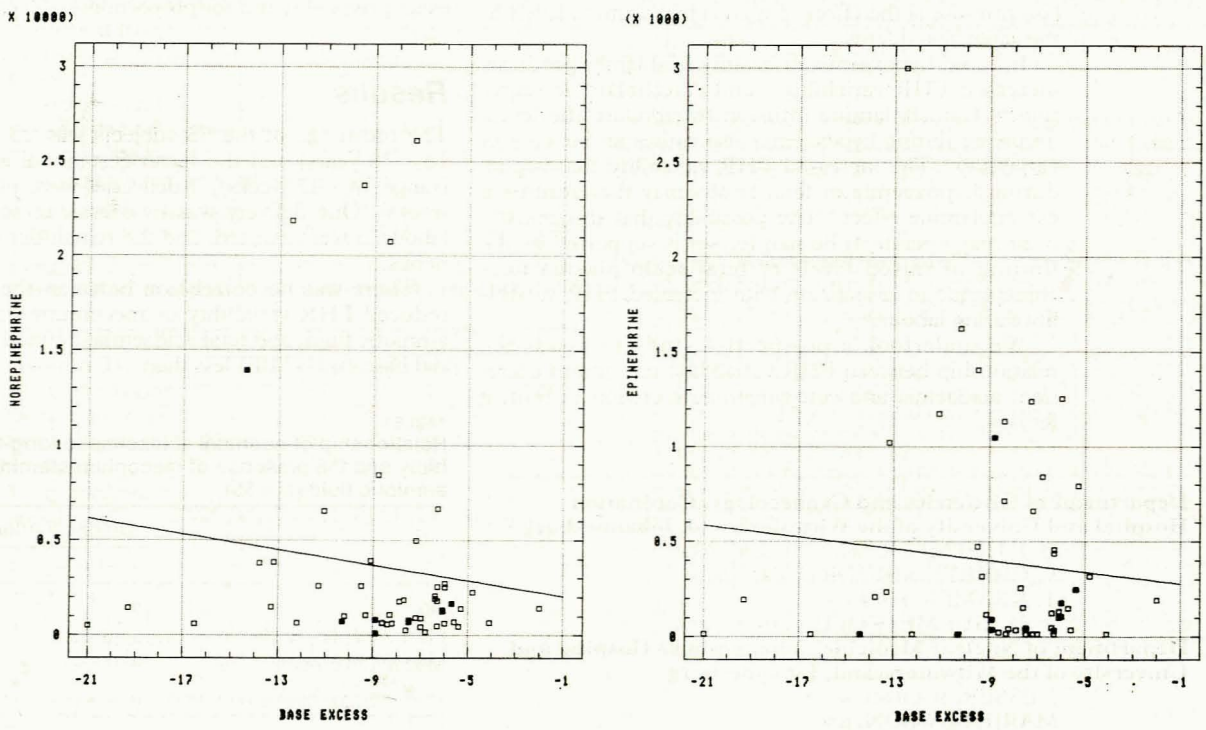

FIG. 1.
Correlation of norepinephrine (above; $r = 0,12$, $P = 0,38$) and epinephrine (below; $r = -0,09$, $P = 0,48$) levels with base excess (■ = meconium-stained amniotic fluid; □ = clear amniotic fluid).

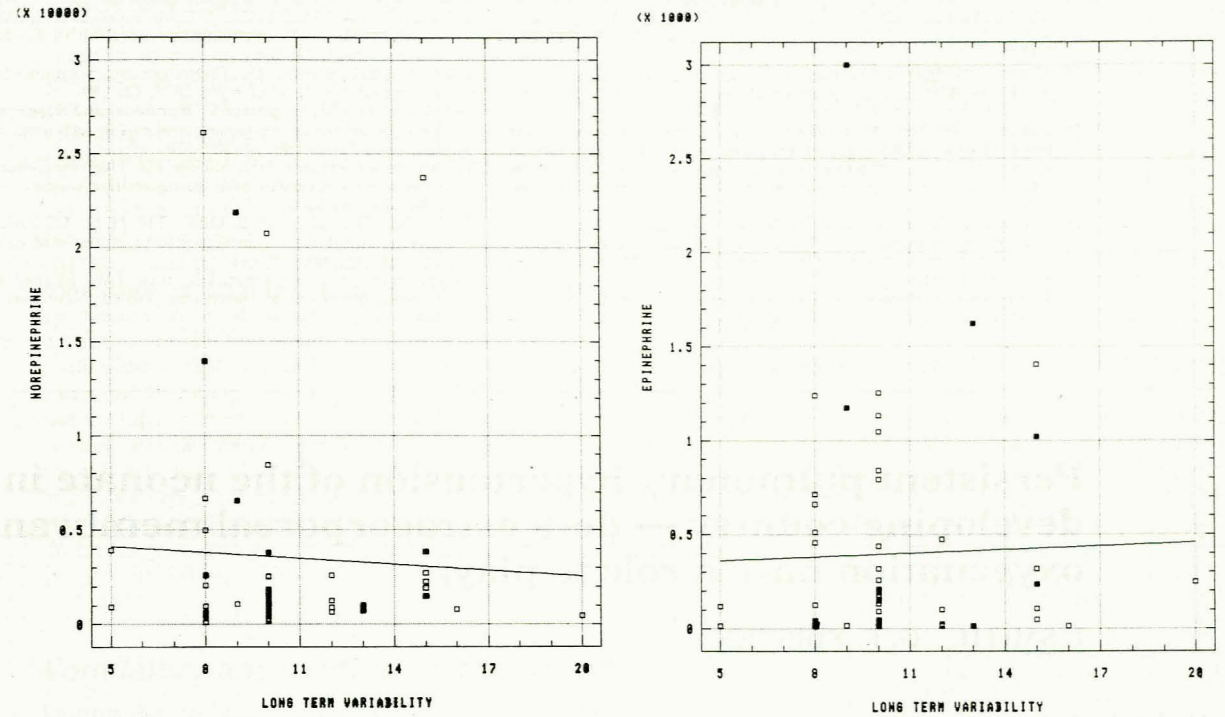

FIG. 2.
Correlation of norepinephrine (above; $r = -0,04$, $P = 0,72$) and epinephrine (below; $r = 0,03$, $P = 0,81$) levels with long-term variability (■ = base excess < −10; □ = base excess ⩾ −10).

liquid absorption[19] and surfactant glycerophospholipid synthesis.[20] In 1990 Anand *et al.*[21] found the hormonal stress response (including catecholamines) in neonates undergoing cardiac surgery to be more extreme than in adults, and the larger responses tended to be associated with poor survival. In cord arterial blood, norepinephrine has been found to be inversely related to pH and oxygen tension (Po_2), and epinephrine to pH.[22] Both were elevated in 3 infants showing late or severe variable FHR decelerations, and meconium staining of the amniotic fluid was associated with significantly higher norepinephrine but not epinephrine values.[22]

We confirmed the overall high catecholamine levels in cord arterial blood and enormously high values in several of the fetuses studied, but were unable to substantiate the hypothesis that normal FHR variability despite fetal acidaemia may be a function of raised catecholamine levels. In the whole group as well as in the acidaemia group, catecholamine levels tended to be lower rather than higher when FHR variability was not reduced.

An unexpected observation was that the presence of meconium tended to be associated with lower rather than higher epinephrine levels. In adults, catecholamines are known to inhibit bowel emptying.[23] We put forward the hypothesis, which will need to be confirmed in a prospective study, that high fetal epinephrine levels during labour may be of importance in inhibiting the passage of meconium.

Conclusions

We conclude that normal FHR variability, despite moderate fetal acidaemia, is not usually associated with higher catecholamine levels. Whether inappropriately normal variability, induced by high catecholamine levels, is a feature of more severe fetal asphyxia could not be addressed in this study. We postulate that high fetal epinephrine levels during labour might be protective against the premature passage of meconium.

We acknowledge the clinical assistance of the nursing and medical staff of Coronation Hospital; statistical calculations by Dr G. Reinach and April Anderson, Institute for Biostatistics, South African Medical Research Council; and financial support from the South African Medical Research Council and the Iris Ellen Hodges Fund of the University of the Witwatersrand.

REFERENCES

1. Sykes GS, Molloy PM, Johnson P, Stirray G, Turnbull AC. Fetal distress and the condition of newborn infants. *BMJ* 1983; **287:** 943-945.
2. Murphy KW, Johnson P, Moorcroft J, Pattinson R, Russell V, Turnbull A. Birth asphyxia and the intrapartum cardiotocograph. *Br J Obstet Gynaecol* 1990; **97:** 470-479.
3. Spencer JAD. Fetal heart rate variability. In: Studd J, ed. *Progress in Obstetrics and Gynaecology*. Edinburgh: Churchill Livingstone, 1990: 103-122.
4. Stange L, Rosen KG, Hökegard KH, *et al.* Quantification of fetal heart rate variability in relation to oxygenation in the sheep fetus. *Acta Obstet Gynecol Scand* 1977; **56:** 205-209.
5. Dalton KJ, Dawes GS, Patrick JE. Diurnal, respiratory and other rhythms of fetal heart rate in lambs. *Am J Obstet Gynecol* 1977; **127:** 414-424.
6. Jones CT, Robinson RO. Plasma catecholamines in fetal and adult sheep. *J Physiol* 1975; **248:** 15-33.
7. Hooper SB, Coulter CL, Deayton JM, Harding R, Thorburn GD. Fetal endocrine response to prolonged hypoxemia in sheep. *Am J Physiol* 1990; **259:** R703-708.
8. Cheung CY. Fetal adrenal medulla catecholamine response to hypoxia — direct and neural components. *Am J Physiol* 1990; **258:** R1340-1346.
9. Jones CT, Ritchie JW. The effects of adrenergic blockade on fetal response to hypoxia. *J Dev Physiol* 1983; **5:** 211-222.
10. Bistoletti P, Lagercrantz H, Lunell NO. Fetal plasma catecholamine concentrations and fetal heart rate variability during first stage of labour. *Br J Obstet Gynaecol* 1983; **90:** 11-15.
11. Causon RC, Carruthers ME. Measurement of catecholamines in biological fluids by high performance liquid chromatography: a comparison of fluorometric with electrochemical detection. *J Chromatogr* 1982; **229:** 301-309.
12. Parer JT. *Handbook of Fetal Heart Rate Monitoring.* Philadelphia: W B Saunders, 1983: 88.

13. Mitri F, Hofmeyr GJ, Van Gelderen CJ. Meconium during labour: self-medication and other associations. *S Afr Med J* 1983; **71:** 431-433.
14. Grant A. Monitoring the fetus during labour. In: Chalmers I, Enkin M, Keirse MJNC, eds. *Effective Care in Pregnancy and Childbirth*. Vol. 2. Oxford: Oxford University Press, 1989: 846-882.
15. Suzuki A, Hashino M, Chiba H, *et al.* Correlation between the levels of catecholamines (noradrenaline, adrenaline) and adrenal steroids (DHA-S, cortisol) in maternal and fetal blood during pregnancy and labour. *Nippon Naibunpi Gakkai Zasshi* 1989; **65:** 704-714.
16. Schneider H, Progler M, Ziegler WH, Huch R. Biochemical changes in the mother and the fetus during labour and its significance for the management of the second stage. *Int J Gynaecol Obstet* 1990; **31:** 117-126.
17. Lagercrantz H, Bistoletti P. Catecholamine release in the newborn infant at birth. *Pediatr Res* 1973; **11:** 889.
18. Stern L, Lees MH, Leduc J. Environmental temperature, oxygen consumption and catecholamine excretion in newborn infants. *Pediatrics* 1965; **36:** 369.
19. Walters DV, Walters RE. The role of catecholamines in lung liquid absorption at birth. *Pediatr Res* 1978; **12:** 239.
20. Mendelson CR, Boggaram V. Hormonal and developmental regulation of pulmonary surfactant synthesis in fetal lung. *Baillieres Clin Endocrinol Metab* 1990; **4:** 351-378.
21. Anand KJ, Hansen DD, Hickey PR. Hormonal-metabolic stress responses in neonates undergoing cardiac surgery. *Anesthesiology* 1990; **73:** 661-670.
22. Padbury JF, Roberman B, Oddie TH, Hobel CJ, Fisher DA. Fetal catecholamine release in response to labour and delivery. *Obstet Gynecol* 1982; **60:** 607-611.
23. Gillman AG, Goodman LS, Rall TW, Murad F, eds. *The Pharmacologic Basis of Therapeutics.* 7th ed. New York: Macmillan, 1985: 155.