when displayed represents a section 18-mm thick through the body. The information gathered provides two images. The first uses proton density as the imaging value and the second uses proton spin-lattice relaxation time (T_1). We find the T_1 images more useful for showing normal anatomical structures and pathological lesions and have used them to illustrate this case.

Case report

A 66-year-old retired fish curer was admitted with a four-month history of increasing anorexia, nausea, and weight loss. In the previous two months he had experienced difficulty in swallowing solids. He also gave a history of right hypochondrial pain, which radiated through to his back. On examination he was found to be a thin anaemic man (haemoglobin 8.8 g/dl), whose abdomen was normal on palpation with no masses or hepatomegaly. A presumptive diagnosis of carcinoma of the oesophagus was made, which was subsequently proved by barium meal examination (fig 1) and oesophagoscopy. A biopsy of the tumour showed it to be a moderately differentiated adenocarcinoma. Because his alkaline phosphatase and gamma-glutamyl transferase activities were raised, at 557 U/l and 362 U/l respectively, a ^{99m}Tc sulphur colloid liver scan was performed, which showed hepatic metastases (figs 2 and 3).

The patient was referred for NMR imaging, which showed the large tumour in the lower third of the oesophagus (fig 4). Sections through the liver clearly showed a number of areas of increased T_1 (fig 5), corresponding to the metastases shown by the radionuclide liver scan. These lesions gave a T_1 of about 330 ms compared with a normal liver T_1 (measured in normal subjects) of 140-165 ms.

In addition to the hepatic metastases, several areas of increased T_1 were noted in some of the vertebral bodies (fig 5). When the vertebral body of T9 in fig 4 is compared with that of T12 in fig 5 a very definite difference in appearance is evident. The T_1 of T9 is the normal range of 190-220 ms and that of T12 291 ms. As the presence of bone metastases had hitherto been unsuspected, a bone scan with ^{99m}Tc -methylene diphosphonate was performed, which showed widespread bone metastases (fig 6).

Conclusion

We present in this paper the thoracic and abdominal images of what we believe to be the first patient to be examined by whole-body NMR imaging. These transverse tomographic images compared favourably with the other diagnostic techniques used to show the lesions in this patient. We believe that the continued clinical trial of this imager will prove it to be an accurate diagnostic aid, which will complement existing techniques for diagnosing intrathoracic and intra-abdominal conditions.

References

- 1 Mansfield P, Maudsley AA. Medical imaging by NMR. *Br J Radiol* 1977; **50**:188-94.
- 2 Hinshaw WS, Bottomley PA, Holland GN. Radiographic thin-section image of the human wrist by nuclear magnetic resonance. *Nature* 1977; **270**:722-3.
- 3 Holland GN, Moore WS, Hawkes RC. NMR neuroradiology. *Br J Radiol* 1980; **53**:253-5.
- 4 Moore WS, Holland GN. Nuclear magnetic resonance imaging. *Br Med Bull* 1980; **36**:297-9.
- 5 Mansfield P, Pykett IL, Morris PG, Coupland RE. Human whole body line-scan imaging by NMR. *Br J Radiol* 1978; **51**:921-2.
- 6 Damadian R, Minkott L, Goldsmith M. NMR in cancer: XXI fonar scan of the live human abdomen. *Physiology, Chemistry and Physics* 1978; **10**:561-3.
- 7 Edelstein WA, Hutchison JMS, Johnson G, Redpath T. Spin warp NMR imaging and applications to whole body imaging. *Phys Med Biol* 1980; **25**:751-6.
- 8 Edelstein WA, Hutchison JMS, Smith FW, Mallard JR, Johnson G, Redpath TW. Human whole-body NMR Tomographic imaging: normal sections. *Br J Radiol* (in press).
- 9 Hutchison JMS, Edelstein WA, Johnson G. A whole-body NMR imaging machine. *J Phys E Sci Instrum* 1980; **13**:947-55.

(Accepted 6 January 1981)

Plasmatic regulation of vascular prostacyclin in pregnancy

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Abstract

Activity of prostacyclin-stimulating factor was measured in six normal, non-pregnant women, six women in early normal pregnancy, six in late normal pregnancy, and six in late pregnancy complicated by severe pre-eclampsia. The activity was lower in the women in late pregnancy than in those in early pregnancy and the

controls but was about normal in those with severe pre-eclampsia.

These results may be relevant to the physiology of pregnancy and the pathogenesis of pre-eclampsia.

Introduction

Pregnancy is physiologically associated with low blood pressure, although blood volume and cardiac output are increased.¹ This is facilitated by arteriolar vasodilatation inducing a reduction in total peripheral resistance. These haemodynamic changes are paradoxically accompanied by a striking activation of the renin-angiotensin-aldosterone system.¹ In contrast with normal pregnancy, pre-eclampsia is characterised by high blood pressure with increased peripheral resistance, low cardiac output, and relative suppression of the renin-angiotensin-aldosterone system.² The observation that pregnant animals and pregnant women have raised plasma concentrations of prostaglandins of the E type suggested that an increase in vasodilatory prostaglandins might account for the low peripheral resistance and high renin activity.³ Prostaglandin E_2 stimulates renin in different

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experimental systems.⁴ Moreover, raised concentrations of vasoconstrictory prostaglandin $F_{2\alpha}$ but low concentrations of vasodilatory prostaglandin E_2 have been found in pregnancies complicated by pre-eclampsia.⁵ Another feature of normal pregnancy is the resistance to the pressor effect of angiotensin, whereas in overt toxemia sensitivity to angiotensin exceeds that found in non-pregnant women.³ Indomethacin reverses the pressor hyporesponsiveness to angiotensin, adding further evidence that prostaglandins may play a part in pregnancy.¹⁻³⁻⁵

The discovery of prostacyclin added an important piece to this puzzle. Might vascular prostacyclin, rather than the classical stable prostaglandins, be responsible for the haemodynamic changes of pregnancy? Results of experimental studies support this possibility.⁶ The instability of prostacyclin, however, and the fact that its generation cannot be easily measured in human vessels make the problem difficult to approach clinically.

The observation that vascular synthesis of prostacyclin may be regulated by a factor present in normal human plasma,⁷

Patients with a family history of hypertension, hydramnios, multiple pregnancy, or diabetes were excluded from the study. All patients and controls denied ingestion of any drug during the month preceding the study.

Plasma samples for measurement of activity of prostacyclin-stimulating factor were prepared from citrated venous blood.¹¹ The samples were incubated with rat aortic rings and the amount of prostacyclin activity generated in the system measured according to the following method. Rat aortas were removed surgically and cut into rings (5-6 mg wet weight) as described.¹² After 10 minutes' incubation with trometamol at room temperature the basal release of prostacyclin was measured as both platelet aggregation inhibitory potency¹³ and the amount of the stable prostacyclin derivative 6-keto-prostaglandin $F_{1\alpha}$ detectable by radioimmunoassay.¹⁴ The rings were then incubated for five minutes at room temperature with 100 μ g angiotensin II to exhaust completely their ability to produce prostacyclin. Then the "exhausted" rings were incubated for 25 minutes at room temperature with 1.5 mmol sodium arachidonate (Sigma)/l (49 mg/100 ml), washed, and resuspended in buffer.

Clinical data on patients, measured at time of determination of prostacyclin-stimulating factor activity

Case No	Age (years)	Maturity (weeks)	Diastolic blood pressure (mm Hg)	Platelet count ($\times 10^9/l$)	Plasma urate (μ mol/l)	Proteinuria (g/l)
<i>Early normal pregnancy</i>						
1	19	4	70	300	190	0.1
2	30	9	55	250	220	0.2
3	24	7	65	310	173	0.1
4	23	10	60	220	167	0.1
5	26	11	70	240	184	0.2
6	30	12	55	230	149	0.1
<i>Late normal pregnancy</i>						
7	28	34	60	250	149	0.1
8	21	40	70	300	190	0.2
9	23	42	70	220	214	0.1
10	30	40	65	270	143	0.1
11	29	40	55	250	214	0.1
12	24	42	60	230	167	0.1
<i>Pre-eclampsia</i>						
13	28	34	125	250	452	4
14	21	41	110	90	327	3.5
15	21	34	110	90	613	4.4
16	24	38	100	190	553	1.6
17	32	35	100	180	327	1
18	24	29	110	125	452	4.5
<i>Normal ranges in non-pregnant controls</i>						
17-35			60-80	235-320	178-297	0-0.2

Conversion: SI to traditional units—Urate: 1 μ mol/l $\approx$ 16.8 μ g/100 ml.

tentatively called prostacyclin-stimulating factor, offered an indirect means of assessing vascular activity of prostacyclin in man. Such an approach was validated by the finding of a good correlation between high activities of prostacyclin-stimulating factor and vascular prostacyclin in patients with severe renal failure and, conversely, low activities of prostacyclin-stimulating factor and vascular prostacyclin in patients with the haemolytic uraemic syndrome.⁸⁻¹⁰

The purpose of the present study was to measure the activity of prostacyclin-stimulating factor in normal and complicated pregnancies.

Patients and methods

We studied six non-pregnant women, six women in early (<13 weeks) normal pregnancy, six in late (>34 weeks) normal pregnancy, and six in late (>29 weeks) pregnancy complicated by severe pre-eclampsia. All were primigravidae. Severe pre-eclampsia was defined on the basis of the simultaneous occurrence of the following abnormalities on at least three consecutive occasions: (1) an increase in blood pressure of over 30 mm Hg systolic and over 20 mm Hg diastolic above the value obtained during the first trimester; (2) an increase in plasma urate concentration above 0.3 mmol/l (5 mg/100 ml); (3) proteinuria in excess of 0.5 g/l in the absence of obvious infection; and (4) generalised oedema.

After this procedure no antiaggregating activity and only a negligible amount of 6-keto-prostaglandin $F_{1\alpha}$ were detectable in the supernatant. Further incubation with normal human plasma, however, renewed the capacity of the aortic tissue to produce prostacyclin.

A strong correlation with the amount of 6-keto-prostaglandin $F_{1\alpha}$ released identified the antiaggregating activity of supernatant as prostacyclin. For practical reasons the antiaggregating effect of prostacyclin was selected as a measure of prostacyclin-stimulating factor. Microlitre amounts of supernatant plasma were added to 250 μ l of platelet-rich plasma obtained from five selected normal subjects whose response to synthetic prostacyclin had been shown to be satisfactorily reproducible over a three-year period of investigation. The aggregation response of this mixture to 0.7-1.4 μ mol adenosine diphosphate/l (30-60 μ g/100 ml) was tested in an aggregometer¹⁵ and the results expressed as percentage of initial platelet aggregation velocity compared with that in normal control plasma studied simultaneously. Appropriate controls were run in parallel with unincubated plasma.

The method for determining activity of prostacyclin-stimulating factor will be described in detail elsewhere.

Results

The table shows the main clinical characteristics of the patients with normal or complicated pregnancies. Blood pressure, urate concentration, and proteinuria were significantly higher in patients

with severe pre-eclampsia than the control group. Four out of six patients with severe pre-eclampsia delivered small babies (1050-1900g).

The figure shows the activity of prostacyclin-stimulating factor in all patients and controls. No significant difference was found between non-pregnant women and women in early pregnancy. In contrast, a significant reduction ($p < 0.01$) in activity was observed in women in late pregnancy. Patients with severe pre-eclampsia showed activities within the range of those in the control, non-pregnant women but significantly higher ($p < 0.01$) than those in comparable women with normal pregnancies.

Activity of prostacyclin-stimulating factor in all women studied expressed as percentage of that in control plasma. Bars indicate mean values.

Discussion

This study shows that in early pregnancy the plasmatic activity of prostacyclin-stimulating factor was comparable with that in non-pregnant women, whereas in late pregnancy the activity was significantly depressed. Activity was not low in patients with severe pre-eclampsia. These results were surprising because both animal and human studies had previously indicated that vascular prostacyclin activity increased in late normal pregnancy.^{6,16}

Recently Lewis *et al.*¹⁷ reported that plasma concentrations of 6-keto-prostaglandin $F_{1\alpha}$ are similar in non-pregnant women and women in early pregnancy but significantly higher in late pregnancy. Possibly the activity of prostacyclin-stimulating factor present in normal plasma is depressed in late normal pregnancy by a feedback mechanism limiting an excessive increase in vascular prostacyclin. In severe pre-eclampsia, when vascular prostacyclin synthesis seems to be depressed,¹⁸ normal activity might act as a reactive defence mechanism. This interpretation is reinforced by the observation that in five patients with malignant hypertension activity of prostacyclin-stimulating factor was within the normal range (unpublished results).

Besides perhaps being relevant to the pathogenesis of pre-eclampsia, the present data suggest that more than one mechanism might operate in the control of vascular prostacyclin production in pregnancy.

The striking similarity between the behaviour of prostacyclin-stimulating factor reported here and the response of blood pressure to angiotensin II in normal and complicated pregnancy merits comment. While the sensitivity to angiotensin II was appreciably reduced in the third trimester of normal pregnancy, it was within the normal range or even higher in patients with pre-eclampsia examined during the third trimester.¹⁹

The increased synthesis of prostacyclin may explain both the resistance to angiotensin and the reduction in activity of prostacyclin-stimulating factor seen in normal pregnancy. Conversely, in pre-eclampsia normal angiotensin sensitivity and

activity of prostacyclin-stimulating factor might reflect a reduction in synthesis of prostacyclin. The relations between the factor(s) modulating sensitivity to angiotensin and the plasma activity of prostacyclin-stimulating factor warrant careful investigation.

Synthetic prostacyclin was kindly provided by Professor C Gandolfi, Carlo Erba Farmitalia, Milan.

We thank Dr E Cappato and Dr D Muratore, division of obstetrics and gynaecology II, Ospedali Riuniti, Bergamo, for helpful co-operation.

This work was supported in part by the Associazione Bergamasca per lo Studio delle Malattie Renali, Bergamo, and the Italian CNR (Farmacologia Clinica e Malattie Rare).

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References

- Kerr MG. Cardiovascular dynamics in pregnancy and labour. *Br Med Bull* 1968;**24**:19-24.
- Wier RJ, Brown JJ, Fraser R, *et al.* Plasma renin, renin substrate, angiotensin II, and aldosterone in hypertensive disease of pregnancy. *Lancet* 1973;ii:291-4.
- Ferris TF. Postpartum renal insufficiency. *Kidney Int* 1978;**14**:383-92.
- Gerber JG, Branch RA, Nies AS, *et al.* Prostaglandins and renin release. II. Assessment of renin secretion following infusion of PGI₂, E₂ and D₂ into the renal artery of anesthetized dogs. *Prostaglandins* 1978;**15**:81-8.
- Demers LM, Gabbe SG. Placental prostaglandin levels in pre-eclampsia. *Am J Obstet Gynecol* 1976;**126**:137-9.
- Terragno NA, McGiff JC, Murray S, Terragno A. Patterns of prostaglandin production in the bovine fetal and maternal vasculature. *Prostaglandins* 1978;**16**:847-56.
- MacIntyre DE, Pearson JD, Gordon JL. Localisation and stimulation of prostacyclin production in vascular cells. *Nature* 1978;**271**:549-51.
- Defreyn G, Vergara Dauden M, Machin SJ, Vermeylen J. A plasma factor in uraemia which stimulates prostacyclin release from cultured endothelial cells. *Thromb Res* 1980;**19**:695-9.
- Remuzzi G, Cavenaghi AE, Mecca G, Donati MB, de Gaetano G. Prostacyclin-like activity and bleeding in renal failure. *Lancet* 1977;ii:1195-7.
- Remuzzi G, Misiani R, Marchesi D, *et al.* Haemolytic-uraemic syndrome: deficiency of plasma factor(s) regulating prostacyclin activity? *Lancet* 1978;ii:871-2.
- de Gaetano G, Miragliotta G, Roncucci R, Lansen J, Lambelin G. Suloctidil: a novel inhibitor of platelet aggregation in human beings. *Thromb Res* 1976;**8**:361-71.
- Remuzzi G, Livio M, Cavenaghi AE, *et al.* Unbalanced prostaglandin synthesis and plasma factors in uraemic bleeding. A hypothesis. *Thromb Res* 1978;**13**:531-6.
- Moncada S, Higgs EA, Vane JR. Human arterial and venous tissues generate prostacyclin (prostaglandin X), a potent inhibitor of platelet aggregation. *Lancet* 1977;ii:18-20.
- Dray F, Pradelles P, MacLough J, Sors H, Bringuier A. Radioimmunoassay of 6-keto-PGF_{1α} using an iodinated tracer. *Prostaglandins* 1978;**15**:715.
- Born GVR, Cross MJ. The aggregation of blood platelets. *J Physiol* 1963;**168**:178-95.
- Remuzzi G, Misiani R, Muratore D, *et al.* Prostacyclin and human foetal circulation. *Prostaglandins* 1979;**18**:341-8.
- Lewis PJ, Boylan P, Friedman LA, Hensby CN, Downing I. Prostacyclin in pregnancy. *Br Med J* 1980;**280**:1581-2.
- Remuzzi G, Marchesi D, Zoja C, *et al.* Reduced umbilical and placental vascular prostacyclin in severe pre-eclampsia. *Prostaglandins* 1980;**20**:105-10.
- Gant NF, Daley GL, Chand S, Whalley PJ, MacDonald PC. A study of angiotensin II pressor response throughout primigravid pregnancy. *J Clin Invest* 1973;**52**:2682-9.

(Accepted 26 November 1980)

Correction

Effect of disothèque environment on epileptic children

An error occurred in this paper by Dr T P Berney and others (17 January, p 180). The test statistic given in the Appendix should have read:

$$U = \frac{D_{1t_2} - D_{2t_1}}{\sqrt{(D_1 + D_2) t_1 t_2}}$$