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Hemodynamic and hemorheological profiles in women with proteinuric hypertension of pregnancy and in pregnant controls

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Summary. We obtained blood samples from 52 patients with pre-eclampsia and from 40 pregnant controls for measurement of plasma urate levels, hematocrit, white cell count and various hemorheoligical parameters (see Table 3). We also used impedance cardiography to measure cardiac output in both groups and from the results derived values for total peripheral resistance and oxygen transport. Central venous pressure was measured with a superior vena cava catheter in patients with pre-eclampsia but not in controls. Women with pre-eclampsia had significantly lower cardiac output and central venous pressure when compared with a control group. A modest correlation was observed between central venous pressure and cardiac output. The majority of pre-eclamptic patients had significantly raised hematocrit, leucocyte count, uric acid and red cell aggregation. Red cell deformability was significantly decreased in patients with pre-eclampsia. Most patients with severe pre-eclampsia (BP diast. > 100 mmHg) had a low Antithrombin III and colloid osmotic pressure level. The leucocyte count was raised when compared with the women with moderate pre-eclampsia. Oxygen delivery was reduced in patients with pre-eclampsia because of impaired rheological properties of their blood.

Key words: Pre-eclampsia – Hemorheology – Cardiac output – Impedance Cardiography

Introduction

Pregnancy-induced proteinuric hypertension (or pre-eclampsia) is associated with exaggregated arterial reactivity (Gant 1973). Although the rate of tissue perfusion is dependent on cardiovascular factors recent studies (Guyton 1963,

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Chien 1972, Schmid-Schönbein 1976) have indicated that the rheological properties of blood can also play a significant role in the regulation of blood flow. Proteinuric hypertension may also be associated with a hyperviscosity syndrome (Mathews 1974, Hobbs et a. 1982, Buchan 1982, Oggolter-Siekmann et al. 1984).

The viscosity of normal blood is a function of hematocrit, plasma viscosity, red cell aggregation and red cell deformability with the last two parameters being flow dependent. In small vessels the concentration and adhesiveness of white cells can also exert a significant effect on flow resistance (Chien 1985, Braide 1984). Postcapillary venules, small veins and the intervillous space of the placenta have the lowest shear stress in the circulation and represent the most likely sites of red cell aggregation (Chien 1969, Scholz et al. 1975). With normal cardiovascular and respiratory function, hematocrit and blood viscosity reflect the rate of oxygen delivery (Chien 1987). It would appear that the physiological mechanisms for the control of red cell volume and plasma are coordinated such that the hematocrit stays in the optimum range.

The optimum hematocrit in pregnancy was given by Garn et al. (1981) and by Murphy et al. (1986) as between 30% and 38%. This entails a hemoglobin content of 10.0–13.2 g/dl (Murphy et al. 1986) or of 10.4–13.3 g/dl (Garn et al. 1981). Hemoglobin values above 13.2 g/dl or a hematocrit above 38% were associated with a statistically significant rise in fetal pathology (perinatal death, premature babies, low birth weight) and also with pregnancy-induced hypertension. In severe proteinuric hypertension and fetal pathology Sagen et al. (1984) found hemoconcentration (Hb more than 13 g/dl) in 82% of cases.

The aim of the present study was to examine the relationship between the rheological properties of blood and hemodynamic and clinical data in a group of pre-eclamptic patients.

Patients and methods

The study was performed on 52 women with pregnancy-induced proteinuric hypertension. No antihypertensive medication was administered before hemodynamic and hemorheological measurements. All patients had a blood pressure which was persistently above 140/85 mmHg and more than 0.1‰ protein in a 24 h urine sample. Hypertension was classifed as severe when the diastolic blood pressure was > 100 mmHg or signs of severe microangiopathy or the HELLP-Syndrome occured constists of hemolysis, elevated liver enzymes and a low platelet count (Weinstein 1985). Poor perinatal outcome was defined as perinatal death or fetal acidosis (pH < 7.2) and/or intrauterine growth retardation (IUGR). 40 women with uncomplicated pregnancies served as controls and contributed a total 235 samples. Samples were longitudinal after the 24th week of gestation until term.

Hemodynamic monitoring

All pre-eclamptic patients (but no controls) had an intravenous right superior vena cava catheter with continous venous pressure monitoring. Cardiac output was derived from calculation of stroke volume multiplied by heart rate. Stroke volume was assessed by the formula of Kubicek (1974). Stroke volume was determined from the signals recorded by an impedance cardiograph (Diefenbach GmbH, Frankfurt). In the Kubicek-formula

$$SV = \frac{R \times L^2 \times T \times dz/dt}{(z_0)^2}$$

was R the resistivity of blood, L the distance between these electrodes, dz/dt the maximum impedance rate changes, T the ventricular ejection time and z_0 the basic chest impedance. Heart rate was derived from an ECG.

Hemorheological parameters

Venous blood was collected in an EDTA tube from the antecubital vein with minimal occlusion, centrifuget at 3500 for 10 min, plasma was aspirated, buffy coat removed by vacuum suction, the suspension was washed twice in isotonic buffer, pH 7.4 and resuspended in the same medium containing 1 g/100 ml of albumin. The hematocrit was adjusted to 10% and the percentage of residual leucocytes after cotton wool filtration was < 15% (Diepenhorst et al. 1972, Stuart 1985).

Erythrocyte deformability

was studied by determining the pressure – flow relationship of RBC suspensions passed through polycarbonate sieves with a pore diameter of 5 μm. The analyses of the initial flow curve was performed by a Filtrometer MF 4 as a function of time and the flow curve is automatically received, processed and printed. In order to derive an average deformation behavior of the entire population we measured the initial relative resistance at the beginning of the filtration process.

Red cell aggregation was determined at 22°C in the "Rheoaggregometer" Typ MAI (Myrhenne GmbH, Roetgen, FRG) with a corrected hematocrit of 40%. This cone plate system rotates the blood 10 s at shear rate of 600 s^{-1}, where after during 10 s the average aggregation is determined by the quantity of infrated light measured by photosensors. The data were processed by a microcomputer and the average aggregation registered on a digital display, expressed in arbitary units. 5 measurements were performed on each blood sample and the average values was assessed.

Plasma viscosity was measured with a capillay viscosimeter at 37°C. The calibration factor was calculated with 0.033. Three measurements were performed on each plasma sample.

Hematocrit, leucocytes and platelets were measured using a Coulter Counter.

Serum osmolality were determined by freezing point depression (Osmometer, Gonotec, Berlin, FRG).

Colloid osmotic pressure with the use of a Colloid Osmometer (Knauer AG, Bad Homburg, FRG).

Plasma fibrinogen was measured according to the method Clauss (1957).

Plasma fibronectin was measured by radial immunodiffusion using antiserum from Behringwerke (Marburg, FRG).

Antithrombin III was measured using chromogenic peptide substrates (Boehringer, Mannheim, FRG).

Plasma urate was assayed by the uricase-method.

Systemic oxygen transport capacity or rate of oxygen delivery to tissues is equal to the product of cardiac output, hematocrit and the Huefner factor (= 1.34 mlO_2/gHb).

Means and standard errors were calculated for the data from each group. Since it was not clear whether the data were normally distributed, Wilcoxon rank-sum testing was used for statistical analysis.

Results

Clinical data

During the study period 52 Primiparae with proteinuric hypertension (but not the controls) were studied by catheterisation of the superior vena cava. The mean gestational age was 33.8 +/− 4.2 weeks (range 25 to 40 weeks) and the mean maternal age was 33.8 +/− 5.3 (range 18 to 39 years). The control group consisted of 40 women with uncomplicated pregnancy (Table 1): the mean gestational age was 38.5 +/− 2.4 (range 36 to 41 weeks) and the maternal age 32.4 +/− 4.6 (17 to 38 years). Seven patients presented signs of microangiopathy (HELLP-Syndrome). The perinatal mortality in the study group was 20.3%. Five patients had an intrauterine fetal death and there were four neonatal deaths. All infants survived in the control group and in the group with the HELLP-Syndrome.

Hemodynamic data

Mean values for arterial blood pressure, central venous pressure, cardiac output and total peripheral resistance are summarized in Table 2. Cardiac output in patients with proteinuric hypertension was low (Mean: 3.11 +/− 1.5 l/min) compared with normal pregnancy (6.56 +/− 0.79 l/min). Forty-one percent (n = 30) had a Cardiac output > 3.0 l/min compared with 82% (n = 32) in normal pregnancy. The mean central venous pressure was 1.47 +/− 4.0 cm (range − 6 to + 14) and was similar in patients with moderate and severe hypertension. 38% (n = 27) of patients in the study group had hypovolemia with a central

Table 1. Clinical data and pregnancy outcome in controls and patients with pre-eclampsia

Parameters	Controls	HELLP-Syndrome	Pre-eclampsia	
			RR diast. ≤ 100 mm Hg	RR diast. > 100 mm Hg
Number (N)	40	7	31	14
Mean age (years)	32.4 ± 4.6 (17–38)	29.1 ± 5.3 (21–36)	26.7 ± 4.8 (18–38)	28.1 ± 6.4 (20–39)
Mean parity (N)	2.3 ± 1.2 (0–7)	0	0	0
Mean gestational age (weeks)	38.5 ± 2.4 (36–41)	33.7 ± 4.4 (27–38)	33.8 ± 4.2 (25–40)	34.0 ± 4.5 (28–40)
Birthweight (g)	3181 ± 441 (2600–3800)	2104 ± 1286 (710–4450)	1874 ± 941 (500–3700)	1672 ± 783 (820–3180)
pH-cord blood	7.25 ± 0.1	7.25 ± 0.04	7.21 ± 0.11	7.17 ± 0.11
Perinatal mortality (N)	0	0	5	4

Table 2. Hemodynamic parameters in controls and patient with pre-eclampsia

Parameters	Controls	HELLP-Syndrome	Pre-eclampsia	
			RR diast. ≤ 100 mm Hg	RR diast. > 100 mm Hg
	(A)	(B)	(C)	(D)
Number	40	7	31	14
RR syst. (mm Hg)	115.4 ± 8.4	160.7 ± 13.0	156.1 ± 9.2	175.7 ± 19.4
RR diast. (mm Hg)	75.4 ± 8.9	91.4 ± 14.6	93.0 ± 7.8	111.2 ± 5.3
Proteinuria (‰)	0	0.5–12.0	0.1–4.0	0.1–5.0
Cardiac output (l/min)	6.6 ± 0.8	2.4 ± 0.5	3.4 ± 1.8[a]	2.9 ± 1.1[a]
Total peripheral resistance (dynsx $cm^{-5} \times 10^3$)	1.1 ± 0.1	4.0 ± 0.9	3.2 ± 1.3[a]	4.3 ± 1.6[a]
Central venous pressure (mm Hg)	n.m.	−5 to +8	−2 to +14	−6 to +9
Oxygen transport capacity (l/min)	289.3 ± 78.4	105.5 ± 24.4	173.6 ± 83.0	152.6 ± 67.1[a]

[a] Avs B: $P < 0.05$. n.m.: not measured

venous pressure of < 0 cm. The relationship between central venous pressure and cardiac output was $r = 0.3$ ($P < 0.05$). Two women had signs of pulmonary oedema with a high CVP, a high cardiac output and a low hematocrit.

The hemodynamic values for normal pregnancy were obtained from a longitudinal study (Siekmann 1985). The technique used in that study was impedance cardiography (Kubicek et al. 1974) and we consider the normal range for cardiac output in the second and third trimesters to be 4.5–8.5 l/min. The total peripheral resistance in normal pregnancy is very low (1.05 +/− 0.11 dyns/s/$cm^{-5} \times 10^3$) when compared with patients with proteinuric hypertension (86.3% above 2.2 dyns/s/$cm^{-5} \times 10^3$).

Hemorheologic data

The hemorheological results are presented in Table 3. Red cell aggregation was significantly higher in patients with proteinuric hypertension than in normal pregnancy ($P < 0.01$), but plasma viscosity and serum osmolalität were similar. The difference in hematocrit and leucocyte count between patients and controls was significant ($P < 0.05$). COP and erythrocyte flow rate were decreased in proteinuric hypertension but we could not show any significant differences between moderate and severe forms of hypertension. Plasma fibrinogen was only higher in the severe hypertensive group compared with normals or moderate hypertensive patients. Plasma fibronectin and uric acid were raised in proteinuric hypertension ($P < 0.001$).

Table 3. Hemorheological data for patients with normal pregnancy, women with HELLP-syndrome and patients with pre-eclampsia

Parameters	Controls (A)	HELLP (B)	Pre-eclampsia		Patients with unsuccessful prenancy (E)
			(C) RR diast. ≤ 100 mmHg	(D) RR diast. > 100 mmHg	
Number	40	7	31	14	9/52 (20.3%)
Hkt (%)	35.2 ± 3.4	32.9 ± 4.8	38.9 ± 4.3	39.2 ± 4.5[a]	41.1 ± 5.9[b]
White cells (/nl)	9.1 ± 1.8	12.6 ± 5.4	11.6 ± 3.4	14.9 ± 5.8[a]	13.1 ± 2.5
Platelets (mm^3)	309 ± 85	82 ± 39	223 ± 67	221 ± 83	183 ± 50
Red cell aggregation (−)	20.3 ± 4.9	23.7 ± 5.8	28.7 ± 4.7	27.5 ± 8.4[a]	30.4 ± 5.9
Plasma viscosity (cst)	1.31 ± 0.04	1.30 ± 0.06	1.28 ± 0.1	1.32 ± 0.07	1.32 ± 0.1
Serum osmolality (mmol/kg)	288 ± 6.8	301 ± 9.1	294 ± 10.2	293 ± 5.3	292 ± 10.3
COP (mmHg)	21.0 ± 3.2	16.1 ± 3.6	18.2 ± 3.9	16.5 ± 3.8[a]	17.4 ± 3.8
Fibrinogen (mg%)	383 ± 57	248 ± 152	393 ± 71	418 ± 100[a]	366 ± 105
Fibronectin (mg%)	28.5 ± 1.8	44.3 ± 10.7	52.9 ± 14.4	56.9 ± 12.6[a]	56.2 ± 12.8
AT III (I.U./ml)	11.5 ± 2.3	7.1 ± 4.6	10.8 ± 2.2	8.2 ± 2.2[a]	9.6 ± 4.3
Red cell deformability (µl/s)	10.7 ± 2.7 (4.8–19.7)	8.4 ± 4.1 (2.9–16.3)	7.8 ± 4.3 (0–18.8)	5.1 ± 4.8[a] (0.08–15.9)	3.9 ± 4.7[b] (0.08–13.5)
Plasma urate (mg%)	3.37 ± 1.8	8.6 ± 2.9	7.8 ± 1.4	6.9 ± 1.4[a]	6.8 ± 1.1

[a] Avs D: $P < 0.05$; [b] Avs E: $P < 0.01$

In cases with perinatal loss of the fetus, maternal red cell deformability was very low (3.9 +/− 4.7 µl/s) and the mean hematocrit at delivery (at a mean of 29 weeks gestation) was high at 41.1 +/− 5.9%. The lower hematocrit of normal pregnancy is associated with a decreased oxygen capacity but with an increased oxygen delivery. In cases with proteinuric hypertension a hematocrit above normal is associated with reduced systemic oxygen transport rate. This fall in oxygen availability is due to impedence of the venous return (low CVP and CO) as a result of increased blood viscosity.

We studied 7 patients with hemolysis, elevated liver enzyme levels and low platelet count (HELLP-Syndrome). They had decreased plasma fibrinogen and Antithrombin III-level and their cardiac output was 2.4 +/− 0.5 l/min and the calculated vascular resistance 4.0 +/− 0.9 dyns/$cm^{-5} \times 10^3$ (Table 2).

Discussion

Previous hemodynamic investigations have revealed a wide range of cardiac output in cases of severe pre-eclampsia. 59% of our pre-eclampsia patients had a low cardiac output. The difference between our results and those of Cotton et al. (1988) may be due to differences in methodology. Most studies use dye dilution (Lees et al. 1967) or thermodilution (Hankin et al. 1984, Groenendijk et al. 1984, Cotton et al. 1987, Rafferty et al. 1980). More recently (Siekmann 1985, Davies et al. 1986) impedance cardiography – a noninvasive technique for the measurement of cardiac stroke volume has been used. Unlike Atkins et al. (1981) and de Swiet (1986) we found that the impedance method permitted repeated measurements to study changes of cardiac output in the same patient during pregnancy (Siekmann 1985). The results of Milson et al. (1983) in late pregnancy show a strong correlation ($r = 0.93$) between impedance and dye dilution technique. Groenendijk et al. (1984) and Wallenburg (1988) suggest that pre-eclampsia is associated with a low cardiac output and a reduced blood volume. This would be in agreement with the view that the plasma volume is reduced in pre-eclampsia (Soffronoff et al. 1977, Gallery et al. 1979, 1981). A decrease in venous return can occur as a result of increased peripheral resistance, vasoconstriction, cava compression or increased blood viscosity. The fact that the viscosity plays an important role in determining the cardiac output or peripheral resistance is generally accepted (Heilmann et al. 1981, Messmer 1981, Goslinga 1984). Low flow states lead to an increase in blood viscosity at a given hematocrit. Under these conditions O_2-delivery is better maintained at a lower hematocrit such as is normal in pregnancy. Experiments have shown that a high hematocrit and viscosity are associated with low oxygen delivery to tissue (Guyton 1963). In agreement with Chien (1972) the oxygen capacity of blood in the low flow areas in pre-eclamptic patients is reduced by 50%. A logical consequence is that at every flow rate, a particular value of hematocrit will be associated with an optimal viscosity and a maximal O_2-transport.

In pre-eclampsia statistically significant differences from normal pregnancy were observed in erythrocyte aggregation, hematocrit and white cell count. The degree of hemoconcentration we found in our patients is in agreement with previously published results (Sagen 1984, Heilmann 1981, Kiesewetter 1983, Buchan 1982, Thornburn et al. 1982, Siekmann et al. 1984). A high hematocrit and a low central venous pressure are the results of inadequate plasma volume expansion. Increased vascular and rheological resistance lead to an endothelial damage with release of mediators and disorders of hemostasis (Saleh et al. 1987, 1988, Oian et al. 1985, Poldre 1987, Weinstein 1985). The release reaction is not only started by the leucocyte (endothelial interaction but also by the polypeptide, Interleukin-1. Interleukin-1 makes neutrophils and hepatocytes release high molecular weight acute phase proteins, i.e. fibrinogen and procoagulant products (Friedmann 1988, Martin 1988).

Fibronectin is a large glycoprotein of 440000 Daltons, presenting either in soluble form in blood or in insoluble form in connective tissue. The fibronectin rise in pre-eclamptic patients would suggest that an endothelial cell abnormality may occur early in patients with gestational hypertension. The mechanisms are

unclear: changes in rates of synthesis and/or consumption, as well as variation in plasma volume have been discussed as causes (Lazarchick et al. 1986).

Red cell aggregation brought about by changes in the suspension stability of blood (Chien 1972) was thought to be a possible mechanism for precapillary plugging. It is now clear that the forces disrupting aggregation in the fastmoving precapillary stream are greater than the forces holding the aggregate together, so that this possibility appears unlikely (Lowe 1987). However, red cell aggregation in the postcapillary and intervillous vessels with resultant stasis is a real possibility. Plasma viscosity did not seem to be influenced by the severity of the hypertension.

In pre-eclamptic patients "hematological stress" (Dinaretto 1984, Stuart et al. 1983, Stuart 1985) leads to arise in the leucocyte count and fibrinogen level. Both factors may decrease the erythrocyte filtration rate because leucocytes show poor deformability (Bagge et al. 1977) and plasma proteins decrease erythrocyte flow (Stuart 1985) through narrow channels in vitro and in vivo. We used Nucleporefilters in our experiments as these have pores similar in diameter to capillaries. Although red cell filterability in pre-eclamptic and normal pregnancies overlapped poor perinatal outcome was associated with decreased flow. The increased erythrocyte rigidity may result from a disturbance of cellular calcium metabolism (Cunningham et al. 1985) or changes in the lipid composition of cell membrane (Worley et al. 1982).

The increased leucocyte count in patients with pre-eclampsia may occlude small vessels and could be a further factor impairing intervillous flow. Trapping of white blood cells may be due to factors released by earlier white cells after an interaction with endothelial and trophoblast cells. These activated white cells would be expected to have altered mechanical and adhesive properties (Ernst et al. 1987). Factors released in such circumstances might include leucotriens, thromboxanes, platelet activating factor and leucocyte derived free radicals (Harlan 1985).

The rheological changes found in this study would be expected to affect the flow of white cells through the microcirculation. Further studies are needed to test specific markers for activation of white cells and to examine whether white cells abnormalities correlate with the clinical severity of pre-eclampsia.

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