Distribution and elimination of crystalloid fluid in pre-eclampsia

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ABSTRACT

Pre-eclampsia (PE) is a disease of pregnancy associated with peripheral oedema and hypovolaemia, but few details are known about how women with PE handle a volume load of crystalloid fluid compared with healthy pregnant women. To study this issue, Ringer’s acetate solution (12.5 ml/kg of body weight) was given by intravenous infusion over 30 min to eight women with PE and to eight healthy pregnant women matched with respect to gestational week (mean, 34 weeks). Venous blood was sampled and excreted urine was collected over 90 min to study the time course of the volume expansion by means of volume kinetic analysis. The results show that the size of the central body fluid space expanded by the infused fluid was smaller in PE (mean, 2940 ml compared with 4240 ml respectively; \( P < 0.04 \)), and the clearance constants for distribution (100 ml/min compared with 43 ml/min; \( P < 0.04 \)) and elimination (125 ml/min compared with 36 ml/min; \( P < 0.02 \)) were higher in the women with PE than in the controls. Less excess volume accumulated in the central body fluid space in the presence of PE, whereas the rates of distribution and elimination were higher during and for 15 min after the infusion. It is concluded that Ringer’s acetate solution fluid is both distributed and eliminated faster in women with PE than in matched pregnant controls.

INTRODUCTION

Pre-eclampsia (PE) is the complication in pregnancy that is the leading cause of morbidity and mortality in the mother and child worldwide [1]. The clinical manifestations are caused by defective placentation and endothelial dysfunction, resulting in hypertension and proteinuria and, sometimes, in peripheral oedema and coagulopathy [1,2]. Cardiovascular changes include impairment of the peripheral blood flow [3] and reductions in plasma volume [4,5], glomerular filtration rate [6] and oncotic pressure [7], whereas capillary permeability is increased [4,7].

Nearly half of the clinics treating patients with PE administer intravenous fluid for plasma volume expansion using albumin, synthetic colloids or crystalloid fluid [8]. Volume expansion improves fetal and maternal blood flow rates [9] and tends to reduce the raised arterial pressure [10]. In healthy humans, however, aggressive volume loading impairs lung function [11], and PE is a risk factor for the development of pulmonary oedema [12]. All the cardiovascular alterations give rise to uncertainty about how intravenous fluid therapy should be planned in the presence of PE. Moreover, it is not clear whether the peripheral oedema is due to the impaired renal function, which might reduce urinary excretion, or to the increased capillary permeability, which translocates plasma proteins and fluid to the interstitial space.

The aim of the present study was to examine in what respect females with moderately severe PE handle infused crystalloid fluid compared with women undergoing a normal pregnancy.

Key words: crystalloid fluid, pharmacokinetics, pre-eclampsia, pregnancy.

Abbreviations: Hb, haemoglobin; \( k_0 \), baseline loss; \( k_i \), infusion rate; \( k_d \), distribution rate constant; \( k_e \), elimination rate constant; PE, pre-eclampsia; \( V \), baseline size of body fluid space expanded by infused fluid; \( V_e \), expanded size of \( V \).

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Methods

Subjects
The Institutional Review Committee approved the study protocol, and the informed consent of all subjects was obtained prior to the experiments. Eight pregnant women undergoing in-hospital evaluation of PE participated in the study, as did eight healthy pregnant females matched with the PE women with respect to gestational week (controls). PE was defined, as suggested by the International Society for the Study of Hypertension in Pregnancy, as a diastolic blood pressure > 90 mmHg developing after 20 weeks of gestation and moderate proteinuria of 500 mg/12 h [13]. Three women with PE had just started medication with a moderate dose of labetalol (100 mg twice daily; Trandate; GlaxoSmithKline, Möln达尔, Sweden) to control blood pressure. None in the control group used any medication in addition to iron supplementation.

Procedure
After fasting overnight, the subjects had a light breakfast consisting of two glasses of water or milk and one sandwich. Participants were weighed and the experiment started between 08:00 and 09:00 hours after a recumbent equilibration period of 30 min, with the baby tilted somewhat to the left of the midline, which was then the only body position allowed.

A cannula was inserted into a cubital vein on each arm. One cannula was used for the infusion of 12.5 ml of Ringer’s acetate (sterile water containing the following electrolytes: 130 mmol/l sodium, 4 mmol/l potassium, 2 mmol/l calcium, 1 mmol/l magnesium, 30 mmol/l acetate and 110 mmol/l chloride) per kg of body weight over 30 min, which was given at constant rate using an infusion pump (Flo-Gard 6201; Baxter Healthcare Ltd, Deerfield, IL, U.S.A.). The cannula placed in the opposite arm was used to draw a blood sample every 5 min for 90 min to measure the haemoglobin (Hb) concentration in whole blood by colorimetry at 546 nm using a Technicon H2 (Bayer, Tarrytown, NY, U.S.A.) with a within-series coefficient of variation of 1.5 %. Hb samples were obtained in duplicate before starting the infusion. The mean was used as the baseline value in the volume kinetic analysis and for calculating the coefficient of variation.

Blood pressure was recorded after each blood sampling using a non-invasive automatic device (Propaq 104; Protocol Systems Inc., Beaverton, OR, U.S.A.). The apparatus also provided continuous monitoring of the heart rate.

All subjects voided just before the study started and when it ended. They were allowed to void using a bedpan during the experiment so as to remain in the recumbent position. Urinary excretion during the 90-min study period was measured.

Volume kinetic analysis
Volume kinetics is a pharmacokinetic method for infusion fluids [14–16], which was adapted in the present study to contrast the tendency of fluid to become excreted by the kidneys with that to become distributed to peripheral parts of the body.

A volume kinetic model was fitted to the Hb and urine data (Figure 1) in which fluid infused at a rate $k_i$ expands a central body fluid space $v$, which strives to return to $V$ by translocation of fluid to or from a much larger peripheral body fluid space at a rate proportional by a constant $k_r$ to the dilution of $V$. Elimination of fluid occurs at a rate proportional by a constant $k_e$ to the dilution of $V$. The calculations also consider a small evaporation loss ($k_b$).

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From a kinetic point of view, fluid infused into the central body fluid space equilibrates readily with cubital venous blood, whereas the peripheral fluid space becomes expanded after a delay. These are functional body fluid spaces which may or may not correspond to the physiological terms plasma volume and interstitial fluid space.

The volume change in $v$ was expressed as:

$$\frac{dv}{dt} = k_i - k_b - k_r \frac{(v - V)}{V} - k_e \frac{(v - V)}{V}$$

(1)

The parameter $k_r$ in the model was calculated from urinary excretion according to eqn (3). The unknown
parameters $V$ and $k_r$ were estimated by applying a nonlinear least-squares regression routine based on a Nelder–Mead simplex method to an analytical solution of eqn (1) until no parameter changed by more than 0.0001 (0.01 %) in each iteration [14,15]. The Nelder–Mead method offers the advantage over the Gauss–Newton method of being able to find a minimum for starting values further away from the final estimates.

Experiments were computed individually using a PC and the MatLab 6.5 software (Math Works Inc., Notich, MA, U.S.A.). Input data consisted of the repeated measurements of the Hb concentration, which were adapted to represent the plasma dilution, as this expression equals the dilution of $V$. Hence

$$\frac{v(t) - V}{V} = \frac{\text{baseline Hb}}{\text{Hb}(t)} - 1$$

A correction of the dilution was made for the loss of 3 ml of blood for each sample withdrawn throughout the experiments based on the assumption that the baseline blood volume was 8.3 % of body weight [18]. This correction for ‘iatrogenic’ dilution has little influence on the final parameter estimates [15].

The integral of the urinary excretion rate from 0 to 90 min is represented by the total urine volume collected during the studied time period $T$. Therefore the parameter $k_r$ could be calculated as the urinary excretion divided by the area under the curve (AUC) for the entire dilution–time profile. After considering that approximately half of the basal fluid losses were represented by excretion of urine, this relationship at any time $t$ was expressed as:

$$k_r = \frac{\sum \text{urine volume}(T) - 0.5 \times k_r \times T}{\text{AUC for }(v(t) - V)/V}$$

Secondary parameters were calculated based on the fact that $k_r$ and $k_1$ are clearance constants and, therefore, the exponent for the elimination function is $-k_r/V$. Since fluid also leaves $V$ by distribution to peripheral tissues, the slope resulting from both distribution and elimination is the sum of both clearance constants divided by $V$. The inverted expressions corresponding to these situations are the elimination half-life and the context-sensitive half-life, the latter representing the time required for the plasma dilution to be reduced by 50 % after infusion with regard to both distribution and elimination [19]. All secondary parameters ignore the minimal contribution of basal fluid losses to the dilution–time curve.

Slope of dilution–time curve $= \frac{k_r + k_1}{V}$

Half-life $= \ln 2 \times \frac{V}{k_1}$

Context-sensitive half-life $= \ln 2 \times \frac{V}{k_r + k_1}$

where $\ln$ is the natural logarithm.

### Statistics

Data with a normal distribution are presented as means (S.D.), and the cases and the controls were compared using repeated measures ANOVA. Data with a skewed distribution are reported as the medians, followed by the interquartile range, and the Wilcoxon rank sum test was used to compare the groups. $P < 0.05$ was considered significant.

### RESULTS

There were no differences in age, body weight, gestational week or Hb concentration between the two groups at enrolment. The heart rates were similar but, as expected, the arterial pressure was significantly higher in the women with PE (Table 1).

In both groups, the maximum plasma dilution occurred at the end of the infusion. The dilution appeared to decrease more rapidly after the infusion in the presence of PE (Figure 2). Heart rate and blood pressure remained virtually constant throughout the experiments. The urine volume measured at the end of the study (90 min) tended to be larger in the PE group [median (interquartile range), 600 (300–712) ml] than in the controls [285 (258–458) ml], but this difference was not statistically significant.

The kinetic analysis showed several differences between the groups (Table 2). The size of $V$ was smaller in PE, whereas $k_1$ and $k_r$ were significantly higher. The modelled slope of the dilution–time curve was steeper in the PE group, and the elimination half-life and also the context-sensitive half-life were markedly shorter. In contrast, the mean square error obtained during the curve-fitting process had the same magnitude in both groups and evolved similarly over time.

Computer simulations indicated that PE was associated with an increased rate of distribution of infused fluid to peripheral tissues and also a faster excretion of infused fluid, whereas the amount of fluid residing in the central
Figure 2  Plasma dilution during and after an intravenous infusion of 12.5 ml of Ringer's acetate solution/kg of body weight over 30 min in women with PE (left panel) and matched controls (right panel)

Each thin line represents one individual. The thick lines are trend curves plotted using the median parameter estimates from the volume kinetic analysis as shown in Table 2.

Table 2  Volume kinetic parameters in pregnant women diagnosed with PE and in a control group of pregnant women matched for gestational age

Wilcoxon’s matched-pair test was used for the statistics. NS, not significant.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PE (n = 8)</th>
<th>Controls (n = 8)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>V (ml)</td>
<td>Median</td>
<td>25th–75th Percentile</td>
<td>Median</td>
</tr>
<tr>
<td></td>
<td>2940</td>
<td>2602–3386</td>
<td>4240</td>
</tr>
<tr>
<td>S.D.</td>
<td>252</td>
<td>152–576</td>
<td>141</td>
</tr>
<tr>
<td>k&lt;sub&gt;t&lt;/sub&gt; (ml/min)</td>
<td>100</td>
<td>60–137</td>
<td>43</td>
</tr>
<tr>
<td>S.D.</td>
<td>27</td>
<td>21–55</td>
<td>23</td>
</tr>
<tr>
<td>k&lt;sub&gt;r&lt;/sub&gt; (ml/min)</td>
<td>125</td>
<td>65–244</td>
<td>36</td>
</tr>
<tr>
<td>10&lt;sup&gt;3&lt;/sup&gt; × Mean square error</td>
<td>7</td>
<td>6–9</td>
<td>9</td>
</tr>
<tr>
<td>10&lt;sup&gt;3&lt;/sup&gt; × Slope of dilution–time curve (min&lt;sup&gt;−1&lt;/sup&gt;)</td>
<td>96</td>
<td>52–148</td>
<td>22</td>
</tr>
<tr>
<td>Half-life (min)</td>
<td>12</td>
<td>8–37</td>
<td>7</td>
</tr>
<tr>
<td>Context-sensitive half-life (min)</td>
<td>7</td>
<td>5–15</td>
<td>32</td>
</tr>
</tbody>
</table>

body fluid compartment was only half as large as in the controls (Figure 3). The distribution and elimination of fluid occurred at a much higher rate in PE during infusion, but the rates later became higher in the controls (Figure 4).

A simplistic comparison between V, k<sub>t</sub> and k<sub>r</sub> in pregnant females with and without PE with those found previously in non-pregnant females is shown in Table 3.

DISCUSSION

The present study confirms that women with PE handle infused Ringer’s solution differently from healthy pregnant controls. The plasma dilution resulting from the infusion was less persistent, and the urinary excretion tended to be larger. More precise expressions for the differences were obtained by using volume kinetics, which were used to calculate k<sub>t</sub> and k<sub>r</sub> of the infused fluid, and also V. By using these parameters, which were obtained by a mathematical analysis, comparisons could be made which do not become apparent from the raw data.

Crystalloid fluid infused in the women with PE resulted in an expansion V that was 30% smaller than in the controls, despite the fact that the body weights were almost identical. This means that the measured plasma dilution is a misleading guide to how much fluid resides in central parts of the body or, more exactly, in the fluid space which readily equilibrates with the sampling site. The clearance constants k<sub>t</sub> and k<sub>r</sub> were both 2–3 times higher in the PE group than in the controls. The fact that V was smaller in PE increased further the differences in half-life and context-sensitive half-life, the latter being an expression for half-life if both kinds of disappearance from V (the sum of distribution and elimination) are considered.

The impact of these differences between parameter values was explored further by computer simulations (Figures 3 and 4). The excess volume in V resulting from the infusion volume load was smaller throughout the experiment in the PE group. Disappearance of fluid from V was speeded up by PE, but only during the infusion and for approx. 15 min post-infusion. Hence the distribution of fluid in the PE and control groups became more equal.
Figure 3 Computer simulation showing how pregnant females with (solid lines) and without (dotted lines) PE during pregnancy handle an intravenous infusion of 12.5 ml of Ringer's acetate solution/kg of body weight over 30 min. The mechanism $k_t$ represents distribution of fluid from the central to a peripheral fluid space, and $k_r$ represents elimination of fluid by voiding. The trend curves are based on the median parameter estimates shown in Table 2.

Figure 4 Comparison between how pregnant females with and without PE handle crystalloid fluid. Women with PE distribute and eliminate the fluid faster during infusion, whereas these rates become lower than in healthy pregnant controls from 15 min after the infusion. The Figure is based on the median parameter estimates shown in Table 2.

Table 3 Differences in how healthy non-pregnant and pregnant women handle infused crystalloid fluid compared with women with PE

<table>
<thead>
<tr>
<th>Kinetic parameter</th>
<th>Not pregnant</th>
<th>Pregnant</th>
<th>PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V$ (per kg of body weight)</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>$k_t$</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>$k_r$</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>

The volume kinetic method used for analysing the dilution–time profiles in venous plasma was developed almost 10 years ago to better characterize the disposition of infusion fluids [13–15]. The size of $V$ can be estimated as the dilution of the blood with respect to Hb is a measure of the distribution of the infused fluid volume and not of Hb. Fitting the kinetic model to data also yields the rate of elimination and sometimes the distribution of fluid into a peripheral body fluid space. In the present study, the measured urinary excretion was not large enough to match the disappearance of fluid from $V$ indicated by the plasma dilution over time, and distribution of fluid to a peripheral fluid space is therefore needed to be assumed. In previous studies [14–16], this situation is known as the ‘two-volume model’, as fluid is distributed to both a central and a peripheral space. In the present study, we chose to use a fairly short duration for the experiment out of consideration for the pregnant females, who frequently had difficulties lying on their back for extended periods of time. Moreover, several women with PE had to be withdrawn, because a decision for an acute Caesarean section was made shortly after they had agreed to participate in our study. This illustrates the fact that the attention these women received from the medical staff while in hospital made extended experiments difficult.

The size of the peripheral fluid space is mainly estimated during the post-infusional phase [22]. Owing to the time required for equilibration, the size of the peripheral fluid space affects the dilution–time curve only to a very limited extent up to 30 min after an infusion [15]. In Figure 2, equilibration with a peripheral space having a relatively low compliance is indicated by flattening of the individual dilution–time curves between 60 and 90 min in the controls, whereas the compliance for peripheral volume expansion was evidently much higher in the PE group. An advantage of expressing the outward translocation of fluid from $V$ by $k_t$ alone, however, is that...
the relationship between distribution and elimination can be evaluated directly by comparing $k_d$ and $k_r$.

Our goal was to study women who were free from medication, but this soon appeared to be virtually impossible. Therefore three women with PE were included who had just started medication with a fairly small dose of a combined $\beta$- and $\alpha$-blocker to combat hypertension. These women had the smallest size of $V$, 32 ml/kg of body weight, whereas the women with PE who were free from medication averaged 40 ml/kg of body weight, and the healthy pregnant females had values of 56 ml/kg of body weight. The lower $V$ may have been the result of medication, but could also reflect a more severe form of PE. The present findings with specific cardiovascular changes in PE. The cation, but could also reflect a more severe form of PE. Healthy pregnant females had values of 56 ml/kg of body weight, whereas the women with PE who were free from medication averaged 40 ml/kg of body weight, and the healthy pregnant females had values of 56 ml/kg of body weight. The lower $V$ may have been the result of medication, but could also reflect a more severe form of PE.

It is tempting, but hazardous, to correlate the kinetic findings with specific cardiovascular changes in PE. The smaller size of $V$ could possibly be related to hypotension, but a more likely scenario is the lowering of the plasma volume that is characteristic of PE [4,5]. In male volunteers, withdrawal of blood results in a dose-dependent lowering of $V$ whereas, in contrast with the situation in PE, $k_1$ and $k_r$ also become reduced [15]. Some volume kinetic characteristics of PE are thus consistent with hypovolaemia, whereas the high figures for $k_1$ and $k_r$, which wastes fluid from the central blood volume instead of keeping it there, indicate that compensatory mechanisms for hypovolaemia do not operate appropriately. This deficiency might be due increased capillary permeability, due to a toxic effect of PE on capillary beds. The high $k_1$ and $k_r$ actually promote hypovolaemia and probably stimulate fluid intake. Women with PE must drink more water if we assume that they strive to hydrate $V$ as much as a healthy pregnant female. For example, to maintain a constant plasma dilution of 10% during 8 h would require that the women with PE drink more than twice as much fluid, if drinking water had the same composition as Ringer's, as the healthy controls. These women would void more, but their peripheral tissues will also be reached by far more fluid that can stretch and distend them, thereby promoting oedema.

Other investigators have suspected that the hypovolaemia in PE puts the fetus at risk and have therefore suggested the use of volume loading as a preventive measure [8], although this view is not undisputed [1]. Our present findings show that attempts to support the plasma volume result in concomitant volume excretion and peripheral fluid accumulation, at least if crystalloid fluid is infused. When providing short-term volume expansion, such as before the induction of anaesthesia, the best strategy would be to infuse fluid at a high rate just before the expansion is needed. In women with PE, the volume expansion levels off very rapidly as soon as the infusion is discontinued.

The issue investigated in the present study is how pregnant women with PE differ from healthy pregnant women with respect to crystalloid fluid kinetics. Another interesting question is how healthy pregnant women compare with healthy non-pregnant women. In a previous study [21], we infused the same amount of Ringer's acetate solution into six females with an average body weight of 58 kg over the same period of time as in the present study. Fortunately, urine was collected at 90 min in five of them, and at very close to 90 min in the last one. Re-analysis of these data, using the same kinetic model as in the present study, shows a ‘best fit’ for the average dilution–time curve which runs between the curves for the two groups of pregnant women (Figure 3, upper left). Despite a 30% lower body weight, the non-pregnant females had a size of $V$ that was virtually identical with that of the healthy pregnant females. If corrected for body weight, however, the size of $V$ was much larger (72 ml/kg of body weight) in the non-pregnant females. $k_1$ was also the same in these healthy non-pregnant and pregnant women.

$k_r$ was similar in the non-pregnant and the PE groups. This can also be illustrated by the fact that the non-pregnant and PE women had voided 70% and 60%, respectively, of the infused fluid volume at 90 min, whereas only 30% could be collected as urine in the healthy pregnant females. These results, which are summarized in Table 3, suggest that pregnancy reduces the size of $V$ when expressed per kg of body weight, which is the most appropriate comparison, and that $V$ is even lower in PE. Pregnancy decreases the diuretic response to crystalloid volume loading, but this adaptation seems to be abolished by PE, perhaps due to the increased release of atrial natriuretic peptide [2,23]. Moreover, PE doubles the clearance constant for distribution of fluid.

In summary, the kinetics of Ringer's acetate in women with PE are characterized by more rapid distribution and elimination than in matched controls. The size of the body fluid space expanded by the fluid is small.

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