The influence of a combined oral contraceptive pill and menstrual cycle phase on digital microvascular haemodynamics

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Summary

1. Nailfold capillary pressure, digital blood flow and skin temperature have been measured on days 7, 14, 21 and 28 of the menstrual cycle in 10 women on a combined oral contraceptive pill and 10 control subjects with normal menstrual cycles.

2. Capillary pressure and digital blood flow were statistically significantly higher in the group taking an oral contraceptive pill compared with control subjects.

3. Capillary pressure values for women failed to show the same positive correlation with skin temperature previously described in normal men.

4. The results are interpreted as evidence for a powerful modulating influence of sex steroids on digital microvascular haemodynamics.

Key words: capillary pressure, microcirculation, oral contraception.

Introduction

In 1975 Keates & Fitzgerald [1] reported the effect of a combined oral contraceptive pill on the peripheral blood flow of women. Women not using a combined oral contraceptive pill showed a significant increase in calf blood-flow volumes during the early luteal phase of the menstrual cycle with a sharp fall premenstrually and during menstrual flow. In contrast, those women using an oral contraceptive pill had a significant midcycle fall in blood-flow volume. In 1977 Gosling & Beasley [2] reported cyclical variation in lower-leg blood flow in only one of 11 women studied. The mean resting flow appeared to be lower in the group of five women taking oral contraceptives, but the differences did not reach normally accepted levels of statistical significance. Toe flows were not significantly different in the two groups.

The present paper extends these observations by describing the influence of menstrual cycle phase and a combined oral contraceptive pill on finger blood flow and nailfold capillary pressure.

Materials and methods

Subjects

The subjects were healthy hospital employees who gave fully informed consent to the procedures carried out. Ten control women (age range 20–44 years, mean 28.8) who were having regular menstrual cycles were compared with 10 women (age range 20–30 years, mean 24.3), nine of whom had been on a combined oral contraceptive pill for at least 6 months. Seven of the control women were able to keep daily recordings of their basal body temperature. The records suggested that their menstrual cycles were ovulatory. The combined oral contraceptive pill group comprised five subjects on a preparation containing ethinyloestradiol (0.03 mg) + levonorgestrel (0.25 mg), one subject on a preparation containing ethinyloestradiol (0.05 mg) + levonorgestrel (0.5 mg) and four subjects on a preparation containing ethinyloestradiol (0.03 mg) + levonorgestrel (0.15 mg). The pills were taken in standard manner, i.e. daily for 21 days followed by seven pill-free days.
Study design

The control women were studied on days 7, 14, 21 and 28 of the menstrual cycle, day 1 being the first day of menstruation. The women on an oral contraceptive pill were studied on days 7, 14, 21 and 28 after the last pill of the previous cycle (i.e. the day before and days 7, 14 and 21 of pill ingestion). Each subject wore similar clothing for the four visits which were at the same time of day at least 1 h after the last food or drink. All measurements were made after a minimum period of 30 min acclimatization in a constant-temperature room maintained at 24°C. Neither menstrual cycle day nor contraceptive status was known to the investigator until the completion of the study.

One of the control group commenced the pill towards the end of the study and so we were able to study a first cycle on an oral contraceptive pill.

Capillary pressure measurements

Capillary pressure was measured in the terminal capillary loops of the finger nailfold as described in detail by Levick & Michel [3] and Tooke [4] with a modification of the Landis micro-injection technique. With the hand steadied on a Plasticine mould at sternal angle height, beneth a stereoscopic microscope, a nailfold capillary loop was cannulated with a micropipette and the transmitted pressure measured manometrically. Penetration of the capillary lumen by the pipette was evidenced by a sudden influx of erythrocytes into the pipette barrel. Manometer pressure was then raised to expel all but a few erythrocytes. Capillary pressure was measured by adjusting manometer pressure until there was no net movement in or out of the pipette, the few remaining erythrocytes oscillating with each heart beat. For the pressure to be regarded as true capillary pressure there had to be no interruption of flow around the capillary loop. The point of cannulation was recorded as arterial limb, summit or venous limb of the nailfold capillary loop (Fig. 1). At the time of pressure measurement digital skin temperature was recorded by an adherent thermocouple. Local heating was minimized by using a fibre-optic cold light source. An average of just over three readings per subject was obtained at each visit. When more than one reading was obtained for a site at a particular study visit, mean site reading was taken for analysis purposes.

Digital blood flow

Digital blood flow was measured by using venous occlusion mercury strain-gauge plethysmography. The occlusion cuff was placed around the digit base and the gauge place at the base of the nail at a defined distance from the tip of the digit. The same digit was used at each visit. The hand and arm were supported comfortably on foam rubber at the height of the sternal angle. Venous occlusion pressure was 50 mmHg and recordings were made by using a Parks electronics plethysmograph, model 270, and an optimally balanced ultraviolet recorder. Blood flow was expressed as the mean of 10 readings made at 1 min intervals over a 10 min period after full acclimatization. A record of skin temperature from the dorsum of the same digit was made at this time with an adherent thermocouple.

Arterial blood pressure

At the end of the study visit arterial blood pressure was measured with the subject remaining seated by using a mercury sphygmomanometer.

Statistical analysis

Digital blood flow and skin temperatures in the two groups were compared by analysis of variance with a repeated-measurements technique. Capillary pressures could not be analysed in the same manner owing to the absence of values for some cannulation sites in some individuals on certain study days. We therefore analysed these results using a one-tailed t-test. Because of the relatively
small number of measurements obtained for any one site on individual study days we have only regarded $P$ values of $<$0.0125 as indicative of statistically significant differences in capillary pressure between the two groups when analysed according to cycle day.

**Results**

**Capillary pressure measurements**

When readings were grouped according to cannulation site and expressed as the mean of values on all study days (Fig. 2) it became clear that capillary pressure was higher in the group taking the oral contraceptive pill ($P < 0.025$ arterial limb values, $P < 0.01$ summit and venous limb values). Table 1 summarizes the capillary pressure data for the various days for each cannulation site for the two groups. There is no significant variation between study days for either group. On all days values for the group taking an oral contraceptive pill are higher than control values for all sites of cannulation. The differences become significantly different for venous limb ($P < 0.0075$) and summit values ($P < 0.0005$) on day 28. Previous work [3,4] has shown that capillary pressure in men is positively correlated with skin temperature. In the present study digital skin temperature showed spontaneous variation despite a constant environmental temperature. However, neither group of women appeared to show a significant positive correlation between capillary pressure and skin temperature ($r = +0.26$, $P > 0.05$ oral contraceptive pill group; $r = +0.25$, $P > 0.05$ controls).

**Digital blood flow**

Mean digital blood flows are shown in Table 2. For the control group no significant variation at the 5% level was observed on any of the 4 study days, but there was a suggestion of a fall on day 28, in keeping with the findings of Keates & Fitzgerald [1]. The oral contraceptive pill group appear to have statistically significantly higher flows ($P < 0.025$), with the highest mean value being recorded on day 28. There is a suggestion of a fall on day 21 again in keeping with the findings of Keates & Fitzgerald [1].

**Skin temperature**

Skin temperature recordings followed the same pattern as blood-flow measurements (Table 3), higher temperatures being observed in the oral contraceptive pill group, but the differences did not reach statistical significance.

**Arterial blood pressure**

There was no significant difference in arterial blood pressure between the two groups (mean pressure 107.1/70.2 controls; 106/70.6 mmHg oral contraceptive pill group). Similarly there was no variation discernible within groups on the various study days.

**Fig. 2.** Mean (+SEM) capillary pressure (all study days) grouped according to cannulation site in cm water. Significance of difference: $*P < 0.025$; $**P < 0.01$. Arterial limb; venous limb.

| TABLE 1. Capillary pressures for various study days and cannulation sites |
|---|---|---|---|---|---|---|---|
| Site | Day of cycle | Day 7 | Day 14 | Day 21 | Day 28 |
| | | Pill | Controls | Pill | Controls | Pill | Controls |
| Arterial limb | 43.8 ± 6.3 | 38.9 ± 3.5 | 43.6 ± 2.9 | 39.5 ± 1.8 | 44.2 ± 3.6 | 38.7 ± 2.3 | 46.6 ± 1.4 | 39.8 ± 4.1 |
| Summit | 40.9 ± 2.5 | 29.3 ± 4.3 | 37.6 ± 4.1 | 29.3 ± 3.4 | 38.0 ± 2.9 | 36.0 ± 5.1 | 39.3 ± 1.6 | 29.9 ± 1.2 |
| Venous limb | 33.3 ± 2.3 | 28.3 ± 4.0 | 31.8 ± 1.7 | 28.9 ± 4.4 | 33.2 ± 3.7 | 27.2 ± 2.1 | 34.0 ± 2.0 | 26.1 ± 2.0 |

Results are means ± SEM.
TABLE 2. Digital blood flow (ml min⁻¹ 100 ml⁻¹ of tissue) for various cycle days for two groups of women
Results are means ± SEM.

<table>
<thead>
<tr>
<th>Group</th>
<th>Day of cycle</th>
<th>7</th>
<th>14</th>
<th>21</th>
<th>28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral contraceptive pill</td>
<td>18.86 ± 6.8</td>
<td>19.1 ± 5.28</td>
<td>16.2 ± 4.29</td>
<td>22.22 ± 6.7</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>8.27 ± 0.83</td>
<td>9.88 ± 2.1</td>
<td>9.05 ± 2.68</td>
<td>5.84 ± 1.1</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.025</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TABLE 3. Skin temperature (°C) for various cycle days for two groups of women
Results are means ± SEM.

<table>
<thead>
<tr>
<th>Group</th>
<th>Day of cycle</th>
<th>7</th>
<th>14</th>
<th>21</th>
<th>28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral contraceptive pill</td>
<td>32.15 ± 0.74</td>
<td>32.14 ± 0.94</td>
<td>31.92 ± 0.88</td>
<td>33.17 ± 0.84</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>31.46 ± 0.58</td>
<td>30.94 ± 0.67</td>
<td>31.21 ± 0.62</td>
<td>30.48 ± 0.65</td>
<td></td>
</tr>
</tbody>
</table>

FIG. 3. Arterial limb (a) and venous limb capillary pressure (b) values recorded for one subject for a non-oral contraceptive pill cycle and the following oral contraceptive pill cycle. O, Pill group; ●, control group.

Cross-over study

One subject commenced an oral contraceptive pill (ethinylestradiol 0.03 mg + levonorgestrel 0.15 mg) towards the end of the study and was followed over the next cycle. Fig. 3(a,b) shows capillary pressure measurements obtained for the two consecutive cycles, a marked difference again apparent on day 28, higher values being recorded while the subject was taking an oral contraceptive pill.

Discussion

Our findings demonstrate a profound influence of a combined oral contraceptive pill on digital haemodynamics resulting in increased blood flow, skin temperature and capillary pressure compared with values obtained in control subjects.

Finger flow mainly comprises flow of the skin [5] and serves two functions: (i) tissue nutrition and (ii) heat dissipation which is facilitated by the arteriovenous anastamotic net-
work present in the hand. Previous studies of the vascular influence of the oral contraceptive pill have centred on calf flow, which probably reflects predominantly muscle perfusion [6]. For this reason an influence of oral contraceptive therapy on skin blood flow observed in the present study may not have been apparent in these previous studies. The increased digital blood flow observed in the oral contraceptive pill group suggested that the peripheral vascular influence of the combined pill might be similar to that conferred by pregnancy; there is general agreement that blood flow to the hand increases markedly during the third trimester of pregnancy, whereas blood flow to the skeletal muscle probably does not change [7].

Skintemperature is determined by the rate of heat delivery to and heat loss from skin. In this study the ambient temperature was kept constant. Thus the rate of heat delivery, i.e. skin blood flow, becomes the main determining variable of skin temperature. It is not therefore surprising that skin temperature and blood flow followed similar patterns. Former studies [3, 4] have revealed a positive correlation between skin temperature and capillary pressure in normal men. In the present study spontaneous fluctuation in skin temperature occurred during the cycle, but no correlation reaching the 5% level of significance between capillary pressure and skin temperature was demonstrable.

The higher capillary pressures observed in the oral contraceptive pill group have several possible explanations. They may simply reflect the higher skin temperatures in this group of women. Alternatively the higher pressures may represent a general response to the raised plasma volume which has been described in women on the pill [8, 9]. A third possibility is that the sustained pressure disturbance in circulating oestrogen and progesterogen in the pill group may serve to modulate the response of the microvascular smooth muscle to vasoconstrictor agents in a manner similar to that described by Altura [10].

As capillary hydrostatic pressure is the most variable determinant of fluid filtration in the capillary bed [3], the demonstration of a hormonal influence on capillary pressure offers a possible explanation for the fluid retention in women with the premenstrual syndrome which resolves with the onset of menstruation. Digital swelling may be a feature in this syndrome and it has been suggested that the swelling may result from excessive water retention before the onset of menstruation [11]. Interestingly, tight rings and digital swelling premenstrually were noted by eight out of 10 of the combined oral contraceptive pill group, and only three of the non-oral contraceptive pill group, perhaps a reflection of the higher pressures and flows in this group premenstrually. This observation supports the contention of O'Brien, Selby & Symonds [12] that many of the progestogenic complications associated with oral contraceptives are similar to the premenstrual syndrome.

Having demonstrated an influence of combined oral contraceptive therapy on digital microvascular haemodynamics one may speculate that a similar hormonal influence might explain the digital swelling observed in late pregnancy and pre-eclampsia in addition to the premenstrual syndrome. Further studies on digital haemodynamics are required in these conditions to see if this hypothesis stands up to experimental examination.

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References