Transport of uterine PGF$_{2\alpha}$ to the ovaries by systemic circulation and local lymphovenous-arterial diffusion during luteolysis in sheep

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The theory of countercurrent vascular transfer of PGF$_{2\alpha}$ during luteolysis was examined. In the first experiment, pulmonary clearance of PGF$_{2\alpha}$ was determined to re-examine whether the total amount of PGF$_{2\alpha}$ was degraded in the lungs after one passage. Cardiac output was measured by the Fick method and PGF$_{2\alpha}$ by radioimmunoassay before and after vascular lung supply, using pulmonary catheterization and the interventional radiology method in ten anaesthetized ewes on day 16 of the oestrous cycle. Cardiac output remained stable (7156 ± 439 ml min$^{-1}$). Infusion of 5 μg oxytocin resulted in an increase in plasma PGF$_{2\alpha}$ concentrations at 30 min in the uterine vein and the pulmonary and femoral arteries (3811 ± 806, 224 ± 55 and 18 ± 4 pg ml$^{-1}$, respectively). The PGF$_{2\alpha}$ concentrations decreased exponentially and the half-time decreases were 27 (r = 0.99), 16 (r = 0.99) and 18 (r = 0.98) min, respectively. Pulmonary clearance of PGF$_{2\alpha}$ was estimated at 6338 ± 451 ml min$^{-1}$. In a second experiment, an arterio-arterial gradient of plasma PGF$_{2\alpha}$ concentrations was analysed between the proximal and distal segments of the ovarian artery to verify whether the total amount of PGF$_{2\alpha}$ flowing to the ovary was from the local venous-arterial countercurrent pathway. Surgical catheterization techniques were performed on 11 ewes on day 16 of the oestrous cycle. The ovarian arterial blood flow was measured by the implantable Doppler method (8 ± 1 ml min$^{-1}$). The maximum plasma PGF$_{2\alpha}$ concentrations in the femoral and distal ovarian arteries were 23 ± 6 and 42 ± 11 pg ml$^{-1}$ (P < 0.05), respectively. Plasma PGF$_{2\alpha}$ decreased exponentially in the femoral artery and the half-time decrease was 26 min (r = 0.98), and in the distal ovarian artery close to the ovary PGF$_{2\alpha}$ decreased linearly and the half-time decrease was 108 min (r = 0.96). Consequently, the arterio-arterial diffusion gradient of PGF$_{2\alpha}$ concentrations was extended to 3 h. These experiments showed that the PGF$_{2\alpha}$ flow rate in the pulmonary artery was 42.275 ± 10.793 μg per 150 min (n = 10) and the systemic arterial PGF$_{2\alpha}$ flow rate was 5.359 ± 1.658 μg per 150 min (n = 10). Therefore, 12% of the PGF$_{2\alpha}$ was not oxidized by the lungs. The proximal ovarian PGF$_{2\alpha}$ flow rate was 6.909 ± 2.341 ng per 150 min, while the distal flow rate was 21.003 ± 5.703 ng per 150 min (n = 11). Thus, 33% of the PGF$_{2\alpha}$ was transported rapidly to the ovary via the systemic route, while 67% was transported by slow local countercurrent diffusion, which extended the duration of luteolytic activity to four times that of the PGF$_{2\alpha}$ surge. These results indicate both rapid systemic transport of PGF$_{2\alpha}$ to the ovaries and a slower buffer mechanism involving a local diffusion pathway, rather than a direct countercurrent system.

Introduction

The endocrine theory of local vascular countercurrent transfer of the luteolysin PGF$_{2\alpha}$ corresponds to a mechanism of local PGF$_{2\alpha}$ transfer from the uterine venous blood to the ovarian arterial blood during the oestrous cycle (Barrett et al., 1971; McCracken et al., 1972, 1981; Land et al., 1976). Uterine cyclic production of PGF$_{2\alpha}$ is responsible for the ovarian cyclicity in most mammals, including ruminants (sheep, goats, cows), pigs, horses, rodents and guinea-pigs (Anderson et al., 1969; Mayer et al., 1973; Ginther, 1974), with the exception of humans and other primates (Neill et al., 1969; Beling et al., 1970). In most species, separation of the uterus and one of the two ovaries results in prolongation of the lifespan of the ipsilateral corpus luteum, whereas the
contralateral corpus luteum regresses at the normal time (Mapledoft and Ginther, 1975). In horses and rabbits, no local effect can be demonstrated and luteal regression occurs even if the ovary is relocated outside the pelvic cavity (Scott and Rennie, 1970; Ginther and First, 1971). However, plasma PGF_{2\alpha} is almost completely inactivated by oxidation in the lungs after one passage in most species, including guinea-pigs, rats, cats, dogs and sheep (Piper et al., 1970; Piper and Vane, 1971; McCracken et al., 1972; Baird, 1978; Einer-Jensen, 1988). Therefore, it is thought that PGF_{2\alpha} crosses from the utero-ovarian vein into the ovarian artery by a local direct countercurrent transfer. This was first proposed in sheep (Barrett et al., 1971; McCracken et al., 1972; Land et al., 1976), and later in guinea-pigs (Poyser, 1976) and pigs (Lindlof et al., 1976; Kotwicka, 1980; Krzymowski et al., 1986). In sheep, as in a number of species including monkeys (Ginther et al., 1974) and humans (Bendz, 1977), an anatomical feature reinforces the possibility of local vascular transfer originating in the abdominal aorta: the ovarian artery is tortuous and in close apposition with the surface of the utero-ovarian vein, a result of the confluence of the uterine vein and the ovarian and oviductal veins near the ovarian hilus (Del Campo and Ginther, 1973). The walls of the utero-ovarian vein and ovarian artery are thinnest at the sites at which the vessels adjoin, although no direct anastomosis between vein and artery has been demonstrated (Coudert et al., 1974a,b; Del Campo and Ginther, 1974; Lee and O’Shea, 1975). Indeed, any such anastomosis would lead to a shunting of blood down the pressure gradient from artery to vein, making the local transfer of PGF_{2\alpha} from uterus to ovary particularly difficult (Baird, 1978). Moreover, a fine network of utero-ovarian lymphatics adheres closely to the venous and arterial vessels in the broad ligament (Staples et al., 1982), and contributes to PGF_{2\alpha} transfer (Heap et al., 1985, 1989).

Although the theory of local countercurrent transfer is well recognized (Leymarie and Martal, 1993), it remains controversial (Thorburn and Mattner, 1971; Baird and Land, 1973; Palmer, 1974; Coudert et al., 1974b; Alwachi et al., 1981; Kotwicka et al., 1983). In engineering countercurrent systems for heat exchange, the efficiency of transfer can be close to 100%, whereas it is less than 2% for [H]PGF_{2\alpha} (McCracken et al., 1972). The industrial and physiological heat or gas countercurrent transfer systems correspond to a very fast exchange (Waites and Moule, 1961; Einer-Jensen, 1974a,b) as opposed to PGF_{2\alpha} transfer, which can take 30 min in sheep (McCracken et al., 1972, 1981; Land et al., 1976) and in cattle (Hixon and Hansel, 1974). Finally, whereas the utero-ovarian vein plays a key role in transporting PGF_{2\alpha} from the uterus to the ovary, it is widely accepted that, in sheep, the means by which it reaches the adjacent ovary remains unknown (Baird, 1978).

This study was conducted to determine the validity of the PGF_{2\alpha} countercurrent theory. The aim was to determine whether PGF_{2\alpha} catabolism is almost complete in the lungs and whether the systemic vascular PGF_{2\alpha} input to the ovary is effectively insignificant, as indicated in the literature. The interventional radiology method was used and a direct ovarian arterio-arterial differential analysis after in situ physiological PGF_{2\alpha} secretion stimulated by oxytocin at oestrus. Native uterine PGF_{2\alpha} was analysed with a sensitive radioimmunoassay to avoid artificial [H]PGF_{2\alpha} infusion.

Materials and Methods

Rationale

Complete PGF_{2\alpha} transfer from the utero-ovarian vein to the ovarian artery by venous-arterial countercurrent mechanism implies that (i) PGF_{2\alpha} is not present in systemic blood perfusing the proximal ovarian artery because the PGF_{2\alpha} discharged into the blood supply is totally oxidized by the pulmonary filter; and (ii) the total amount of PGF_{2\alpha} transported to the ovary is apparent along the length of the ovarian artery.

Pulmonary clearance of PGF_{2\alpha} was determined to verify whether the total amount of PGF_{2\alpha} is inactivated by the lungs. Cardiac output and PGF_{2\alpha} concentrations were measured before and after vascular lung supply using the pulmonary catheterization procedure.

The presence of an arterio-arterial gradient in plasma PGF_{2\alpha} concentrations between the proximal segment of the ovarian artery (before the vascular area exchange) and the distal segment (close to the ovary, according to the nomenclature in cardiovascular physiology) was investigated to determine whether the total amount of PGF_{2\alpha} flowing to the corpus luteum and the ovary is provided by venous-arterial countercurrent transfer. Data pertaining to the plasma PGF_{2\alpha} concentrations perfusing the beginning of the ovarian artery and the end of this artery were required. These studies were performed using surgical catheterization techniques on the reproductive tract supply.

PGF_{2\alpha} flow rates were calculated in different vessels as the product of the mean PGF_{2\alpha} blood concentration during the experiment and the blood flow to characterize PGF_{2\alpha} exchange and yields. Cardiac output was determined by the Fick method and the ovarian arterial blood flow by the implantable Doppler method. PGF_{2\alpha} concentrations in the vessels under study were also determined.

Animals

The study was performed on 28 multiparous ewes of the Préalpes du Sud breed aged 3 ± 1 years and weighing 53 ± 4 kg. All the animals were fasted for 36 h before anaesthesia. Each protocol was carried out on day 16 of the oestrous cycle. After oxytocin stimulation, a uterine PGF_{2\alpha} blood surge was obtained between natural endogenous releases in 21 of the 28 ewes.

Anaesthetic administration

Anaesthesia was induced by a 20 ml mixture of Pentothal® (2% (w/v), sodium thiopental; Abbott, France), Nembutal® (0.6% (w/v), sodium pentobarbital; Sanofi, France) and atropine sulfate (0.003% (w/v); Agettant, France) per ewe administered i.v. (external jugular vein), and maintained by
inhalation of a mixture of 2–3% halothane (Fluothane®; Zeneca Pharma, Cergy, France) and 97–98% oxygen. As soon as the animal was anaesthetized sufficiently, tracheal cannulation and ventilation with the anaesthetic gas mixture were performed and the ewe was placed supine on the operating table. The animal was heparinized (75 iu kg⁻¹; Choay, France). One of the jugular veins was cannulated with a catheter (G18, Cathelon®; Critikron-France, Chatenay) for saline solution and drug infusions.

**Pulmonary artery catheterization protocol**

An introducer (F7; Terumo, Japan) was placed into the right femoral vein and a catheter (G20, Cathelon®; Critikron-France, Chatenay) into the right femoral artery. A Swan-Ganz catheter (F6) was introduced into the femoral vein through the desilet, and advanced through the inferior vena cava, the right auricle and ventricle to the pulmonary artery. The catheterization procedure was performed under X-ray control to verify the position of the Swan-Ganz catheter during the entire experiment (Stensoscop 9600®; General Electric, France).

Blood samples (1 ml) were obtained from pulmonary and femoral arteries for the determination of the blood gases, pH, haemoglobin concentration, and percentage of saturated haemoglobin in O₂, on a radiometer haemoximeter (ABL 3®; Radiometer, Copenhagen). Blood samples (5 ml) from pulmonary and femoral arteries were collected for further measurements of plasma PGF₂α concentrations (Fig. 1). Meclofenamic acid (50 µl, 0.1% (w/v)) was added to each blood sample immediately after collection. Blood samples were collected 15 min before and just before infusion of 5 iu oxytocin (Syntocinon®; Sandoz, Rueil-Malmaison) into the jugular vein. Blood samples were taken every 15 min for 150 min. After collection of each blood sample, all catheters were filled with heparinized saline (100 iu ml⁻¹).

**Surgical protocol**

The uterus and annexes were exposed by laparotomy along the alba linea. The ovaries and uterine and ovarian vessels were examined and the side in which the corpus luteum was present was noted. The uterus was fixed in place with a nylon thread to maintain it on the exterior of the peritoneal cavity. On the side containing the corpus luteum, the ovarian artery was isolated and dissected. This artery was carefully separated from the utero-ovarian vein and a segment of 0.1–0.2 cm was isolated 5–6 cm before the ovarian hilus for application of the Doppler microdevice. Catheters were carefully introduced into the uterine vein between the uterus and the ovary under study (G22, Cathelon®; Critikron-France, Chatenay), into the distal and straight segment of the ovarian artery just at the ovarian hilus (G24, Cathelon®; Critikron-France, Chatenay), and into one of the femoral arteries, for collection of blood samples and determination of plasma PGF₂α concentrations (G20, Cathelon®; Critikron-France, Chatenay) (Fig. 1). All catheters were placed and advanced 1–2 cm retrogradely without any ligation to maintain arterial and venous circulation in the reproductive tract supply. After collection of each blood sample, all catheters were filled with heparinized saline (100 units ml⁻¹).

Mean velocity and diameter of the ovarian artery were monitored with an 8 MHz Doppler ultrasonic crystal applied directly to the vessel. The Doppler crystal was a piezoelectric crystal energized by a pulsed Doppler unit (Echovar® AL 40; Alvar, Montreuil). The repetition frequency of pulse was set at 31.25 kHz (Belouchif et al., 1990). Doppler measurements from the ovarian artery and blood samples from the uterine vein and the ovarian and femoral arteries in sequence were performed 15 min before and just before oxytocin infusion. The measurements and blood samples were continued every 15 min for 150 min after infusion.

**PGF₂α measurements**

Plasma PGF₂α concentrations were determined by radioimmunoassay without extraction as described by Andrianakis et al. (1989) with the following modifications. Briefly, 500 µl plasma sample was added to specific anti-PGF₂α antiserum (Institut Pasteur®, Paris) at a final dilution of 1:12000 and to tritiated PGF₂α ([5,6,8,9,11,12,14,15-³H(N)])...
PGF2α, NEN; Dupont De Nemours®, Les Ulis). Immune complexes were incubated for 2 h at room temperature and then overnight at 4°C. Free and antibody bound hormone were separated by precipitation using 2 ml 20% (w/v) polyethylene glycol 6000 and centrifugation at 3000 g for 20 min (Heraeus Christ®, Cryofuge 6-6). Centrifugation pellets were solubilized with 200 μl NaOH (0.1 mol l⁻¹) and radioactivity was measured in a 460C Packard counter (Packard®, Rungis). Plasma samples were run in duplicate. The limit of sensitivity was 2 pg ml⁻¹ and intra- and interassay coefficients of variation were 9% and 15%, respectively. The immunological crossreactivities of the PGF₂α antiserum at 50% displacement were: 12% with PGF₂β; 3% with PGD-2 and DH-PGF₂α (13,14-dihydro PGF₂α); 2% with 19 OH-PGF₂α (19-hydroxy-PGF₂α); 0.4% with PGD-1 and DH-PGF₂α (13,14-dihydro-PGF₂α; 0.03% with PGE-1 and PGE-2; 0.04% with 6-keto-PGF₁α; and < 0.01% with DHE-PGF₂α (13,14-dihydro-15-keto-PGF₂α), PGA-1, PGA-2, PGB-1, K-PGF₂α (15-keto-PGF₂α), DHK-PGF₂α (13,14-dihydro-15-keto-PGF₂α), K-PGF₂ (15-keto-PGF₂), K-PGF₂α (15-keto-PGF₂α) and TXB-2.

Measurements and calculations

PGF₂α pulmonary clearance was calculated according to the following formula (Lockhart, 1983a):

\[ Cl_{PGF_2a} = Q_i \times (1 - C_{fa}/C_{pa}) \]

where \( Cl_{PGF_2a} \) is the PGF₂α pulmonary clearance (ml min⁻¹), \( Q_i \) represents the cardiac output (ml min⁻¹), \( C_{fa} \) is the femoral artery PGF₂α concentration, and \( C_{pa} \) is the pulmonary artery PGF₂α concentration (both pg ml⁻¹).

Cardiac output was calculated using the Fick equation (Lockhart, 1983b):

\[ Q_c = V_{O_2}/DAV_{O_2} \]

where \( V_{O_2} \) is the oxygen consumption (ml min⁻¹) estimated by the product of the body weight in kg and the mean O₂ consumption for the ewe (3.66 ml min⁻¹ per kg) (Ruckebusch, 1977), and \( DAV_{O_2} \) is the arterio-venous difference in O₂ content calculated from the femoral and the pulmonary arteries (ml per 100 ml). The blood O₂ contents were calculated as the sum of the O₂ bound by haemoglobin and O₂ solubilized in plasma. Owing to the anaesthetic gas mixture used in the study, all animals were submitted to hyperoxia, which involved a marked increase in the plasma O₂ concentration.

Haemoglobin binding O₂ content was calculated according to the following equation:

\[ O_2 \text{ content} = S_d O_2 \times Hb \times 1.36 \text{ (ml per 100 ml)} \]

where \( S_d O_2 \) is the percentage haemoglobin O₂ saturation, \( Hb \) is the haemoglobin concentration (g per 100 ml), and 1.36 is the haemoglobin O₂ binding capacity (ml g⁻¹) (Even, 1983).

Non-haemoglobin binding O₂ content was calculated according to the formula of Henry’s Law (Even, 1983):

\[ O_2 \text{ content} = (P_{O_2}/P_{atm}) \times 0.023 \times 100 \text{ (ml per 100 ml)} \]

where \( P_{O_2}/P_{atm} \) is the O₂ fraction in the blood and 0.023 is the O₂ coefficient solubility in plasma.

Ovarian artery blood flow was calculated using the following formula (Lockhart, 1983b):

\[ Q = \pi (D/2)^2 \times V_{mean} \times 60 \]

where \( Q \) is the blood flow (ml min⁻¹), \( D \) represents the diameter of the vessel (cm), and \( V_{mean} \) is the mean velocity (cm s⁻¹), both determined by Doppler techniques.

PGF₂α flow rates were calculated according to the formula (Lockhart, 1983b):

\[ PGF_2a \text{ flow rate} = c \times bf \times t \]

where \( c \) is the mean PGF₂α blood concentration during the observation period, \( bf \) is the blood flow and \( t \) is the time of the observation period (150 min). The PGF₂α blood concentrations were calculated as the product of plasma PGF₂α concentrations and a factor (1 − \( Ht \)) where \( Ht \) is the haematocrit (%). PGF₂α flow rates were determined in the pulmonary artery, the aorta, the proximal ovarian artery and the distal ovarian artery. For the pulmonary artery, the pulmonary PGF₂α blood concentrations and the cardiac output were used for the calculation. This pulmonary arterial PGF₂α flow rate was representative of the total PGF₂α produced in the uterus during stimulation and transported to the lungs. PGF₂α blood concentrations in the femoral artery and cardiac output were used for calculation of the post-pulmonary PGF₂α flow rate, which represents PGF₂α not oxidized by the lungs that could flow by systemic circulation to the organs, especially the ovaries. For the proximal ovarian artery, the ovarian blood flow and PGF₂α blood concentrations in the femoral artery, similar to concentrations at the beginning of the artery, were used. For the distal ovarian artery, PGF₂α blood concentrations determined from blood samples taken from the distal ovarian artery at the ovarian hilus (Fig. 1) and the ovarian blood flow were used.

Statistical analysis

An ANOVA for repeated measurements was applied to compare data recorded before and during PGF₂α stimulation and a paired Student’s t test was used to compare data recorded at the same stage of the protocol. The PGF₂α kinetics of decrease were assessed using linear and exponential regressions and half-time decrease was calculated (STATVIEW, Power Macintosh). The level of significance was set at \( P < 0.05 \). All values represent mean ± SEM unless otherwise specified.

Results

The measured blood gases, haemoglobin concentration, haemoglobin O₂ saturation percentage and O₂ content remained stable throughout the pulmonary catheterization procedure (Table 1). The calculated cardiac mean output was 7156 ± 439 ml min⁻¹ for the ten catheterized ewes. Pre-treatment (t₀) plasma PGF₂α concentration in the uterine vein, at the moment of luteolysis, that is, on day 16 of the oestrous cycle, was 1429 ± 444 pg ml⁻¹ (Table 2). Infusion of oxytocin
**Table 1.** Haemoglobin concentration, O₂ partial pressure and percentage O₂ saturation in haemoglobin, cardiac output O₂ consumption and O₂ content in pulmonary and femoral arteries during catheterization procedures in a study of uterine PGF₂α transport in ewes

<table>
<thead>
<tr>
<th></th>
<th>Femoral artery oxygen content (n = 10 ewes)</th>
<th>Pulmonary artery oxygen content (n = 10 ewes)</th>
<th>Cardiac output (n = 10 ewes)</th>
<th>Arterio-venous difference in O₂ content (ml 100 ml⁻¹)</th>
<th>O₂ consumption (ml min⁻¹)</th>
<th>Cardiac output (ml 100 ml⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (g 100 ml⁻¹)</td>
<td>10.68 ± 0.05</td>
<td>88.36 ± 1.28</td>
<td></td>
<td>2.80 ± 0.21</td>
<td>191 ± 5</td>
<td>7156 ± 439</td>
</tr>
<tr>
<td>Haemoglobin O₂ saturation (%)</td>
<td>99.64 ± 0.10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin binding O₂ content (ml 100 ml⁻¹)</td>
<td>14.83 ± 0.34</td>
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<td></td>
<td></td>
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<tr>
<td>O₂ partial pressure (mm Hg)</td>
<td>389 ± 35</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Non-haemoglobin binding O₂ content (ml 100 ml⁻¹)</td>
<td>1.12 ± 0.10</td>
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<tr>
<td>O₂ content (ml 100 ml⁻¹)</td>
<td>15.95 ± 0.34</td>
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</tbody>
</table>

**Table 2.** Plasma PGF₂α concentration in the uterine vein, femoral artery (proximal ovarian artery) and distal ovarian artery before and after oxytocin stimulation in ewes

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Uterine vein PGF₂α concentration (pg ml⁻¹)</th>
<th>Femoral artery PGF₂α concentration (pg ml⁻¹)</th>
<th>Distal ovarian artery PGF₂α concentration (pg ml⁻¹)</th>
<th>Difference in distal–proximal ovarian artery PGF₂α concentrations (pg ml⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-15</td>
<td>2192 ± 583</td>
<td>7 ± 3</td>
<td>9 ± 6</td>
<td>2 ± 5</td>
</tr>
<tr>
<td>0</td>
<td>1429 ± 444</td>
<td>5 ± 2</td>
<td>14 ± 7</td>
<td>9 ± 6</td>
</tr>
<tr>
<td>15</td>
<td>3285 ± 670*</td>
<td>20 ± 8*</td>
<td>31 ± 12*</td>
<td>11 ± 7</td>
</tr>
<tr>
<td>30</td>
<td>3811 ± 806*</td>
<td>23 ± 6*</td>
<td>42 ± 11*</td>
<td>20 ± 9</td>
</tr>
<tr>
<td>45</td>
<td>3347 ± 649*</td>
<td>17 ± 6*</td>
<td>43 ± 10*</td>
<td>26 ± 8*</td>
</tr>
<tr>
<td>60</td>
<td>2664 ± 626*</td>
<td>15 ± 6*</td>
<td>35 ± 8*</td>
<td>21 ± 6</td>
</tr>
<tr>
<td>75</td>
<td>1760 ± 444</td>
<td>6 ± 3</td>
<td>36 ± 13*</td>
<td>30 ± 11</td>
</tr>
<tr>
<td>90</td>
<td>1105 ± 318</td>
<td>5 ± 4</td>
<td>31 ± 9*</td>
<td>26 ± 6*</td>
</tr>
<tr>
<td>105</td>
<td>784 ± 305</td>
<td>4 ± 3</td>
<td>22 ± 5</td>
<td>18 ± 4</td>
</tr>
<tr>
<td>120</td>
<td>433 ± 133</td>
<td>3 ± 2</td>
<td>21 ± 6</td>
<td>19 ± 6</td>
</tr>
<tr>
<td>135</td>
<td>256 ± 64</td>
<td>1 ± 1</td>
<td>22 ± 7</td>
<td>21 ± 7</td>
</tr>
<tr>
<td>150</td>
<td>226 ± 68*</td>
<td>1 ± 1</td>
<td>15 ± 5</td>
<td>14 ± 5</td>
</tr>
</tbody>
</table>

Measurements were taken 15 min before, just before (t = 0), and every 15 min for 150 min after oxytocin stimulation (n = 11 ewes). PGF₂α concentration reached a maximum at 30 min and then decreased.

*P < 0.05 compared with values at t = 0.

resulted in an increase in the concentration to 3811 ± 806 pg ml⁻¹ at 30 min, which remained stable for 15 min and then decreased according to an exponential function (half-time decrease of 27 min, r = 0.99) (Fig. 2).

In the pulmonary artery (Table 3), maximum plasma PGF₂α concentration as a result of oxytocin stimulation was obtained at 30 min (224 ± 55 pg ml⁻¹), and the concentration then decreased according to an exponential function (half-time decrease of 15 min 47 s, r = 0.99) (Fig. 3). Maximum plasma PGF₂α concentration in the femoral artery was 18 ± 4 pg ml⁻¹ at 30 min (Table 3) and decreased exponentially and the half-time decrease was 18 min (r = 0.98) (Fig. 3). The lungs oxidized about 88% of the PGF₂α secreted by the uterus and measured in the pulmonary artery for 150 min after oxytocin stimulation (Fig. 1), and PGF₂α pulmonary clearance was estimated at 6338 ± 451 ml min⁻¹ (Table 4).

In the surgical experiments, ovarian blood flow remained stable at 8 ± 1 ml min⁻¹ (Table 4). The maximum plasma PGF₂α concentration in the proximal ovarian artery (that is, the femoral artery) was 23 ± 6 pg ml⁻¹ at 30 min and decreased according to an exponential function (half-time decrease of 26 min, r = 0.98) (Table 2, Fig. 4). In the distal ovarian artery close to the ovary, the maximum value was higher than in the proximal segment of the artery (42 ± 11

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Fig. 2. Plasma PGF$_{2\alpha}$ concentrations in the uterine vein after injection of 5 iu oxytocin (OT) into the jugular vein in ewes ($n = 11$). The concentration decreased 30 min after injection according to an exponential function and the half-time decrease was 27 min ($r = 0.99$).

Table 3. Plasma PGF$_{2\alpha}$ concentration in the pulmonary and femoral arteries before and after oxytocin stimulation in ewes

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Pulmonary artery PGF$_{2\alpha}$ concentration (pg ml$^{-1}$)</th>
<th>Femoral artery PGF$_{2\alpha}$ concentration (pg ml$^{-1}$)</th>
<th>Percentage of PGF$_{2\alpha}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>-15</td>
<td>100 ± 24</td>
<td>10 ± 2</td>
<td>10</td>
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<tr>
<td>0</td>
<td>98 ± 23</td>
<td>8 ± 4</td>
<td>8.2</td>
</tr>
<tr>
<td>15</td>
<td>158 ± 42</td>
<td>12 ± 4</td>
<td>7.6</td>
</tr>
<tr>
<td>30</td>
<td>224 ± 55*</td>
<td>18 ± 4*</td>
<td>8</td>
</tr>
<tr>
<td>45</td>
<td>107 ± 30</td>
<td>10 ± 2</td>
<td>9.3</td>
</tr>
<tr>
<td>60</td>
<td>66 ± 17</td>
<td>9 ± 3</td>
<td>13.6</td>
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<tr>
<td>75</td>
<td>36 ± 15</td>
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<tr>
<td>90</td>
<td>21 ± 11*</td>
<td>2 ± 1</td>
<td>9.5</td>
</tr>
<tr>
<td>105</td>
<td>11 ± 5*</td>
<td>1 ± 1</td>
<td>9.1</td>
</tr>
<tr>
<td>120</td>
<td>5 ± 3*</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>135</td>
<td>2 ± 1*</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>150</td>
<td>1 ± 1*</td>
<td>0</td>
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</tr>
</tbody>
</table>

Measurements were taken 15 min before, just before ($t = 0$), and every 15 min after oxytocin stimulation ($n = 11$ ewes).

*PGF$_{2\alpha}$ concentration reached a maximum at 30 min and then decreased.

P < 0.05 compared with values at $t = 0$.

versus $23 \pm 6$ pg ml$^{-1}$, $P < 0.05$) (Table 2), and decreased linearly. The half-time decrease was 108 min and thus the concentration remained higher in the distal segment than in the proximal segment during the observation period (Fig. 4). The difference between distal and proximal plasma PGF$_{2\alpha}$ concentrations increased from the moment of stimulation to reach a maximum at 75 min and then decreased (Table 2, Fig. 4).

Total PGF$_{2\alpha}$ secreted in the circulatory supply was calculated as the pulmonary artery PGF$_{2\alpha}$ flow rate, $42.275 \pm 10.793$ µg per 150 min (Table 4). The flow rate of PGF$_{2\alpha}$ not oxidized by the lungs and flowing in the systemic arterial supply was calculated as $5.359 \pm 0.836$ µg per 150 min, and PGF$_{2\alpha}$ clearance was stable throughout the experiments (Table 4). The proximal ovarian PGF$_{2\alpha}$ flow rate was $6.906 \pm 2.341$ ng per 150 min, while the distal rate was $21.003 \pm 5.703$ ng per 150 min (Table 4).

Thus, total PGF$_{2\alpha}$ flowing in the systemic veins to the
Fig. 3. Plasma PGF$_{2a}$ concentrations in (○) the pulmonary artery and (■) the femoral artery after injection of 5 iu oxytocin (OT) into the jugular vein in ewes (n = 10). The concentration in the pulmonary artery decreased 30 min after injection according to an exponential function and the half-time decrease was 15 min 47 s (r = 0.99). The concentration in the femoral artery also decreased according to an exponential function and the half-time decrease was 18 min (r = 0.98).

Table 4. PGF$_{2a}$ flow rates for the pulmonary artery, the arterial blood flow, the proximal ovarian artery and the distal ovarian artery after oxytocin stimulation in ewes

<table>
<thead>
<tr>
<th>Results from pulmonary artery catheterization procedure (n = 10)</th>
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<tbody>
<tr>
<td>Cardiac output (ml min$^{-1}$)</td>
<td>7156 ± 439</td>
</tr>
<tr>
<td>PGF$_{2a}$ pulmonary clearance (ml min$^{-1}$)</td>
<td>6338 ± 451</td>
</tr>
<tr>
<td>PGF$_{2a}$ flow rate in pulmonary artery over 150 min$^a$ (µg)</td>
<td>42.275 ± 10.793</td>
</tr>
<tr>
<td>PGF$_{2a}$ flow rate after the lungs over 150 min$^b$ (µg)</td>
<td>5.359 ± 1.658</td>
</tr>
<tr>
<td>Percentage PGF$_{2a}$</td>
<td>12.28 ± 1.68</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Results from surgical procedure (n = 11 ewes)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian blood flow (ml min$^{-1}$)</td>
<td>8 ± 1</td>
</tr>
<tr>
<td>PGF$_{2a}$ flow rate in proximal ovarian artery over 150 min$^c$ (ng)</td>
<td>6.906 ± 2.341</td>
</tr>
<tr>
<td>PGF$_{2a}$ flow rate in distal ovarian artery over 150 min$^d$ (ng)</td>
<td>21.003 ± 5.703</td>
</tr>
</tbody>
</table>

$^a$For the pulmonary artery, the plasma PGF$_{2a}$ concentrations, the haematocrit and the cardiac output were used for calculation of PGF$_{2a}$ flow rate. This pulmonary arterial PGF$_{2a}$ flow rate was representative of the total PGF$_{2a}$ produced by the uterus after oxytocin stimulation and transported to the lungs.

$^b$For the arterial blood flow, the plasma PGF$_{2a}$ concentrations in the femoral artery and the cardiac output were used for calculation of the flow rate. This post-pulmonary PGF$_{2a}$ flow rate was representative of PGF$_{2a}$ not oxidized by the lungs that could flow by systemic circulation to the organs and ovaries.

$^c$For the proximal ovarian artery, the ovarian blood flow and PGF$_{2a}$ concentrations in the femoral artery, similar to concentrations at the beginning of the artery, were used to calculate flow rate.

$^d$For the distal ovarian artery, concentrations used for calculation of the flow rate were determined from blood samples taken from the distal ovarian artery at the ovarian hilus.
lungs was partially degraded, permitting infusion of the ovarian artery with non-degraded PGF$_{2\alpha}$: 33% of the PGF$_{2\alpha}$ was transported to the ovary by systemic circulation and 67% by diffusion along the artery.

**Discussion**

When considering the supply pathways to the genital tract in ewes, which includes a coiled ovarian artery close to the utero-ovarian vein, four compartments were identified: (i) an area for synthesis and release of PGF$_{2\alpha}$: the uterus; (ii) an area of transfer: the broad ligament containing the vessels; (iii) an area of PGF$_{2\alpha}$ catabolism: the lungs; and (iv) an effector organ: the ovary containing the corpus luteum. The area of PGF$_{2\alpha}$ transfer has two inputs: the uterine vein and the proximal ovarian artery; and two outputs: the distal ovarian artery close to the ovary and the utero-ovarian vein.

With regard to the two inputs and the area of degradation, the kinetics of PGF$_{2\alpha}$ decrease described exponential functions, that is, in the uterine vein, the proximal ovarian artery and the pulmonary artery. The half-time decreases were lower during the PGF$_{2\alpha}$ pulmonary experiments (approximately 16 min in the pulmonary artery and 18 min in the femoral artery) than in the ovarian PGF$_{2\alpha}$ arterio-arterial gradient experiments (27 min in the uterine vein and 26 min in the femoral artery). This discrepancy could be due to the use of two different ventilatory apparatuses, one located in the catheterization room and the other in the surgical room. The hyperoxia in the surgical room was lower (arterial $P_{O_2}$ of 250 mmHg) than that in the catheterization room (arterial $P_{O_2}$ of 389 mmHg). Indeed, PGF$_{2\alpha}$ degradation in the lungs consists of oxidation by prostaglandin 15 hydroxydeshydrogenase and prostaglandin $\Delta^5$ reductase in the 13,14 dihydro-15 keto-PGF$_{2\alpha}$ (Piper et al., 1970; Sun and Armour, 1974). Although it is possible that degradation of PGF$_{2\alpha}$ was accelerated in the pulmonary artery catheterization experiments, PGF$_{2\alpha}$ pulmonary clearance of about 90% was observed, permitting infusion of the systemic arterial supply with about 10% of the total PGF$_{2\alpha}$ secreted by the uterus, especially the proximal ovarian artery. Taking into account the hyperoxia during these experiments, it is possible that the PGF$_{2\alpha}$ pulmonary clearance was over-estimated and, consequently, that the systemic PGF$_{2\alpha}$ arterial flow rate to the ovary was underestimated. Indeed, the calculated PGF$_{2\alpha}$ flow rate to the ovary (6.906 ng per 150 min) was higher in the experiments in which the arterio-arterial gradient of plasma PGF$_{2\alpha}$ concentrations was determined than that estimated from PGF$_{2\alpha}$ concentrations in the femoral artery during determination of PGF$_{2\alpha}$ pulmonary clearance (5.359 ng per 150 min). These results therefore indicate an increase in PGF$_{2\alpha}$ pulmonary catabolism due to hyperoxia.

With regard to the two output areas of PGF$_{2\alpha}$ transfer, in the utero-ovarian vein, the kinetics of PGF$_{2\alpha}$ decrease

![Graph](image)

**Fig. 4.** Plasma PGF$_{2\alpha}$ concentrations in (●) the proximal ovarian artery and (○) the distal ovarian artery, 30 min after injection of 5 iu oxytocin (OT) into the jugular vein in ewes ($n = 11$). The concentration in the proximal ovarian artery (that is, the femoral artery) decreased according to an exponential function and the half-time decrease was 26 min ($r = 0.98$). The concentration in the distal ovarian artery (close to the ovary) decreased according to a linear function and the half-time decrease was 108 min ($r = 0.96$). The difference between the plasma PGF$_{2\alpha}$ concentration in the proximal and distal ovarian arteries (●) described a square function ($r = 0.89$).
followed the same exponential function as in the uterine vein because a very small amount of PGF$_{2\alpha}$ diffuses out of the vein, and in the distal ovarian artery close to the ovary, the kinetics of decrease followed a linear regression and the half-time decrease was extended considerably (108 min). Moreover, the ovarian arterio-arterial difference in PGF$_{2\alpha}$ was maximal in the 90 min after oxytocin stimulation, 60 min after the maximum PGF$_{2\alpha}$ concentration was reached in the ovarian artery. This delay implies a mechanism of slow diffusion between the vessels under consideration and prolongs the PGF$_{2\alpha}$ infusion of the ovary to more than 216 min. This delay was determined from the intersection of the linear regression of PGF$_{2\alpha}$ concentrations in the distal ovarian artery and the time axis. The calculated PGF$_{2\alpha}$ arterio-arterial differential gradient therefore represents the rate of PGF$_{2\alpha}$ diffusion through the vessel walls and broad ligament. It is probable that hyperoxia plays a role in the tissue catabolism of PGF$_{2\alpha}$ particularly in the broad ligament.

The calculated relative rate of PGF$_{2\alpha}$ transported to the ovary by the systemic circulation is 33%. Two research teams (Abdel-Rahim et al., 1983; 1984; Heap et al., 1985, 1989) have demonstrated that, in sheep, diffusion in the area of PGF$_{2\alpha}$ transfer derives from both the utero-ovarian vein (about 50%) and the uterine lymphatics (about 50%). Therefore, it is proposed that about one-third of the total PGF$_{2\alpha}$ secreted by the uterus is transported to the ovary by arterial systemic circulation, one-third by diffusion from the utero-ovarian vein and one-third by diffusion from the uterine lymphatics (Fig. 5).

Therefore, in ewes, PGF$_{2\alpha}$ transfer by arterial systemic circulation represents a rapid route to the ovary. PGF$_{2\alpha}$ transfer by local diffusion represents a slow route that prolongs the stimulation to four times that of the duration of

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**Fig. 5.** PGF$_{2\alpha}$ systemic and local vascular pathway between the uterus and ovary in sheep. PGF$_{2\alpha}$ transfer from the uterus to the ovary is achieved by systemic circulation and local diffusion. Of the PGF$_{2\alpha}$ secreted by the uterus during 150 min (approximately 42 μg), 0.05% reaches the ovary and corpus luteum (approximately 21 ng). One-third of the PGF$_{2\alpha}$ is transported to the ovary by systemic circulation and the proximal ovarian artery (approximately 7 ng). PGF$_{2\alpha}$ secreted by the uterus returns to the lungs in the venous system. About 12% of the PGF$_{2\alpha}$ passes through the lungs without degradation and flows by the arterial systemic circulation, in particular by the ovarian artery, to the ovary. This represents a rapid transport of PGF$_{2\alpha}$ to the ovary and a maximum blood surge 30 min after oxytocin stimulation, corresponding to the maximum secretion in the uterine vein. The kinetics of the decrease in PGF$_{2\alpha}$ follow an exponential function and the half-time decrease is 26 min. Two-thirds of the PGF$_{2\alpha}$ is transported to the ovary by diffusion from the utero-ovarian vein (one-third, approximately 7 ng) and the uterine lymphatics (one-third, approximately 7 ng) to the ovarian artery, which is tortuous and in close proximity to the vein and the lymphatics. This represents slow transport of PGF$_{2\alpha}$ to the ovary and the estimated maximum duration is 75 min. In addition, the arterial systemic circulation and local diffusion from the utero-ovarian vein and the uterine lymphatics prolong the transfer of PGF$_{2\alpha}$ as the kinetics of the decrease in the transfer to the ovary follow a linear function and the half-time decrease is 108 min.
a native PGF₁₂α surge (half-life in the distal ovarian artery of 108 min versus PGF₁₂α half-life in the proximal ovarian artery of 26 min). Thus, PGF₁₂α delivery to the ovary is considerably extended with regard to the original vascular network in the genital tract. The impact of the general and local vascular organization on the biodistribution and delivery to the effector organ of a hormone PGF₁₂α is clearly demonstrated. The original local vascular pathway functions as a buffer mechanism. Nevertheless, the yield of this type of mechanism is very low since only 0.05% (Fig. 5) of the total PGF₁₂α released by the uterus reaches the ovary through both arterial systemic and local diffusion pathways. The efficiency of local PGF₁₂α diffusion is about 0.035%, as reported by Heap et al. (1989), who found that the estimated percentage transfer of [³H]PGF₁₂α from the uterine vein into the ovarian artery was less than 0.1%. In a study by McCracken et al. (1972) on the local countercurrent transfer of infused tritiated PGF₁₂α, it was calculated that > 2% of the total radioactivity infused into the uterine vein. With regard to the estimation of [³H]PGF₁₂α, including extraction, reverse-phase partition chromatography, silicic acid chromatography and GLC-mass spectrometry, the discrepancy in results between the two methods is small. In the present study, the sensitive radioimmunoassay used to determine PGF₁₂α concentrations is much more precise. Furthermore, the release of uterine PGF₁₂α by oxtocin mimics physiological conditions more closely than infusion of radioactive PGF₁₂α. Walsh et al. (1979) reported a local diffusion countercurrent transfer for [⁴H]progesterone in ewes and an estimated efficiency rate of about 0.035%, compared with 0.5–1% reported by Einer-Jensen and McCracken (1981).

The observation that one-third of the PGF₁₂α returns to the ovary by the systemic arterial circulation is significant, since it corresponds to one-third of the total amount of PGF₁₂α that is transported to the ovary. In addition, local transfer of PGF₁₂α from the utero-ovarian vein to the ovarian artery is by a normal local diffusion pathway from both venous and lymphatic vessels into the ovarian artery. It has been proposed that this mechanism is a countercurrent transfer for the following reasons: (i) the close apposition of the ovarian artery and the ovarian vein; (ii) the existence of extensive coils in the ovarian artery that increase the potential area of exchange; and (iii) the opposing direction of blood flow in the two vessels (Einer-Jensen and McCracken, 1981). However, a number of observations indicate that it is not a local countercurrent system but a local vascular diffusion pathway. Firstly, the time course of PGF₁₂α transfer from the utero-ovarian vein to the ovarian artery is particularly short and has a time-lag of 15–30 min and a duration of several hours (McCracken et al., 1972; Land et al., 1976; Moore et al., 1986). In the present study, a new approach was used in the arterio-arterial analysis to demonstrate both the time-lag and the very slow diffusion of local transfer from the utero-ovarian vein to the ovarian artery. Secondly, the efficiency rate of PGF₁₂α transfer is particularly low in all studies, indicating a mechanism of slow diffusion rather than a countercurrent system.

The term ‘countercurrent system’ should not be used to avoid confusion, with the exception of when it is associated with the word diffusion, as in ‘countercurrent diffusion system’ (Free and Jaffe, 1975). In a number of reports alternative definitions have been used, including the terms ‘local steroid concentrating mechanism’ (Walsh et al., 1979), ‘local veno-arterial pathways’ (Ginther, 1974) or ‘lymphatic-vascular transfer of PGF₁₂α’ (Heap et al., 1985, 1989).

Vascular countercurrent transfer from the utero-ovarian vein to the ovarian artery has also been reported for heat, xenon, krypton, tritiated water, progesterone, testosterone and small peptides such as relaxin and oxytocin (Waites and Moule, 1961; Schramm et al., 1986a,b; Einer-Jensen, 1988).

Heap et al. (1989) compared the mechanisms of lymphatic-vascular transfer of [³H]PGF₁₂α in sheep, 8–15 days after ovulation, with transfer of [¹⁴C]mannitol, which is transferred by the paracellular route. Transfer occurred according to the sequence [³H] PGF₁₂α > [³H]mannitol, indicating that [³H]PGF₁₂α is not transferred by rapid diffusion as is [¹⁴C]mannitol, but by a slower process possibly involving facilitated diffusion. The estimated percentage transfer of [³H]PGF₁₂α from the uterine arterial lymph into the utero-ovarian vein plasma was 27% and into the ovarian artery was 1%, whereas less than 0.1% of the total amount infused from the uterine vein into the ovarian artery (Heap et al., 1989). It is noteworthy that the proportion of labelled PGF₁₂α transferred by the lymphatic-arterial pathway was greater (1%) than that observed for transfer between utero-ovarian vein and ovarian artery (0.1%). The latter rate was similar to that (0.1–0.56%) reported by Land et al. (1976) and (0.3%) by Heap et al. (1985). Therefore, PGF₁₂α can pass from the lymph vein to the utero-ovarian vein, in which the blood flow is concurrent, or to the ovarian artery, in which blood flow is countercurrent. The discrepancy in the percentage transfer of [³H]PGF₁₂α from the lymph into the utero-ovarian vein and directly into the ovarian artery also indicates that PGF₁₂α is not first transferred into the utero-ovarian vein and then into the ovarian artery, but probably occurs into both simultaneously. Estimation of the total amount of [³H]PGF₁₂α transferred from the lymph into the ovarian venous blood gave a value similar to that for transfer from a uterine vein to the ovarian artery (0.4% versus 0.3%) (Heap et al., 1985). There is no evidence for retrograde lymph flow between the uterus and ovaries, but the close proximity of the utero-ovarian lymphatics, utero-ovarian vein and ovarian artery provide pathways for countercurrent diffusion of PGF₁₂α or progesterone, for instance.

The duration of PGF₁₂α diffusion observed in this present study (150 min) is compatible with that of physiological PGF₁₂α pulsatile release during luteolysis (Martal et al., 1997). Zarco et al. (1988a,b) showed that the average interpulse interval for PGF₁₂α pulses associated with luteolysis was 7.7 h and each one lasted about 3 h.

It would be interesting to determine the importance of the systemic route for transfer of PGF₁₂α in non-anaesthetized ewes on day 16 of the oestrous cycle. The significance of this pathway is of particular interest in species such as pigs, horses and rabbits. In rabbits, PGF₁₂α catabolism in the lungs is largely dependent on the physiological state (Sun and Armour, 1974), especially during pregnancy. In horses and
rabbits, in which a unilateral luteolytic effect has not been demonstrated and the ovarian artery and ovarian vein are independent, the systemic PGF_20 pathway is probably particularly predominant. Finally, in primates, and particularly in humans, even if control of luteolysis is not dependent on uterine PGF_20, the extensive area of contact between the utero-ovarian vein and the ovarian artery implies that several lympho-veno-arterial diffusion pathways, for example, of PGF_20 and progesterone, may be important.

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