WHOLE BODY OXYGENATION USING INTRAPERITONEAL PERFUSION OF FLUOROCARBONS

N. S. FAITHFULL, J. KLEIN, H. T. VAN DER ZEE AND P. J. SALT

SUMMARY

A preliminary study was undertaken to assess the feasibility of increasing the arterial oxygen tension, and decreasing the arterial carbon dioxide tension, in intact animals, by means of peritoneal perfusion with the perfluorocarbon-containing, oxygen-transporting blood substitute, 20% Fluosol-DA. Perfusion was carried out in rabbits using a bubble oxygenator and circulator pump, delivering Fluosol at a rate of 25 ml min\(^{-1}\). Control blood-gas measurements were carried out at various \(F_{O_2}\) between 0.5 and (if the animal was not severely hypoxic) 0.16. The measurements were repeated during the intraperitoneal perfusion of Fluosol. At all values of \(F_{O_2}\), significant increases in \(P_{aO_2}\) were seen \((P<0.05)\). Significant decreases of \(P_{aCO_2}\) \((P<0.05)\) were seen if the animals were not hypoxic \((P_{aCO_2} > 10 \text{ kPa})\).

Perfluorocarbons are chemical substances which have a high solubility for oxygen. Two of these, perfluorodecalin and perfluorotripropylamine, are available in an emulsified form in "Fluosol-DA" which has been released recently for limited clinical trials. This plasma substitute, which is available as a 20% solution of perfluorocarbons, can carry 5.5 ml of oxygen per 100 ml of solution at a partial pressure of oxygen of 80 mm Hg (Naito and Yokoyama, 1978).

The surface area of the peritoneum is relatively large and approximately equal to that of the skin (Mackenzie and Macbeth, 1964). Thus, it was postulated that irrigation of the peritoneal cavity with oxygenated Fluosol might induce increases in the partial pressure of oxygen and decreases in the partial pressure of carbon dioxide in the blood. To this end, a pilot study was undertaken, the results of which are reported in this communication.

MATERIALS AND METHODS

Adult New Zealand white rabbits, ranging in weight from 2.8 to 3.1 kg, were used. Anaesthesia was induced with nitrous oxide and halothane in oxygen. After intubation of the trachea with a 20-French gauge Rusch tube, the lungs were ventilated with nitrous oxide and oxygen using a Rosche Baby Kontrol ventilator. Positive end-expiratory pressure was not used in view of the relatively small increases in intra-abdominal pressure that occurred during peritoneal perfusion. These amounted to a maximum of 2–5 mm Hg above baseline in preliminary experiments.

Neuromuscular blockade was induced and maintained with a continuous infusion of pancuronium bromide 5.5 \(\mu\)g kg\(^{-1}\) min\(^{-1}\) i.m. using a Braun Melssungen Perfusor apparatus. A 1.5-mm external diameter Braun Melssungen Venen Katheter cannula was introduced to the femoral artery and arterial pressure monitored (Gould Statham P23 ID transducer) on a Grass 7D polygraph and inkwriting oscillograph. Expired carbon dioxide was monitored continuously using a Gould Godart capnograph Mark III, and recorded on the Grass polygraph.

A small midline upper abdominal laparotomy was performed and a 40-cm Argyle 7-French gauge oxygen catheter inserted and advanced into the left paracolic gutter. This served for the inflow of the Fluosol perfusion, which was removed from the abdominal cavity through a 28-gauge Argyle "Saratoga" sump drain. The latter was inserted via the same laparotomy incision and placed in the right paracolic gutter.

Fluosol was oxygenated using a home-made bubble oxygenator, through which 100% oxygen was bubbled. No carbon dioxide was added as attempts were made to achieve carbon dioxide excretion via the peritoneal cavity. The alkaline perfusate had a pH of 7.97 ± 0.05 SEM \((n = 11)\). Oxygenation of the Fluosol was assessed at regular intervals (Radiometer ABL 1 acid–base laboratory) and, in a series

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of 11 measurements, the mean $P_{O_2}$ was 66.8 kPa ± 4.0 (SEM). The oxygenated Fluosol was warmed to 37°C by circulating water from a Stöpler TB 75 thermostatically-controlled heater/circulator and was circulated at a rate of 25 ml min⁻¹ using a rheostatically controlled roller pump (Driessen).

Before perfusion with Fluosol was commenced, baseline values for arterial oxygen tension ($P_{O_2}$) and arterial carbon dioxide tension ($P_{CO_2}$) were obtained at various fractional concentrations of oxygen ($F_{O_2}$). The rate of ventilation and the tidal volumes were not altered during the investigation.

The $F_{O_2}$ was decreased progressively in a step-wise fashion from an initial value of 0.5. After allowing at least 5 min (and often longer) for stabilization, arterial blood was drawn into a heparinized syringe for the immediate estimation of blood-gas tensions. The change in arterial $P_{O_2}$ is normally rapid and Kwan and Fatt (1971), using online sub-conjunctival $P_{O_2}$ sensing in anaesthetized rabbits noted that: "within 1.5–2 minutes after changing the composition of the inspired oxygen mixture, a maximal and steady state tissue/oxygen tension was found." Therefore, it was considered that 5 min was adequate for equilibration.

$F_{O_2}$ was decreased carefully at values below 0.3 to ensure that severe hypoxia was not suffered by the animals, and at no time in this control procedure did the arterial oxygen saturation decrease to less than 80%. The $F_{O_2}$ of the inspired gas mixture was measured using an Instrumentation Laboratory oxygen monitor 404.

After the control investigations had been performed at various $F_{O_2}$, perfusion with Fluosol was commenced and $F_{O_2}$ was set to 0.5. The first measurements of arterial blood-gas tension were obtained after perfusing for at least 30 min. Subsequently, $F_{O_2}$ was decreased progressively during peritoneal perfusion (as described above) and blood-gas measurements were performed regularly. At the end of the experiments, and after at least 4 h of intraperitoneal perfusion, arterial blood was taken and centrifuged for 15 min in a Christ haematological centrifuge to ascertain if measurable quantities of fluorocarbons had entered the circulation. On no occasion was a measurable fluorocrit obtained.

**RESULTS**

The blood-gas measurements for each animal are presented in table I. The values for control measurements are presented alongside those obtained during the intraperitoneal perfusion with Fluosol.

The changes in $P_{O_2}$ following intraperitoneal Fluosol at different $F_{O_2}$ are depicted in table II, and it can be seen that these were significant at each $F_{O_2}$ as assessed by paired $t$ tests (or in the case of $F_{O_2} = 0.16$, at which there were only three measurements, the unpaired $t$ test). The mean increase in arterial oxygen tension was 3.04 kPa ($± 0.38$ SEM) ($P < 0.001$; Student paired $t$ test).

The $P_{O_2}$ values were plotted against the $F_{O_2}$ values in regression diagrams and shown in figure 1. Correlation coefficients were good under control conditions ($r = 0.96$) and during perfusion with Fluosol ($r = 0.97$). Under control conditions the regression equation was:

$$P_{O_2} = -1.1 + 52.1 \times F_{O_2}$$

and during fluorocarbon perfusion it was:

$$P_{O_2} = +1.2 + 54.1 \times F_{O_2}.$$
**Table I. Blood-gas tension (kPa) in rabbits ventilated at various \textit{Fio}_2 before (C) and during (F) intraperitoneal 20% Fluosol-DA**

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<tr>
<td>0.5</td>
<td>23.0</td>
<td>14.7</td>
<td>28.4</td>
<td>17.6</td>
<td>24.8</td>
<td>14.7</td>
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<tr>
<td>0.4</td>
<td>19.4</td>
<td>21.5</td>
<td>23.7</td>
<td>20.6</td>
<td>21.1</td>
<td>17.5</td>
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<tr>
<td>0.3</td>
<td>14.7</td>
<td>21.5</td>
<td>17.6</td>
<td>20.6</td>
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<td>17.5</td>
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<tr>
<td>0.2</td>
<td>11.1</td>
<td>15.1</td>
<td>11.2</td>
<td>13.8</td>
<td>6.8</td>
<td>9.4</td>
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<td>7.5</td>
<td>9.0</td>
<td>6.8</td>
<td>5.3</td>
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<tr>
<td>0.10</td>
<td>8.9</td>
<td>5.3</td>
<td>5.5</td>
<td>3.9</td>
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Although these results might indicate that "excretion" of oxygen was occurring at the lower inspired concentrations of oxygen, further studies would be necessary to elucidate this point.

The mean decrease in arterial carbon dioxide tension was less marked and amounted to only 0.29 kPa (±0.31 SEM). These changes were not significant (paired \textit{t} test). However, if all measurements were excluded where the pre-Fluosol \textit{PaO}_2 was less than 10 kPa, these mean changes amounted to 0.20 kPa (± 0.03 SEM). These changes, although

**Table II. Changes in \textit{PaO}_2 (kPa ± 1 SEM) following intraperitoneal perfusion of 20% Fluosol-DA (25 ml min\textsuperscript{-1}) at various values of \textit{Fio}_2. Statistical significance: *P < 0.05; **P < 0.01**

<table>
<thead>
<tr>
<th>\textit{Fio}_2</th>
<th>\textit{PaO}_2 change</th>
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<tr>
<td>0.5</td>
<td>3.03*</td>
</tr>
<tr>
<td>0.4</td>
<td>3.30**</td>
</tr>
<tr>
<td>0.3</td>
<td>3.88**</td>
</tr>
<tr>
<td>0.2</td>
<td>2.08**</td>
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<tr>
<td>0.16</td>
<td>2.90*</td>
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**Fig. 2. Regression lines for oxygen tension (\textit{PaO}_2) against inspired oxygen concentration (\textit{Fio}_2) during intraperitoneal perfusion: one between \textit{Fio}_2 of 0.5 and 0.3 (---) and the other at 0.3 and below (——).**
small, were significant (paired $t$ test; $P<0.05$). It should be noted that changes occurring if the $P_{aO_2}$ was less than 10 kPa were insignificant; in many cases increases in $P_{aCO_2}$ occurred when hypoxia was relieved. This was probably a reflection of increased carbon dioxide production in the face of improved oxygenation.

Figure 3 demonstrates the change in $P_{aCO_2}$ following intraperitoneal Fluosol against the $P_{aCO_2}$ during the control period. Although the correlation coefficient is only 0.55, it is significant ($P<0.05$). It should be noted that overlap of points occurs in this figure and that the line drawn may not, at first glance, appear to be correct. However, inspection of table I reveals that in 10 of 20 pairs of measurements, the $P_{aCO_2}$ decreased by 0.4 kPa or more, and on seven occasions decreased by 0.5 kPa or more. It may be argued that the whole correlation is dependent on the three points in which the $P_{aCO_2}$ decreased by 1.0 kPa or more; this is not so, as exclusion of these three points actually increases the correlation coefficient to a value of 0.70 ($P<0.05$). Therefore, it is suggested that intraperitoneal Fluosol may decrease $P_{aCO_2}$ if the diffusion gradient is high enough.

DISCUSSION

Intraperitoneal oxygenation has been attempted using oxygen (Awad, Brassard and Caron, 1970), or solutions of hydrogen peroxide ($H_2O_2$) (Awad et al., 1970). Small increases in oxygen tension were observed and, although higher concentrations of hydrogen peroxide caused greater increases in oxygen tension, they also caused embolization of the lungs and the coronary arteries. Carbon dioxide extraction was negligible.

Approximately 17% of the cardiac output of the rabbit flows along the portal vein. White and colleagues (1967) obtained values of $100 \text{ml min}^{-1}$ (± 5.7 SEM) in rabbits of mean body weight of 2.7 kg. The oxygen tension in the peritoneal cavity is relatively low and mean tensions of 5.5 kPa have been measured by Klossner, Kivisaari and Niinikosi (1974). At this value the haemoglobin will be approximately 72% saturated (Altman and Dittmer, 1970). The mean haemoglobin concentration of the rabbit is $11.9 g/100 ml$ blood (Albritton, 1952). If it is assumed that the oxygen-combining power of the rabbits' haemoglobin is somewhere near the theoretically obtained value ($1.39 ml/g$ haemoglobin, based on the determination of the molecular weight of haemoglobin (Braunitzer, 1963)), full saturation of the portal venous blood by the intraperitoneal Fluosol would deliver:

$$\frac{28}{100} \times 11.9 \times 1.39 = 4.6 \text{ ml of oxygen per minute}.$$ 

This amount, which is calculated on the basis of a non-hypoxic animal, is not sufficient to supply the total requirements of $9.3 \text{ ml kg}^{-1} \text{ min}^{-1}$ (Altman and Dittmer, 1970). However, under conditions of hypoxia, not only may large increases of cardiac output occur, but it is probable that the oxygen saturation in the splanchnic bed may be reduced considerably. Hence, under these conditions, considerable amounts of oxygen may be taken up from the peritoneal cavity.

The above discussion assumes free passage of oxygen across the peritoneum and penetration of oxygenated Fluosol solutions between folds of the intestines as they lie in the abdominal cavity. Penetration is probably assisted by the low viscosity of 20% Fluosol-DA which is lower than that of blood and, in contrast to blood, is increased minimally at low shear rates (Naito and Yokoyama, 1978).

It could be argued that the presence of alkaline Fluosol in the peritoneal cavity might effect splanchnic blood flow adversely. This is unlikely in view of the work of Gelman and Ernst (1977), who have shown that increasing the pH in the portal circulation actually leads to a significant increase in portal blood flow. Therefore, under these circumstances, the high pH of Fluosol might be advantageous.
The perfusion rate of Fluosol was 25 ml min\(^{-1}\). Assuming full saturation of the solution with oxygen, this would result in the delivery of no more than 1.25 ml of oxygen per minute. Hence, in order to achieve full "portal oxygenation", a flow rate of about 100 ml min\(^{-1}\) would be necessary.

It could be claimed that the observed changes in \(P_{aO_2}\) might be caused by increases in cardiac output in the presence of an increased intrapulmonary shunt. Although no attempts were made to measure these variables, it is unlikely that gross changes were occurring. Marked increases in cardiac output, caused by sudden compression of the splanchnic bed, are unlikely in view of the relatively small and gradual changes in intra-abdominal pressure that occurred during the perfusion. It is more likely that decreases in cardiac output would have been produced and these would tend to decrease the contribution of the shunt to arterial \(P_{aO_2}\).

It might be argued that exclusion of \(P_{aCO_2}\) measurements, where control values of \(P_{aO_2}\) were less than 10 kPa, was unjustifiable. The degree of hypoxia suffered by the animals during the control measurements was not gross. Mean \(P_{aO_2}\) was 7.7 kPa (± 0.44 SEM), but there is evidence that this degree of hypoxia may be sufficient to cause decreases in oxygen consumption (\(V_O_2\)). Harzbecker and co-workers (1979) have demonstrated mean decreases in \(V_O_2\) (in man) of 10.1% in the presence of a mean \(P_{aO_2}\) of 6.9 kPa (± 0.73 SEM). Levitan and Bungo (1982) have observed changes in mean \(V_O_2\) of a similar magnitude at simulated altitudes of 2440 m (this, they state, accords with a \(P_{aO_2}\) of 7.9 kPa). Assuming a constant respiratory quotient, decreases in \(V_O_2\) in the present study would have resulted in decreases in carbon dioxide production. Hence, \(P_{aCO_2}\) would increase when hypoxia was relieved and the mean \(P_{aO_2}\) during Fluosol perfusion increases to 10.1 kPa (± 0.35 SEM).

The results of this preliminary trial have shown the feasibility of extrapulmonary oxygenation using peritoneal lavage. It should be noted, of course, that in these experiments the mass of oxygen being transferred to the splanchnic bed was very small in the "normal range" of \(P_O_2\) and mass transfer of oxygen would only be occurring at values of \(P_O_2\) at which substantial desaturation of arterial blood was present. Salt (personal communication) has obtained good results working with rats, but a number of questions remain to be answered concerning the efficacy and safety of this treatment in larger animals. The question of possible oxygen toxicity of the peritoneal surfaces must be investigated, and the degree of absorption of fluorocarbons ascertained carefully if accumulation and possible hepatic toxicity are to be avoided.

No fluorocarbons were detected by measuring the fluorocrit—in which the blood is very rapidly centrifuged and the fluorocarbon layer sedimenting below the red cells measured. However, this method is not very sensitive and detection of fluorocarbons is probably not possible at ranges below 0.2%. Assuming the blood volume to be 57.3 ml kg\(^{-1}\) (Armin et al., 1952), this would represent (for a 3-kg rabbit) absorption of 3.4 ml of fluorocarbons. In view of the fact that no significant changes occurred in haemoglobin concentrations (and hence no haemo-dilution or -concentration), it is thus unlikely that much absorption of Fluosol was occurring during the experiments.

It is possible that peritoneal oxygenation may find application in the treatment of some forms of respiratory failure. It would be particularly indicated in cases of pulmonary damage by oxygen radical formation in paraquat poisoning.

**REFERENCES**


Armin, J., Grant, R. T., Pels, H., and Reeve, E. B. (1952). The plasma, cell and blood volumes of albino rabbits as estimated by the dye (T 1824) and 32P marked cell methods. *J. Physiol. (Lond.),* 116, 59.


In a pilot study, the possibility was investigated of whether it is possible to increase the arterial oxygen tension and decrease the arterial carbon dioxide tension in intact animals by intraperitoneal perfusion with the oxygen-carrying blood substitute Fluotol-DA 20%, which contains perfluorocarbon. Rabbits were perfused intraperitoneally with Fluosol at a rate of 25 ml min$^{-1}$. Blood-gas measurements were made at various $F_{\text{IO}_2}$ values between 0.5 and 0.16 (if the animal was not severely hypoxic). Measurements were repeated during the intraperitoneal perfusion of Fluosol. At all $F_{\text{IO}_2}$ values, significant increases of $P_{\text{aO}_2}$ ($P<0.05$) were observed if the animals were not hypoxic. Significant decreases of $P_{\text{aCO}_2}$ ($P<0.05$) were observed when the animals were not hypoxic ($P_{\text{aO}_2} > 10$ kPa).