Effects of Low Oxygen and of Carbon Monoxide on the Renal Circulation in Unanesthetized Rabbits

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With the technical assistance of Yvonne Paseoe

The circulatory response of the normal unanesthetized rabbit to acute hypoxia differs from that of man or the dog. For the first few minutes after breathing low O2 mixtures, bradycardia and a small rise in blood pressure were observed. The steady state response following more prolonged exposure was variable with an increase in cardiac output and heart rate in some animals and persistent bradycardia and a reduction in cardiac output in others. In contrast to this variable response, man and the dog usually develop an increase in cardiac output and heart rate when breathing low O2 mixtures. The experiments of Bernthal et al., Daly and Scott, and Downing et al. suggest that in the dog this response is not primarily the result of stimulation of the arterial chemoreceptors. When the carotid chemoreceptors were perfused with hypoxic blood in dogs with controlled ventilation, bradycardia, reduction in cardiac output and systemic vasoconstriction were observed. When chemoreceptor perfusion was carried out in the same animals during spontaneous respiration a variable response not unlike the picture in the conscious rabbit during the steady state was obtained; for example, under these conditions the heart rate remained unchanged, or increased or decreased. These results suggest that the circulatory effects of chemoreceptor stimulation in the dog may be modified in the spontaneously breathing animal.

In contrast to the variable effects of low O2 mixtures in the rabbit, breathing small concentrations of carbon monoxide in air resulted in a uniform increase in cardiac output and blood pressure and a reduction in cardiac output. In contrast to this variable response, man and the dog usually develop an increase in cardiac output and heart rate when breathing low O2 mixtures. The experiments of Bernthal et al., Daly and Scott, and Downing et al. suggest that in the dog this response is not primarily the result of stimulation of the arterial chemoreceptors. When the carotid chemoreceptors were perfused with hypoxic blood in dogs with controlled ventilation, bradycardia, reduction in cardiac output and systemic vasoconstriction were observed. When chemoreceptor perfusion was carried out in the same animals during spontaneous respiration a variable response not unlike the picture in the conscious rabbit during the steady state was obtained; for example, under these conditions the heart rate remained unchanged, or increased or decreased. These results suggest that the circulatory effects of chemoreceptor stimulation in the dog may be modified in the spontaneously breathing animal.

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Supported by a Grant-in-Aid from the National Heart Foundation of Australia.

Received for publication November 1, 1962.

Circulation Research, Volume XII, April 1963

mixtures in the rabbit, breathing small concentrations of carbon monoxide in air resulted in a uniform increase in cardiac output, tachycardia and relatively little increase in respiratory minute volume. Breathing CO reduces the O2-carrying capacity of the blood and produces an "anemic" type of hypoxia at the tissue level. The results with CO in the rabbit were similar to the effects observed in man by Asmussen and Chiodi and in the dog by Chiodi et al. These workers found that breathing small concentrations of CO produced slight elevation in arterial carbon dioxide pressure (PaCO2), but left the arterial oxygen pressure (PaO2) essentially within normal limits. The differences between the rabbit's response to low O2 mixtures and CO might thus depend on differences in ventilation, PaCO2 and PaO2. The effects of PaCO2 and PaO2 on ventilation and cardiac output and heart rate were excluded by the experiments of Korner and Edwards, who showed that little effect was observed when PaCO2 was elevated in the presence of a normal or elevated PaO2; however, in the presence of a low PaO2 elevating the PaCO2 produced bradycardia and reduction in cardiac output. This response differs considerably from the effects with CO. The difference in the arterial oxygen tension in the two types of hypoxia thus appeared to be an important factor in accounting for the difference in the circulatory response of the rabbit to low O2 mixtures and CO. A comparison of the circulatory effects in these two types of hypoxia thus offers the possibility of assessing the role of the PaCO2 in various aspects of circulatory regulation in the intact, unanesthetized rabbit.

The renal blood flow accounts for a large
fraction of the resting cardiac output and might be expected to play a part in the circulatory adjustments to low O₂ mixtures and carbon monoxide. In moderate arterial hypoxia in man and the dog only minor changes in renal blood flow (RBF) and glomerular filtration rate (GFR) have been observed, but in severe arterial hypoxia the RBF and GFR were markedly reduced. In asphyxia marked reductions in RBF have been described in the anesthetized rabbit and in diving mammals. The effects of CO on the renal circulation have not been investigated. However, in anemia the reduced O₂-carrying capacity of the blood leads to the development of a somewhat similar type of "tissue" hypoxia with an essentially normal PₐO₂. The changes in the renal circulation reported in anemia have been variable, probably as a result of differences in the types of anemia studied and due to uncertainty regarding the renal PAH extraction ratio in anemia. The present study was therefore undertaken to determine the part played by changes in the renal circulation in the circulatory adjustments to low O₂ mixtures and to carbon monoxide in the unanesthetized rabbit, and to investigate which components of the renal vascular response were under direct nervous control.

Methods

The experiments were carried out on 91 inbred male rabbits of mixed breed varying in weight from 1.5 to 3.5 kg. Details of operative, experimental and analytical procedures have been described elsewhere. In 50 animals all operative procedures were carried out using local anesthesia. In 39 rabbits where renal vein catheterization was carried out, and in 25 animals subjected to bilateral ureteric catheterization, the preliminary operative procedures were carried out using light sodium thiopental anesthesia. In the latter two groups the determination of renal clearances, cardiac output, etc. commenced about four hours after recovery from anesthesia. There was no obvious difference in the response of these animals to the various inspired gas mixtures when compared to completely unanesthetized animals. The general plan of the experiment was, except where stated otherwise, as shown in figure 1. All clearance determinations during control and "treatment" periods were carried out during moderate water and mannitol diuresis as described previously. Following the control observations the animals breathed one of the following inspired "treatment" mixtures: 21% O₂ in N₂; 9.4-9.8% O₂ in N₂ (9.6% O₂); 0.1% CO + 21% O₂ in N₂ (0.1% CO); 0.2% CO + 21% O₂ in N₂ (0.2% CO). In some experiments different low oxygen mixtures ranging from 8% O₂ in N₂ to 11.8% O₂ in N₂ were used in relation to special test procedures described in the text. The gas mixtures were freshly prepared just before use, from cylinders of air, N₂ and 0.5% CO in 21% O₂. The gases were passed through rotameters at appropriate flow rates, and the mixtures were stored in a 100-liter Douglas bag. The animals breathed the mixtures through a respiratory valve from a very light polythene bag, as described.
Results of Mean Values for Renal PAH Extraction Ratios, $S_{am}$ (or $S_{am}'$), Renal Vein $S_{ao}$ (or $S_{ao}'$), Renal O2 Consumption and Renal Blood Flow (RBF), in 16 Animals Subjected to Renal Vein Catheterization. Each Group Breathed Room Air During the Control Period ($C$), but Breathed 21% $O_2$, or 9.6% $O_2$, 0.2% CO + 21% $O_2$ in $N_2$, During the Treatment Period ($T$). The Calculation of the Standard Error (SE) Has Been Determined for Individual (Control-Treatment) Differences Since Each Animal Acts as its Own Control.

<table>
<thead>
<tr>
<th>Treatment No. of animals</th>
<th>100% $O_2$</th>
<th>9.6% $O_2$</th>
<th>0.2% CO</th>
</tr>
</thead>
<tbody>
<tr>
<td>D.E. $O_2$ ratio per cent</td>
<td>C</td>
<td>T</td>
<td>C</td>
</tr>
<tr>
<td>Renal PAH extraction ratio per cent</td>
<td>92.4</td>
<td>91.7</td>
<td>97.7</td>
</tr>
<tr>
<td>$S_{ao}$ or $S_{ao}'$ per cent</td>
<td>96.0</td>
<td>96.3</td>
<td>96.0</td>
</tr>
<tr>
<td>Renal vein $S_{ao}$ or $S_{ao}'$ per cent</td>
<td>82.0</td>
<td>81.1</td>
<td>81.5</td>
</tr>
<tr>
<td>Renal $O_2$ ml/min STPD</td>
<td>2.28</td>
<td>2.39</td>
<td>0.846</td>
</tr>
<tr>
<td>RBF, ml/min</td>
<td>84</td>
<td>81</td>
<td>5.5</td>
</tr>
</tbody>
</table>

$^*$Results in brackets represent mean from 4 animals breathing 9.6% $O_2$, omitting results from 1 animal where extraction ratio fell by 19%.

$^t$4 animals only in each group.

$^P$Treatment effect statistically significant. ($P < 0.05$)

Previously,2-29 Inspired oxygen concentration ($F_{io2}$) was measured with a Beckman model E2 $O_2$ analyzer, and carbon monoxide ($F_{ico}$) was measured with an Infra Red Development Co. $CO$ analyzer. In about half the experiments where the inspired treatment mixture was 9.6% $O_2$ a period of breathing 11.5% $O_2$ in $N_2$ for 30 minutes preceded the change to 9.6% $O_2$ since it had been shown previously that the animals tolerated the latter mixture better in this way. However on this occasion there was no significant difference in response in the "acute" 9.6% $O_2$ group and the "gradual induction" 9.6% $O_2$ group and the results from both groups have accordingly been pooled.

NOTATION IN CARBON MONOXIDE AND LOW O2 EXPERIMENTS

Since the presence of carboxyhemoglobin profoundly alters the oxyhemoglobin dissociation curve,4-59 the symbol $S_{aoP}$ with appropriate suffix is used to denote the ratio of ($O_2$Hb)/(COHb + HbO2 + Hb) in the blood, in the presence of significant amounts of carboxyhemoglobin. Thus $S_{am}$ refers to the arterial ($O_2$Hb)/(total Hb) ratio in the presence of carboxyhemoglobin, and $S_{am}'$ refers to arterial $O_2$ saturation in the absence of carboxyhemoglobin.

RESULTS

EFFECT OF BREATHING 9.6% $O_2$ AND 0.2% CO ON RENAL PAH EXTRACTION RATIO

Renal vein catheterization was carried out in 16 animals. Each animal breathed room air during the control period. During the subsequent treatment period five animals breathed 21% $O_2$, five animals breathed 9.6% $O_2$ and six animals breathed 0.2% CO. The results in table 1 show that the effect on the renal PAH extraction ratio of breathing low $O_2$ mixtures was small and barely significant. In these experiments there was significant reduction in renal vein $S_{ao}$ (or $S_{ao}'$ in the CO experiments), indicating that there was probably significant reduction in the renal $O_2$ content in both experiments. The results show that the use of uncorrected PAH clearances when breathing 9.6% $O_2$ or 0.2% CO will result in negligible errors when equating these clearances with true renal plasma flow (RPF). Reduction in the renal $O_2$ consumption occurred in the experiments with 9.6% $O_2$ and 0.2% CO only when there was a reduction of more than 30% in the RBF.

EFFECT OF BREATHING 9.6% $O_2$

Following control observations with all animals breathing room air, 24 animals breathed 9.6% $O_2$ during the control period (fig. 1), and 12 animals breathed 21% $O_2$. There was a considerable increase in respiratory minute
FIGURE 2
$S_\text{a}O_2$ (or $S'_\text{a}O_2$) in relation to the change in ventilation, expressed as percentage of each animal's own control value (upper panels), and the Right Atrial $S_\text{a}O_2$ (or $S'_\text{a}O_2$) (lower panels). Open circles—breathing 21% $O_2$ during treatment period; black circles—breathing 9.6% $O_2$; half-black circles—breathing 0.1% or 0.2% CO in 21% $O_2$.

volume (upper left panel fig. 2). Although the animals breathed a gas mixture of approximately constant composition the magnitude of the respiratory response varied between individual animals. The range of $S_\text{a}O_2$ values varied from 84% to 46%, reflecting variation in ventilation:perfusion ratios between different animals. The right atrial $S_\text{a}O_2$ was reduced below normal values whilst breathing 9.6% $O_2$. In the 24 animals breathing 9.6% $O_2$ during the treatment period the $O_2$ consumption was 23.7 ml/min STPD when breathing room air, and 20.9 ml/min STPD when breathing the low $O_2$ mixture (difference 2.8 ± 0.85 (SE) ml/min). In the 12 animals breathing 21% $O_2$ during the treatment period corresponding values for $S_\text{a}O_2$ were 25.6 ml/min STPD while breathing room air, and 24.8 ml/min STPD whilst breathing 21% $O_2$ (difference 0.8 ± 1.5 (SE) ml/min).

The effect of arterial hypoxia on the urine flow was variable. The mean urine flow whilst breathing room air was 0.72 ml/min and 0.50 ml/min whilst breathing 9.6% $O_2$. Changes in above measurements are expressed as percentage of the animals own control value. Each animal is represented by only one point.

FIGURE 3
Arterial $S_\text{a}O_2$ in relation to changes in cardiac output (C.O.), renal blood flow (RBF), ear artery pressure (BP), and filtration fraction (FF) in animals breathing 21% $O_2$ during treatment period (open circles), and 9.6% $O_2$ (black circles). Each animal is represented by only one point.

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O₂ mixtures was greater than observed previously,² possibly as a result of further reduction in the amount of handling and excitement to which the animals were subjected. The heart rate at the time of the clearance determinations in animals breathing 9.6% O₂ was 93.5 ± 2.9 (SEM) % of the control value (taken as 100%). There was no significant change in arterial pressure with increasing hypoxia. There was reduction in RBF related to the degree of severity of hypoxia (fig. 3). Although the GFR was also reduced, the effect was smaller than the effect on the RPF and there was thus an increase in filtration fraction at low S_aO₂ values. The results indicate that there was an overall increase in the renal vascular resistance with a selective increase in postglomerular resistance with increasing severity of hypoxia.

EFFECT OF BREATHING 0.1 AND 0.2% CO

Twenty-seven animals breathed 0.1 or 0.2% CO during the treatment period. There was a small, but statistically significant increase in respiratory minute volume. The percentage of carboxyhemoglobin varied between 30% and 58% depending on the concentration of inspired CO. The mixed venous S_aO₂ was reduced in relation to the reduction in arterial O₂-carrying capacity (fig. 2). The O₂ consumption was 26.4 ml/min STPD while breathing room air, and 22.9 ml/min STPD when breathing CO mixtures (difference 3.5 ± 0.60 (SEM) ml/min).

There was usually some reduction in urine flow in the course of breathing CO mixtures, the urine flow of the group being 0.60 ml/min while breathing room air and 0.37 ml/min while breathing CO.

Figure 4 shows that the cardiac output increased in relation to the reduction in S_aO₂. The mean heart rate while breathing carbon monoxide was 112.9 ± 2.45% (SEM) of the control value and tachycardia was observed in most animals. There was reduction in ear artery pressure, RBF and GFR, each variable being reduced by approximately 20%. The GFR and RPF were reduced to approximately the same degree, so that there was no significant change in filtration fraction with reduction in S_aO₂. There was no significant effect in the group on the renal vascular resistance.

The fall in arterial pressure, RBF and GFR, did not appear to be closely related to the degree of reduction in arterial O₂-carry-
TABLE 2
Mean Values in 3 Groups of Babbits Subjected to Following Treatment Sequences. Group A: Each Animal Breathed Successively Room Air—21% O₂ —0% CO. Group B: Each Animal Breathed Successively Room Air—0.1% CO. Group C: Each Animal Breathed Successively Room Air—0.2% CO—9.6% O₂.

<table>
<thead>
<tr>
<th>Group</th>
<th>number of animals</th>
<th>Treatment</th>
<th>Cardiac output ml/min</th>
<th>Heart rate/min</th>
<th>B.P. mm Hg</th>
<th>R.B.F. ml/min</th>
<th>G.F. ml/min</th>
<th>Ventilation ml/min STPD</th>
<th>Sa0₂ or S’a0₂</th>
<th>Sv0₂ or SV0₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td>Control period</td>
<td>537 ± 109</td>
<td>565</td>
<td>93'</td>
<td>114</td>
<td>17.4'</td>
<td>1200</td>
<td>2370</td>
<td>1400</td>
</tr>
<tr>
<td>B</td>
<td></td>
<td>11%</td>
<td>119</td>
<td>114</td>
<td>72±5</td>
<td>76±2</td>
<td>105±5</td>
<td>100±5</td>
<td>120</td>
<td>41</td>
</tr>
<tr>
<td>C</td>
<td></td>
<td>0.2%</td>
<td>17.4</td>
<td>17.4</td>
<td>16.6</td>
<td>20.2</td>
<td>17.0</td>
<td>17.4</td>
<td>16.6</td>
<td>13.5</td>
</tr>
</tbody>
</table>

*Significantly different from control value (P < 0.05)
†Significantly different from first treatment value (P < 0.05)

It appeared possible that such a relationship might be obscured by variation in response between individual animals. Accordingly the effect of two levels of inspired CO was tested in each of four animals (table 2 Group B). The results indicate that the degree of reduction in the arterial pressure was significantly greater when breathing 0.2% CO compared to 0.1% CO. There was no significant additional effect on the RBF and GFR in these animals when breathing 0.2% CO. The maintenance of constant RBF and GFR with 0.2% CO despite an additional fall in blood pressure suggests the occurrence of some renal vasodilatation with this gas mixture.

COMPARISON OF EFFECTS OF 9.6% O₂ WITH CARBON MONOXIDE

There was a significantly larger effect on the respiratory minute volume in animals breathing 9.6% O₂. In the range of Sa0₂ values of 50% to 70% the respiratory minute volume was 198 ± 3.5 (se) per cent of control with 9.6% O₂. In animals breathing 0.1 or 0.2% CO with values of S’a0₂ in the range of 50% to 70% the increase in ventilation was 116 ± 5.4 (se) per cent of the control value, the difference being statistically significant. In contrast to the immediate maximal respiratory response with 9.6% O₂, the ventilation increased more slowly and gradually in animals breathing CO. The large increase in ventilation with 9.6% O₂ suggests a reduction in Pao₂ in agreement with previous observations in the rabbit. In the present experiments measurements of Pao₂ and pH were not carried out and only approximate estimates of oxygen pressures in mixed venous blood of the Pvo₂ can therefore be made from the data shown in figure 2. In animals breathing 9.6% O₂ the S’v0₂ (right atrial) varied from 50% to 18%. Using the rabbit's oxyhemoglobin dissociation curve and assuming a Pao₂ of 15 mm Hg and body temperature of 40°C (normal rabbit body temperature), the estimated range of Pvo₂ values was 24 to 12 mm Hg. In animals breathing CO the S’v0₂ varied from 30% to 22%. Assuming a carboxyhemoglobin saturation of 50% (average with 0.2% CO), a Pao₂ of 40 mm Hg, a pH of 7.40 and a temperature of 40°C, and estimating the Pvo₂ as suggested by Douglas et al., Roughton and Darling, and Lillenthal et al., the limits of Pvo₂ in the CO experiments may be estimated as ranging from 30 to 11 mm Hg. It seems reasonable to infer considerable overlap in Pvo₂ even though the Pao₂ probably varied widely between animals even when breathing a given treatment mixture.

The cardiac output increased to approxim-
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The RBF was reduced to a greater extent in animals breathing 9.6% O₂ than in those breathing CO despite the fact that the blood pressure remained unchanged in the former group, but was reduced in the latter. This suggests that renal vasoconstriction occurs with 9.6% O₂. The difference in the renal vascular response between low O₂ mixtures and CO can be demonstrated more clearly by observing the response to both mixtures in a given animal (table 2, Group C). Figure 5 shows that when a rabbit breathed 0.2% CO the arterial and mixed venous O₂ content were reduced. There was increase in cardiac output, some increase in ventilation, and reduction in arterial pressure, RBF and GFR. When the inspired gas was changed to 9.8% O₂ further increase in ventilation occurred. The O₂ content of the arterial and mixed venous blood increased slightly. The blood pressure increased from its previous level, but despite this there was further significant reduction in RBF, clearly indicating the occurrence of renal vasoconstriction. This effect was observed in all four animals tested in this way and is in agreement with the results observed in the main groups shown in figures 3 and 4.

THE ROLE OF THE RENAL VASOMOTOR NERVES IN THE RESPONSE TO 9.6% O₂

Whilst the above experiments demonstrate the occurrence of renal vasoconstriction in animals breathing 9.6% O₂, they do not indicate the mechanism involved. Vasoconstriction could be due to increased sympathetic constrictor tone, or due to the liberation of humoral agents such as epinephrine. The part played by the renal vasomotor nerves was studied in 14 animals where separate clearance estimations for each kidney were carried out. In seven of these the left kidney was denervated six to eight days before an experiment.

Figure 6 shows the effects of 9.6% O₂ on the innervated and denervated kidney of an unanesthetized rabbit. The RBF was reduced to a greater extent in the innervated kidney when breathing 9.6% O₂ than in the denervated kidney. On resuming air breathing the RBF increased in the innervated kidney, but there was little change in flow to the denervated kidney. Breathing 8% O₂ again resulted in a marked difference between the two sides. The results of all experiments are summarized in figure 7. In animals with both kidneys in-
Experiment showing effect of breathing 9.6% $O_2$ and 8% $O_2$ on cardiac output, arterial pressure, RBF and GFR in rabbit with chronic denervation of left kidney. Separate clearance determinations were carried out from each kidney. White—breathing room air. Black—breathing low $O_2$ mixture.

Figure 7 shows that there was no difference in filtration fraction on innervated and denervated sides, and the increase in filtration fraction with reduction in $S_aO_2$ (figs. 3 and 7) is thus not the result of direct nervous action on the renal blood vessels.

Because of variation in the renal vascular response between animals it is not obvious from the results in figure 7 if there is a threshold for the occurrence of renal vasoconstriction. The effects of a number of different low $O_2$ mixtures were studied in greater detail in two animals, and the result of one experiment

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is shown in figure 8. There was no difference in the behaviour of RBF and GFR on innervated and denervated sides when the animal breathed 11.8% O₂ (SaO₂ 85%). A small degree of vasoconstriction could be demonstrated on the innervated side when breathing 10.4% O₂ and 9.6% O₂ (SaO₂ 78% and 77% respectively), and this became marked with increasing severity of hypoxia. This result demonstrates that renal vasoconstriction requires the presence of a more severe degree of arterial hypoxia than is required to bring about an increase in ventilation.

In order to further investigate the relationship of the Pₐₐ₀ to renal vasoconstriction, bilateral denervation of the carotid and depressor nerves was carried out in two animals in two stages, eight days before the experiment. Figure 9 shows the result of one experiment. The animals were not able to tolerate 9.6% O₂ and higher inspired O₂ pressures were used. The ear artery pressure was 103 mm Hg preceding the test period and was 114 mm Hg in the other animal. These values are lower than might be expected following complete baroreceptor denervation. It is possible that baroreceptor denervation may not have been complete, or the prolonged period of rest in the experimental cage following the operative procedures may have reduced the blood pressure. Chemoreceptor denervation was probably adequate as judged by the very small increase in ventilation with very severe
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THE ROLE OF THE RENAL VASOMOTOR NERVES IN THE RESPONSE TO 0.2% CO

This was investigated in nine animals, five of which left renal denervation had been carried out. There was much less difference in the response between innervated and denervated kidney with CO than with 9.6% O2 (fig. 10). In all animals there was a slightly greater reduction in RBF (table 3) and GFR on the innervated side during the first 10 to 20 minutes of breathing CO. During steady state conditions, however, there was no difference in behaviour between the two sides. In all animals the characteristic constrictor response to low O2 mixtures was demonstrated at the end of the experiment (fig. 10). The part played by the renal vasomotor nerves in the reduction in RBF and GFR in the CO experiments thus appears to be small.

Figure 10 shows that the maximum fall in RBF occurred in both innervated and denervated kidney during the initial fall in blood pressure. Subsequently there was no change or a slight increase in RBF despite further fall in arterial pressure. This suggests the occurrence of some renal vasodilatation with 0.2% CO.

Discussion

The experiments demonstrated significant differences in the response of the renal circulation of the rabbit following exposure to low oxygen mixtures and to carbon monoxide. The mean reduction in RBF was greater in animals breathing 9.6% O2 than in those breathing 0.2% CO, black—breathing 8% O2.

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TABLE 3

Ratios of Right RBF/Left RBF in 7 Rabbits* Breathing 0.2% CO in Air. C Control Periods With Animals Breathing Room Air Before and After Breathing Carbon Monoxide; the Other Periods Represent Successive 10 Minute Collection Periods Whilst Breathing Carbon Monoxide

<table>
<thead>
<tr>
<th>Period</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(left kidney denervated)</td>
<td>(both kidneys innervated)</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>Mean</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-10</td>
<td>0.92</td>
<td>0.93</td>
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<tr>
<td>11-20</td>
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<td>21-30</td>
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<td>51-60</td>
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<td>61-70</td>
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<td>0.99</td>
</tr>
<tr>
<td>71-80</td>
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<td>1.01</td>
</tr>
<tr>
<td>81-90</td>
<td>0.85</td>
<td>1.01</td>
</tr>
</tbody>
</table>

*In two additional animals only steady state response studied.

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Transient and slight renal vasocostriction occurred in the initial period of breathing CO, at the time of the steepest fall in blood pressure and it is possible that this may have been of baroreceptor origin, though the present experiments provide no proof of this. Denervation of the carotid sinus region and of the depressor nerve was carried out in two animals and in both of these reduction in renal vascular resistance with relatively slight effects on renal blood flow was observed in place of the usual constrictor response. The renal vasocostriction which occurs in the innervated kidney of the rabbit breathing 9.6% O2 would thus appear to be reflexly mediated with excitation of the carotid and aortic chemoreceptors initiating the reflex.

In contrast to the results with low O2 mixtures there was no evidence of reduction in RBF due to nervous constriction during the steady state in the CO experiments and the response appeared to be partly passive due to fall in blood pressure, and partly the result of local renal dilatation. The passive reduction in RBF due to the fall in arterial pressure is consistent with the results of pressure-flow studies in the isolated kidney.

Circulation Research, Volume XII, April 1965

and norepinephrine. Since these substances are known to be liberated in severe hypoxia it is possible that they may have played a part in the post-glomerular constriction in the rabbit, but the present experiments provide no proof of this. It appears that more severe reduction in Pao2 is required to bring about renal vasocostriction, than is required to produce an increase in ventilation, and that the filtration fraction increases only during the most severe degrees of hypoxia.

Denervation of the carotid sinus region and of the depressor nerve was carried out in two animals and in both of these reduction in renal vascular resistance with relatively slight effects on renal blood flow was observed in place of the usual constrictor response. The renal vasocostriction which occurs in the innervated kidney of the rabbit breathing 9.6% O2 would thus appear to be reflexly mediated with excitation of the carotid and aortic chemoreceptors initiating the reflex.

In contrast to the results with low O2 mixtures there was no evidence of reduction in RBF due to nervous constriction during the steady state in the CO experiments and the response appeared to be partly passive due to fall in blood pressure, and partly the result of local renal dilatation. The passive reduction in RBF due to the fall in arterial pressure is consistent with the results of pressure-flow studies in the isolated kidney.

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two types of experiments, with a respiratory alkalosis in the low \( O_2 \) experiments and a mild respiratory acidosis in the CO experiments.

Previous experiments in the rabbit have shown that increasing the ventilation by increasing the \( \text{Pa}_\text{O}_2 \), in the presence of a normal or elevated \( \text{Pa}_\text{CO}_2 \), had no significant effect on cardiac output and heart rate during the steady state. Increasing the \( \text{Pa}_\text{CO}_2 \) when breathing low \( O_2 \) mixtures resulted in more marked reduction in cardiac output and bradycardia than occurred with low \( O_2 \) mixtures alone, thus differing from the response to carbon monoxide. It therefore seems unlikely that the differences in arterial \( \text{P}_\text{ca} \) account for the differences in response to low \( O_2 \) mixtures and CO. The difference in \( \text{Pa}_\text{O}_2 \) in the two types of experiments appears to be a major contributing cause for the different responses. The CO experiments showed a smaller increase in respiratory minute volume, a finding consistent with the view that with this gas mixture there was less stimulation of the arterial chemoreceptors than with low \( O_2 \) mixtures. This is supported by the direct observations of Duke et al. and Joels and Neil, who showed that concentrations of COHb in excess of those used in the present experiment were without effect on carotid body discharge rates. The demonstration in the present experiments that the renal response to low \( O_2 \) mixtures becomes rather similar to the response to CO mixtures after chemoreceptor denervation also suggests that differences in \( \text{Pa}_\text{O}_2 \) acting via the arterial chemoreceptors account for the different responses to these gas mixtures. Whilst the experiments do not exclude contributing effects of differences in pH and \( \text{Pa}_\text{CO}_2 \), they indicate that differences in \( \text{Pa}_\text{O}_2 \) were a major factor in the two types of response.

Comparison of the present results with low \( O_2 \) mixtures in the rabbit with those of man and the dog suggest that reduction in RBF may occur somewhat more readily in the rabbit. The rabbit appears to reach its limit for increasing its ventilation more readily than does man or the dog, and lower values of \( \text{Pa}_\text{O}_2 \) may thus be produced by a given inspired \( O_2 \) mixture. Whilst there may be quantitative differences in the various species in response to low \( O_2 \) mixtures the present results indicate that even in the rabbit considerable reduction in the \( \text{Pa}_\text{O}_2 \) is required before renal vasoconstriction takes place.

Summary

The effects of breathing 9.6% \( O_2 \) in \( N_2 \) and of breathing 0.1% to 0.2% \( CO \) in air on the renal blood flow (RBF), glomerular filtration rate (GFR) and renal PAH extraction ratio were studied in the unanesthetized rabbit in relation to changes in cardiac output, heart rate, blood pressure and ventilation. All experiments were carried out during moderate water and mannitol diuresis. The RBF and GFR were reduced in both types of hypoxia but this effect was produced by different mechanisms. With low \( O_2 \) mixtures reduction in RBF and GFR occurred mainly as a result of nervous vasoconstriction acting on the afferent arteriole. The arterial chemoreceptors played a part in the production of vasoconstriction. With carbon monoxide, reduction in RBF and GFR occurred mainly as a result of passive reduction in blood pressure, and only slight transient nervous vasoconstriction could be demonstrated in the early period of exposure to this gas. The results suggest that differences in arterial oxygen pressure (\( \text{Pa}_\text{O}_2 \)) were of major importance in accounting for the differences in renal circulatory effects of low \( O_2 \) mixtures and CO in the rabbit.

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Effects of Low Oxygen and of Carbon Monoxide on the Renal Circulation in Unanesthetized Rabbits

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doi: 10.1161/01.RES.12.4.361

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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