Local effects of $O_2$ and $CO_2$ on limb, renal, and coronary vascular resistances

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DAUGHERTY, ROBERT M., JR.; JERRY B. SCOTT; JOE M. DABNEY, AND FRANCIS J. HADDY: Local effects of $O_2$ and $CO_2$ on limb, renal, and coronary vascular resistances. Am. J. Physiol. 213(5): 1102-1110. 1967. - The effects of local changes in the tension of oxygen and carbon dioxide on forelimb, renal, and coronary vascular resistances and left ventricular contractile force were studied by passing blood, without reservoirs, through an isolated ventilated lung and perfusing it into the bed’s arterial supply at a constant rate. Effects of changes in flow on resistance while perfusing with deoxygenated blood were also studied. Forelimb and coronary resistances and contractile force were unaffected by any $PO_2$ above 40 mm Hg but were quickly reduced by a $PO_2$ below this level. Renal resistance fell only with prolonged severe hypoxemia. Elevation of carbon dioxide tension produced a fall in forelimb, renal, and coronary resistances and force. The autoregulation seen on elevation of flow was still observed in the kidney perfused with hypoxicemic blood ($PO_2 > 10$ mm Hg). While this response was not seen in the coronary bed, myocardial activity greatly improved upon perfusion with deoxygenated blood.

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hypercapnia; hypocapnia; hyperoxia; graded hypoxemia; left ventricular contractile force; local regulation; autoregulation

OXYGEN AND CARBON DIOXIDE have been causally implicated in local blood flow regulation because the concentrations of these two agents are seen to vary in the venous blood during active (exercise) hyperemia, reactive hyperemia, and autoregulation. However, before such a causal relationship can be entertained, it must be established that these agents are in fact immediately vasoactive in vascular beds that exhibit local regulation and that this vasoactivity is manifest over the range of concentrations seen in local regulation. In order that studies of vasoactivity will have relevance to local regulation, the concentration of oxygen or carbon dioxide must be quickly altered only in the blood perfusing the intact organ and not in the systemic circulation as a whole. Such studies have been accomplished in only a few vascular beds and these studies are not in complete agreement.

Fleisch et al. (5) found that local hypoxemia did not produce dilation in the cat hindlimb and intestine until the hypoxemia was severe but that a small elevation in carbon dioxide concentration produced significant dilation. Therefore, they concluded that carbon dioxide but not oxygen was an important factor in local regulation. On the other hand, Ross et al. (18) observed dilation in the dog hindlimb with slight local hypoxemia and because of this concluded that oxygen is important in local blood flow regulation. Molnar et al. (16) and Hall and Sackner (10) found that alteration of the oxygen content over the range of the usual arteriovenous difference had little effect on the dog forelimb and hindlimb vascular beds, respectively. Similarly in the Molnar study, altering the carbon dioxide content by 15.8 vol% did not produce a significant change in forelimb resistance. The studies in the coronary vascular bed are in better agreement. Hilton and Eichholtz (13), utilizing a heart lung preparation, reported that perfusion with deoxygenated blood produced a large increase in coronary flow. Gremels and Starling (7) found that the increase in flow occurred at about 40% saturation in the perfusing blood. Berne (2) observed that this flow increase occurred when the sinus blood oxygen content fell below 5.5 vol%. Hilton and Eichholtz (13) and Gremels and Starling (7) also found an increase in coronary blood flow during administration of carbon dioxide. There apparently are no truly local

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2 This investigation was supported, in part, by Public Health Service Fellowship 25,783 from the National Heart Institute. Present address: Depts. of Physiology and Medicine, Michigan State University, East Lansing, Mich. 48823.
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studies on the effect of oxygen and carbon dioxide on the intact blood-perfused renal vascular bed.

In the present study the effects of changes in oxygen and carbon dioxide tensions on the intact blood-perfused forelimb, coronary, and renal vascular beds were observed with a system which permitted rapid local changes in one variable without affecting the other. The studies demonstrate that both oxygen and carbon dioxide are in fact locally vasoactive. However, the studies also suggest that neither oxygen nor carbon dioxide can individually account for all types of local regulation.

METHODS

The effects of local changes in the tension of oxygen or carbon dioxide on forelimb, renal, and coronary vascular resistance and left ventricular contractile force were studied in 134 anesthetized dogs. This was accomplished by passing the dogs' femoral arterial or venous blood through an isolated right lung, removed from another animal, and then pumping it at a constant rate into the brachial, renal, or left common coronary artery while measuring perfusion pressure. The oxygen or carbon dioxide tension of the perfusing blood was altered by ventilating the isolated lung with various mixtures of oxygen, carbon dioxide, and nitrogen. The changes in oxygen tension were temporally of two types: 1) rapid reduction or elevation to very low or very high levels and 2) stepwise reduction to very low levels. The carbon dioxide tension was simply reduced or elevated to low or high levels.

All dogs were anesthetized with adequate doses of intravenous sodium pentobarbital and ventilated with a mechanical respirator via an intratracheal cannula. After injecting heparin intravenously, an extracorporeal lung-perfusion circuit, free of reservoirs, was established between the right femoral artery or vein and either the right brachial, left renal, or left common coronary artery (Fig. 1). Prior to cannulation of the brachial artery (31 experiments) all muscle and connective tissue at the elbow of the forelimb was encircled with ligatures, causing all blood, with the exception of bone flow, to enter the limb through the brachial artery and to exit via the brachial and cephalic veins. The forelimb nerves were left intact. Cannulation of the left renal artery was accomplished through a left-flank incision (51 experiments). In the case of the coronary vascular bed (52 experiments), the heart was exposed through the third left intercostal space and a suture passed around the left common coronary artery. A curved metal cannula was inserted into the aorta via the left subclavian artery with the pump operating. Without stopping the pump, the cannula was manipulated down the ascending aorta into the mouth of the left common coronary artery and tied into position with the previously placed suture. Left ventricular contractile force was measured with a 120-ohm strain-gauge arch (J. L. Butterfield, P. O. Box 412,
TABLE 1. Effect of graded hypoxemia on brachial, renal, and coronary artery perfusion pressure and left ventricular contractile force at constant blood flow

<table>
<thead>
<tr>
<th>Ventilatory Mixture</th>
<th>Limb (N = 9)</th>
<th>Kidney (N = 10)</th>
<th>Heart (N = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PA&lt;sub&gt;0&lt;/sub&gt; mm Hg</td>
<td>P&lt;sub&gt;PA&lt;/sub&gt;&lt;sub&gt;0&lt;/sub&gt; mm Hg</td>
<td>P&lt;sub&gt;0&lt;/sub&gt;&lt;sub&gt;2&lt;/sub&gt; mm Hg</td>
</tr>
<tr>
<td>20.0%</td>
<td>117</td>
<td>103</td>
<td>105</td>
</tr>
<tr>
<td>10.0%</td>
<td>120</td>
<td>112</td>
<td>56*</td>
</tr>
<tr>
<td>5.0%</td>
<td>121</td>
<td>108</td>
<td>32*</td>
</tr>
<tr>
<td>2.5%</td>
<td>121</td>
<td>87*</td>
<td>8*</td>
</tr>
<tr>
<td>0.0%</td>
<td>119</td>
<td>138</td>
<td>104</td>
</tr>
</tbody>
</table>

Ventilatory mixture = percent of oxygen in the 5% CO<sub>2</sub> in N<sub>2</sub> mixture ventilating the isolated lung. Perfusion was femoral arterial blood. P<sub>A</sub> = aortic pressure; P<sub>PA</sub> = brachial artery perfusion pressure; P<sub>RA</sub> = renal artery perfusion pressure; P<sub>CA</sub> = coronary artery perfusion pressure; P<sub>O</sub> = perfusate oxygen tension; O<sub>2</sub> = perfusate oxygen content; pH = perfusate H<sup>+</sup> ion concentration; F = left ventricular contractile force. * P < 0.01 relative to control value.

Fig. 3. Average effects of graded hypoxemia on resistance to blood flow through the forelimb, kidney, and heart and left ventricular contractile force.

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Charleston, S. C.) sutured to the surface of the left ventricle. These cannulation techniques have been described in detail in a previous paper (9).

The femoral artery or vein blood was pumped (Sigmamotor Pump, model T-GSH, Sigmamotor Inc., Middleport, N. Y.) into the pulmonary artery of the isolated lung. The venous effluent, obtained by tying a cannula into the partially preserved left atrium, passed an oxygen tension probe (oxygen macroelectrode, Beckman Instruments Inc., Spinco Division, Palo Alto, Calif.) and then sequentially ventilating the isolated lung with ambient air, low oxygen mixture, high oxygen mixture, ambient air, high carbon dioxide mixture, and ambient air at a more rapid rate (perfusate = arterial blood). During the first five periods, the stroke volume and frequency of the respirator were constant. However, the ventilatory minute volume exceeded normal while the pulmonary blood flow of the isolated lung was less than normal. This permitted rapid equilibration between alveolus and blood but at the same time caused alkalosis during the first four periods. Therefore, in a second series of experiments, ventilation was accomplished with 5% CO<sub>2</sub>-20% O<sub>2</sub>-75% N<sub>2</sub> mixture ventilating the isolated lung with gas mixtures containing 20% (control), 10%, 5%, 2.5%, 0%, and 20% (control) oxygen in nitrogen. Regardless of the oxygen concentration, each gas mixture contained 5% carbon dioxide. The perfusate was always arterial blood. Each level of hypoxemia was terminated when the continuously measured parameters became stable (approximately 4 min, except in the case of the heart on the 0% oxygen mixture). More prolonged carbon dioxide deprivation in the heart and hypoxemia in the kidney were studied in two additional series of animals. Thus in heart experiments, ventilation was switched from 5% CO<sub>2</sub>-20% O<sub>2</sub>-75% N<sub>2</sub> to air and
was then quickly raised to a level in excess of 650 mm Hg, which reduced from 114 (16 ~01%) to 2 (0.9 ~01%) mm Hg, but did not affect left ventricular contractile force. Elevation of Po2 to a level in excess of 650 mm Hg did not increase perfusion pressure or contractile force above the control value. However, using venous blood as the perfusate, reduction of Po2 to 8 mm Hg (0.4 vol %) with pH constant at 7.40, quickly produced a 48 % fall in perfusion pressure and a 30 % fall in contractile force (N = 4).

Unlike the forelimb and coronary vascular beds, the renal vascular bed failed to respond greatly to any degree of acute hypoxemia. Using arterial blood as the perfusate (N = 6), reduction of Po2 to 33 mm Hg (pH constant at 7.57) produced a 9 % fall in renal artery perfusion pressure but elevation of Po2 to a level in excess of 650 mm Hg did not raise perfusion pressure above the control value. Using venous blood as the perfusate, reduction of Po2 to 6 mm Hg (0.7 vol %) with pH constant at 7.28 (N = 8) failed to affect perfusion pressure. However, the ischemic maneuver revealed that the bed was capable of dilation (Fig. 2).

These studies suggested that sudden severe hypoxemia lowers resistance to flow through the forelimb and coronary vascular beds but has an irregular effect on the renal vascular bed. It also appeared that the greatest effect in limb and heart occurs only after the Po2 falls below 30 mm Hg. The following experiments were therefore performed to more precisely answer these questions.

Graded changes in Po2. Table 1 shows the effects of graded hypoxemia on perfusion pressure in the three vascular beds and on left ventricular contractile force. It is apparent that reduction of perfusate Po2 to approximately 30 mm Hg (approximately 12 vol %) was without effect in any of the three vascular beds. Further reduction to 17 mm Hg (6.8 vol %) and 5 mm Hg (0.9 vol %) was also without effect on the renal vascular bed. In contrast, reduction of perfusate Po2 to 21 mm Hg (7 vol %) in the coronary vascular bed produced a significant fall in perfusion pressure, contractile force and aortic pressure. The effects were even greater at a Po2 of 9 mm Hg (1.3 vol %). The latter level could not be maintained for more than a few minutes without complete failure of heart pumping ability. Though the effect was not as striking as in the heart, a Po2 of 8 mm Hg...
Hg (1.8 vol%) also significantly reduced forelimb perfusion pressure. These changes expressed in percent of control resistance and contractile force, are graphically illustrated in Fig. 3.

Severe hypoxemia of 8 min duration using venous blood as the perfusate (Fig. 2) and of 4 min duration using arterial blood as the perfusate (Table 1) failed to produce a significant fall in renal vascular resistance. In order to determine whether more prolonged hypoxemia would produce dilation of the renal vascular bed, the lung was ventilated with the 5% CO₂-95% N₂ for 15 min while perfusing with arterial blood. Table 2 shows the results of these experiments. It is apparent that perfusion pressure was not affected by 2 min of severe hypoxemia. By 8 min, however, the perfusion pressure had fallen 14 mm Hg (below control in 10, equal to control in 3, and above control in 3 experiments). By 15 min, perfusion pressure was 22 mm Hg below the control value (below control in 13, equal to control in 1, and above control in 2).

Since perfusion pressure did not rapidly fall as it did in the limb and heart, and in some cases actually rose with time and since the renal vascular bed is known to be highly sensitive to platelet aggregates (11, 12), platelet counts were made across the kidney in five experiments. There was no significant change in the arteriovenous platelet difference after about 5 min of severe hypoxemia. High plasma potassium causes constriction of the renal bed (9). Therefore, renal arterial and venous plasma potassium concentrations were determined in 11 experiments. There was no significant change in the arteriovenous potassium difference after about 5 min of severe hypoxemia.

Carbon Dioxide.

Table 3 and Fig. 4 show the effects of a large sudden decrease in pH of the perfusing blood, evoked by raising the carbon dioxide tension, on the resistance to blood flow through the limb and kidney. Within a very short period of time, perfusion pressure fell in each experiment in both organs. These changes in perfusion pressure always disappeared when the carbon dioxide was suddenly withdrawn. A slight rise in P₀₂ was regularly observed on addition of CO₂.

Table 4 and Fig. 5 show the results of the same maneuver in the heart. Table 4 shows, in addition, the effect of a more prolonged period of CO₂ deprivation. Carbon dioxide produced a biphasic effect on coronary vascular resistance. Within 1 min following the addition of carbon dioxide, perfusion pressure rose above the value seen on air ventilation (f = 11). This transient increase was quickly replaced by a fall in perfusion pressure. At this time, left ventricular contractile force was reduced. The withdrawal of carbon dioxide also produced a biphasic effect on coronary resistance. Within 1 min of air ventilation at a rapid rate (f = 35), perfusion pressure fell below the stable level seen on 20% CO₂ ventilation but then quickly rose. This was associated with an increase in contractile force above the value seen during the first period of air ventilation.

Examination of the individual records revealed that perfusion pressure was still rising at the end of the period of air ventilation (f = 35). A second series of experiments were, therefore, performed to determine whether a more prolonged period of CO₂ deprivation results in a rise in resistance. Switching from 5% CO₂ to air ventilation caused a transient fall in perfusion pressure followed by a rise to a level which by 9 min.

### Fig. 4. Typical responses of brachial and renal artery perfusion pressures to sudden decrease in pH of the perfusing blood.
was significantly above that seen during ventilation with
the 5% CO₂ mixture (Table 4). Contractile force immediately rose and then leveled off at an intermediate value. Despite this rise in contractile force, aortic pressure fell.

**Effect of Severe Hypoxemia on the Resistance**

**Response to Changes in Flow**

It is of interest to know whether autoregulation can occur in the near absence of oxygen. One form of autoregulation is seen on alteration of flow, i.e., sudden elevation of flow to a new constant level is followed by a gradual rise in perfusion pressure (21). This maneuver was accomplished in the kidney (N = 8) while perfusing with blood having an average PO₂ of 3 mm Hg at the low flow and 7 mm Hg at the high flow. Average blood flow was suddenly elevated from 28 to 156 ml/min. Perfusion pressure was 145 mm Hg immediately after elevation of flow. It then rose to a steady-state value of 182 mm Hg in about 2 min. Similar autoregulatory responses have been observed in the hindlimb perfused with equally hypoxic blood (20).

Elevation of flow with hypoxic blood did not produce this autoregulatory response in the coronary vascular bed but it did improve left ventricular contractile force and aortic pressure. In 12 experiments, left common coronary artery blood flow was suddenly elevated from 59 ml/min (PO₂ 8 mm Hg) to 219 ml/min (PO₂ 11 mm Hg). Perfusion pressure was 90 mm Hg immediately after elevation of flow. Four minutes later it was 92 mm Hg. However, aortic pressure and left ventricular contractile force rose 41 and 79%, respectively, on transition from the low flow to the high flow. While perfusing with hypoxic blood at the low flow, aortic pressure fell to 51 mm Hg and would have fallen further if conditions had been maintained. Elevation of flow, hypoxemia continuing, resulted in an aortic pressure rise to 72 mm Hg. The preparation flow appeared to be capable of more sustained activity. A typical example of this is shown in Fig. 6.

**DISCUSSION**

**Oxygen**

These studies show that reduction of the oxygen tension and oxygen content of the perfusing blood over the range of the normal arteriovenous difference produces little change in forelimb, renal, or coronary vascular resistance or in left ventricular contractile force. More severe hypoxemia quickly decreases the resistance to flow through the forelimb and coronary vascular beds as well as left ventricular contractile force but has no regular effect on renal vascular resistance. Prolonged severe hypoxemia is required to reduce resistance in the kidney.

These findings implicate oxygen in local regulation of blood flow in some instances but not in others. The absence of an immediate response to hypoxemia in the kidney suggests that oxygen does not participate to an important extent in renal autoregulation of blood flow and perhaps not even in renal reactive hyperemia. The conclusion regarding autoregulation is supported by other studies. Renal autoregulation occurs in the presence of only a 4 mm Hg fall in renal venous oxygen tension (21). Further, renal autoregulation still occurs when this small fall in oxygen tension is prevented by ventilation with 100% O₂ (21). It also seems unlikely that oxygen participates in the limb and heart autoregulation which follows elevation of arterial pressure. In this instance, venous oxygen tension (and by inference, tissue oxygen tension) is changed over the range in which oxygen was found to be without effect. On the other hand, oxygen could well participate in the autoregulation which follows reduction of perfusion pressure, active hyperemia, and reactive hyperemia seen in limb and heart. Under these circumstances, venous oxygen tension may fall to levels which in this study were found to be quickly vasoactive. However, even here, other factors may be involved. Ross et al. (19) found that perfusion of the gastrocnemius muscle with hypoxic blood does not produce as great an increase in flow as is seen during muscular activity even though the venous Po₉ levels are identical. Furthermore, in similar studies, Rudko (20) found that exercise dilation still occurs when the venous Po₉ is not permitted to fall below the control level by the administration of oxygen. Additional evidence bearing on this point will be considered below.

A stimulus, applied locally, can affect vascular resistance either by influencing blood viscosity or blood vessel caliber. A change in caliber may be mediated directly or indirectly. Thus, a stimulus may act directly on vascular smooth muscle or indirectly by altering the concentration of vasoactive substances bathing the vascular smooth muscle. It may also act indirectly by altering vascular transmural pressure, perhaps by changing the mechanical activity of the surrounding parenchymal cells. Results of this and other studies indicate that the response to oxygen may involve more

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**Table 4. Effect of local hypercapnia and hypocapnia on coronary artery perfusion pressure and left ventricular contractile force at constant flow**

<table>
<thead>
<tr>
<th>Ventilatory Mixture</th>
<th>i</th>
<th>PmHg mm Hg</th>
<th>PCO₂ mm Hg</th>
<th>F_i % Control</th>
<th>PO₂ mm Hg</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air (f = 11)</td>
<td>T</td>
<td>106</td>
<td>112</td>
<td>100</td>
<td>89</td>
<td>7.65</td>
</tr>
<tr>
<td>20% CO₂ (f = 11)</td>
<td>T</td>
<td>0.7</td>
<td>105</td>
<td>125*</td>
<td>90</td>
<td>91</td>
</tr>
<tr>
<td>Air (f = 35)</td>
<td>T</td>
<td>3.0</td>
<td>101</td>
<td>55*</td>
<td>70*</td>
<td>107*</td>
</tr>
<tr>
<td>Air (f = 35)</td>
<td>S</td>
<td>7.0</td>
<td>102</td>
<td>101†</td>
<td>76</td>
<td>7.80†</td>
</tr>
<tr>
<td>5% CO₂ (f = 20)</td>
<td>T</td>
<td>1.0</td>
<td>84</td>
<td>84*</td>
<td>166*</td>
<td>109</td>
</tr>
<tr>
<td>Air (f = 20)</td>
<td>S</td>
<td>9.0</td>
<td>76†</td>
<td>105†</td>
<td>139*</td>
<td>108</td>
</tr>
</tbody>
</table>

Abbreviations as in Tables 1 and 3. * P < .01 relative to control value. † P < .01 relative to preceding value.
than one mechanism. Carrier et al. (3) found that the resistance to flow through isolated arterial segments decreases as a function of the oxygen tension of the perfusing blood. Detar and Bohr (4) found that the response of isolated strips of rabbit aorta to epinephrine decreases as a function of the oxygen tension of the bathing fluid. Both studies suggest a direct effect of lowered oxygen tension on vascular smooth muscle. On the other hand, Berne (2) found the breakdown products of adenosine in coronary sinus blood during cardiac hypoxia and suggested an indirect effect of hypoxia on vascular smooth muscle. Furthermore, the present study and others (6) show that hypoxia depresses myocardial contraction suggesting another indirect effect in the heart, i.e., passive coronary dilation due to a rise in vascular transmural pressure.

The absence of an immediate response of the kidney to hypoxemia perhaps deserves special comment. Although there are no similar studies in the literature, the results of this study seem clear. The kidney did not immediately exhibit a regular response to any grade of hypoxemia. In an attempt to explain this finding, perhaps through changes in blood viscosity or through indirect effects on caliber, several ancillary studies were performed. Platelet counts across the kidney did not provide evidence suggesting platelet aggregation. In addition renal venous blood was assayed at 5 and 15 min for a pressor substance in those animals presented in Table 2. The blood did not exhibit increased pressor activity at these times (23). Neither was the potassium concentration in venous blood greatly affected. It is, however, of interest to recall that the renal vascular bed responds to intra-arterial injection of adenosine and AMP with a rise in resistance rather than a fall in resistance as is seen in most other vascular beds (21). This rise in resistance does not seem to be related to platelet aggregation (unpublished observations) and, therefore, probably results from a reduction in blood vessel caliber. Perhaps hypoxemia causes an increase in adenosine and/or AMP levels in the plasma and interstitial fluid which antagonizes a direct vasodilating effect.

Carbon Dioxide

The studies show that a reduction in pH of the perfusing blood by raising the carbon dioxide tension produces a fall in the resistance to flow through limb and kidney. In the heart, the fall in resistance is preceded by a transient rise in resistance and is associated with a fall in left ventricular contractile force. Elevation of pH of the perfusing blood by lowering the carbon dioxide tension produces the reverse effects.

These findings indicate that local changes in carbon dioxide tension and pH are associated with immediate changes in vessel caliber. The direction of the changes are the same as those seen in some forms of local regulation. For example, activation of skeletal muscle produces a 0.03- to 0.07-unit fall in pH and a 4- to 5-mm Hg rise in PCO₂ of the venous blood (14, 19, 20) and a fall in resistance (14, 19, 20). Similarly, release of mechanical arterial occlusion in skeletal muscle produces a 0.03- to 0.10-unit fall in pH and a 7- to 10-mm Hg rise in PCO₂ of venous blood and a fall in resistance (14, 15, 20). Thus, it is possible that carbon dioxide and the hydrogen ion play a role in local regulation. However, the extent to which they participate is difficult to predict from the data at hand. Information useful to such an evaluation would be the effect of smaller changes in carbon dioxide tension and pH than those evoked in the present study. Additional information of value would be the carbon dioxide tension and pH in tissue fluid during local regulation. In this regard, renal autoregulation occurs in the absence of a change in renal venous blood pH (21). However, it is possible that there are changes in tissue fluid pH not reflected in the venous blood.

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**FIG. 5.** Typical responses of coronary artery perfusion pressure and left ventricular contractile force to a sudden decrease in pH of the perfusing blood.
These studies do not bear on the question of whether the active agent is carbon dioxide or the hydrogen ion. Regardless of the nature of the effective substance, it, like oxygen, may affect resistance through more than one mechanism. For example, the fall in coronary resistance on elevation of carbon dioxide tension observed in this study could have resulted from the net action of 1) a direct effect on coronary arterioles, 2) an indirect effect on coronary arterioles via a reduced metabolite concentration, and 3) an indirect effect via a rise in vascular transmural pressure. The latter two possibilities are inferred from the decrease in myocardial activity which has also been observed by others (1). An indirect metabolic effect might account for the absence of a large rise in resistance on withdrawal of carbon dioxide because, in this instance, the increment in activity of the heart was marked. However, despite the increased cardiac activity during carbon dioxide deprivation aortic pressure fell below the control value. The mechanism of this peculiar response is not apparent but very likely is related to the forces which influence left ventricular filling.

The transient changes in coronary resistance are of interest. Similar transients have been observed by Fleisch et al. (5) in the cat intestine and hindlimb and by Kontos et al. in the human forearm (personal communication). It is possible that these changes are related to addition of the carbon dioxide to blood rather than to tissue fluid as occurs naturally. The addition of carbon dioxide to arterial blood could affect the serum concentration of ionized calcium, the serum concentration of potassium, the blood oxygen tension, and the red cell size. These changes might transiently influence resistance in a direction opposite to that seen when the carbon dioxide tension is first altered in the tissue fluid rather than in the perfusing blood. Obviously, if this question is to be satisfactorily answered, further studies must be initiated.

Effect of Severe Hypoxemia on the Resistance Response to Changes in Flow

This study and the study of Rudko (20) show that measurable autoregulation can still be evoked in kidney and hindlimb in the virtual absence of perfusate oxygen. Although this response cannot be evoked in the heart, elevation of flow in the near absence of perfusate oxygen does improve myocardial activity.

These findings and those described (see Oxygen) and cited (19, 20, 21) above provide firm evidence that oxygen is not solely responsible for local regulation. Furthermore, these findings and those of Ross et al. (19) and Rudko (20) suggest that agents other than oxygen participate even in the local regulation seen under conditions where the oxygen tension is below the critical level of 30 mm Hg. It might be argued that the moderate autoregulation seen on elevation of flow resulted from the 4 mm Hg average rise in oxygen tension of the perfusate. However, in some experiments, autoregulation occurred in the face of no change in oxygen tension. Moreover, this argument would not be applicable to the regulation seen in the Ross et al. (19) and Rudko (20) studies.

The finding of improved myocardial activity during rapid perfusion with hypoxemic blood is of particular
interest. It is known that alterations in flow with oxygenated blood influence myocardial work capacity (1). This effect has been attributed to a change in both oxygen tension and metabolite concentration in myocardial tissue fluid. The present finding supports the hypothesis that metabolites do in fact participate be-

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