Afferent Neural Pathway in the Regulation of Cardiopulmonary Responses to Tissue Hypermetabolism

CHANG-SENG LIANG, M.D., PH.D., AND WILLIAM B. HOOD, JR., M.D.

SUMMARY We studied the role of neural transmission from hypermetabolic peripheral tissues in the regulation of cardiac output and pulmonary ventilation in chloralose-anesthetized dogs. Cross-circulation techniques with femoral-femoral or femoral-aortic anastomoses were used to produce a vascularly isolated, but normally innervated, hindlimb or lower half-body. 2,4-Dinitrophenol (DNP) was infused into the arterial side of the perfusion circuit to triple oxygen consumption and to increase lactate production by the cross-perfused area. After infusion of DNP, cardiac output and mean systemic arterial blood pressure increased, but neither heart rate nor pulmonary artery wedge pressure changed significantly. Pulmonary minute ventilation and arterial pH also increased, while arterial Pco2 fell. These changes were abolished when the nerve connections between the perfused limb and its parent body were severed. Normal saline, when administered in a similar manner, did not increase either ventilation or cardiac output, and simple denervation without previous infusions of DNP also had no effect. These results indicate that there are receptors sensitive to metabolic changes in the tissue, and that neural transmission is an important afferent link in regulating the cardiopulmonary responses to increased tissue metabolism.

BOTH CARDIAC output and pulmonary ventilation are increased during tissue hypermetabolism induced by 2,4-dinitrophenol (DNP). Levine and Huckabee showed that the respiratory stimulation which follows DNP infusion is not a result of direct action of DNP on the brain or carotid chemoreceptors, hence the primary stimulus for these responses probably occurs in the peripheral hypermetabolic tissue from which it is transmitted to the central nervous system, heart, and lungs via neural or humoral pathways.

Earlier, Ramsay infused DNP into the normally innervated hindlimb of a dog (recipient dog), which was separated vascularly from its own central circulation and perfused by a second dog. He found that ventilation of the recipient dog was stimulated after DNP infusion and that this response was abolished when the nerve connections between the limb and the body were severed. These findings suggest that a neural pathway is involved in the regulation of pulmonary ventilation during tissue hypermetabolism. These findings, however, were not confirmed by Bailen and Horvath, who also used a hindlimb preparation but administered a smaller dose of DNP than did Ramsay. This difference in doses might explain in part the discrepancies between their experimental results. In addition, the mass of tissue that could be rendered hypermetabolic in the hindlimb preparation is small, and the magnitude of stimulus generated in such areas by the small dose of DNP used in the experiments of Bailen and Horvath might not have been sufficient to produce a significant increase in pulmonary ventilation.

In our present experiments, we attempted to study the role of neural transmission in the regulation of pulmonary ventilation and cardiac output during tissue hypermetabolism. In addition to a cross-perfused hindlimb preparation similar to that of Bailen and Horvath, we also used a preparation in which the lower half-body was cross-perfused and which allowed us to produce a larger mass of hypermetabolic tissue after infusion of DNP. Two doses of DNP were infused into the cross-perfused areas; the total amount exceeded that used by either of the previous two groups of investigators. Our results show that cardiac output and pulmonary ventilation can indeed be increased by a neural reflex caused by DNP-induced hypermetabolic changes in the peripheral tissue.

Methods

Adult dogs weighing between 16.5 and 28 kg were anesthetized with intravenous chloralose (60 mg/kg) after induction with vaporized methoxyflurane (Penthane, Abbott Laboratories). The trachea was cannulated with a T-tube connected to a Benedict-Roth spirometer to record the rates of oxygen consumption and respiration and pulmonary minute ventilation. A femoral artery was cannulated with a Cournand catheter (No. 8 Fr.) and the main pulmonary artery with a Swan-Ganz catheter (No. 7 Fr.) (Edwards Laboratories, Inc., Santa Ana, Calif.) inserted through the right external jugular vein; both catheters were connected to Sanborn 267-AC pressure transducers and a Sanborn 7700 recorder to measure systemic arterial blood pressure, pulmonary artery wedge pressure, and heart rate. The "effective" pulmonary artery wedge pressure was calculated by subtracting from the measured pressure an
intrathoracic pressure which was recorded through a PE 190
catheter inserted percutaneously into the thoracic cavity
through the right 4th intercostal space. Another No. 8 Fr.
catheter was inserted into a carotid artery and connected to
a Gilford-Colson 103 densitometer to determine cardiac
output with indocyanine green (Cardio-Green). Mean sys-
temic arterial blood pressure was measured by electronic
integration and divided by cardiac output to obtain total
peripheral vascular resistance. Heparin (30 U/kg) was
administered intravenously to prevent clotting.

Cardiac output also was measured by the direct Fick
principle. Blood pH, pH, and PCO₂ were measured on a
Radiometer PHM 71 acid-base analyzer. Blood samples
were collected and analyzed for lactate and pyruvate.
Blood oxygen content was analyzed with a Beckman GC-2A
gas chromatograph. Blood oxygen capacity was determined
by a cyanmethemoglobin method.

In the cross-perfused hindlimb preparation, the hindlimb
of a recipient dog, completely separated from its parent
body except for the femoral and sciatic nerves, was perfused
by the circulation of a second dog (donor) through femoral-
femoral anastomoses. The femoral head was disarticulated
and the free ends of excised muscle bundles were cauterized.
Tygon tubing of a size selected to fit the caliber of the
individual vascular lumen was used. After the anastomoses
had been established, 4 g of 4-aminoantipyrine were
administered intravenously to prevent clotting.

To determine the extent of vascular leaks through the
arterial side of the perfusion circuit prior to DNP
infusion. Twenty minutes later, the plasma 4-aminoantipy-
rine concentration in the donor dog was 34.8 ± 3.3 mg/100
ml, whereas the concentration in the upper part of the
recipient dog was 1.2 ± 0.2 mg/100 ml (n = 6), only 3.4 ±
0.7% of that in the donor dog. Because DNP is a vasodila-
tor, greater vascular leaks might have been expected to
occur after DNP infusion. Therefore, the same amount of
4-aminoantipyrine was administered into the perfusion
circuit after DNP infusion. The plasma 4-aminoantipyrine
concentration in the upper half-body of the recipient dog 20
minutes after administration was 1.4 ± 0.5 mg/100 ml (n =
5), again demonstrating the lack of significant vascular

Results

VASCULAR SEPARATION IN CROSS-PERFUSION
PREPARATIONS

There were no vascular connections between the isolated
perfused area and its parent body in the perfused hindlimb
preparation, but such connections might exist via vertebral
circulation in the cross-perfused lower half-body prepara-
tion. To determine the extent of vascular leaks through the
vertebral circulation, 4 g of 4-aminoantipyrine were infused
into the arterial side of the perfusion circuit prior to DNP
infusion. Twenty minutes later, the plasma 4-aminoantipyrine
concentration in the donor dog was 34.8 ± 3.3 mg/100
ml, whereas the concentration in the upper part of the
recipient dog was 1.2 ± 0.2 mg/100 ml (n = 6), only 3.4 ±
0.7% of that in the donor dog. Because DNP is a vasodila-
tor, greater vascular leaks might have been expected to
occur after DNP infusion. Therefore, the same amount of
4-aminoantipyrine was administered into the perfusion
circuit after DNP infusion. The plasma 4-aminoantipyrine
concentration in the upper half-body of the recipient dog 20
minutes after administration was 1.4 ± 0.5 mg/100 ml (n =
5), again demonstrating the lack of significant vascular
leakage between the lower and upper half-bodies of the recipient dogs.

**EFFECTS OF DNP IN CROSS-PERFUSED AREAS**

Table 1 shows the effects of DNP on blood flow and tissue metabolism in the cross-perfused area. In both the cross-perfused hindlimb and lower half-body preparations, infusion of DNP produced increases not only in blood flow and oxygen consumption in the cross-perfused area, but also in anaerobic metabolism, as evidenced by increases in venous lactate concentration and lactate to pyruvate ratio. Lactate production also was increased in the cross-perfused area after DNP infusion. In contrast, none of these changes was seen after similar administration of normal saline (Table 1).

**HEMODYNAMIC AND VENTILATORY RESPONSES TO DNP INFUSION**

The circulatory and respiratory responses in the recipient dog to regional infusion of DNP are illustrated in Figure 1 and summarized in Table 2. For both hindlimb and lower half-body preparations, DNP infusion increased cardiac output and stroke volume. Pulmonary minute ventilation and respiratory rate also increased; as a result, arterial blood 
Pco2 fell and pH rose. In the case of the cross-perfused lower half-body preparation, but not the cross-perfused hindlimb preparation, systemic arterial blood pressure increased significantly after DNP infusion; total peripheral vascular resistance, however, decreased slightly in both preparations. Heart rate and pulmonary artery wedge pressure did not change in either preparation. Arterial blood lactate and pyruvate concentrations, and the lactate to pyruvate ratio in the recipient dog, also did not change significantly after DNP infusion.

**TABLE I**

Effects of Infusion of 2,4-Dinitrophenol (DNP) on Blood Flow and Tissue Metabolism in the Cross-perfused Area

<table>
<thead>
<tr>
<th>Blood flow (ml/min)</th>
<th>VO2 (ml/min)</th>
<th>Venous [L] (mmol/liter)</th>
<th>Venous L/P</th>
<th>Lactate production (umol/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C</strong></td>
<td><strong>NS 1</strong></td>
<td><strong>NS 2</strong></td>
<td><strong>DNP 1</strong></td>
<td><strong>DNP 2</strong></td>
</tr>
<tr>
<td>51 ± 10</td>
<td>44 ± 7</td>
<td>39 ± 5</td>
<td>85 ± 5*</td>
<td>83 ± 9*</td>
</tr>
<tr>
<td>2.7 ± 0.4</td>
<td>2.5 ± 0.3</td>
<td>2.3 ± 0.2</td>
<td>10.5 ± 1.2*</td>
<td>12.4 ± 1.6*</td>
</tr>
<tr>
<td>3.89 ± 0.87</td>
<td>4.91 ± 1.25</td>
<td>5.35 ± 1.41</td>
<td>7.50 ± 1.66*</td>
<td>14.59 ± 0.90*</td>
</tr>
<tr>
<td>13.81 ± 1.47</td>
<td>15.58 ± 2.27</td>
<td>15.61 ± 2.30</td>
<td>33 ± 7</td>
<td>33 ± 7</td>
</tr>
<tr>
<td>30 ± 8</td>
<td>36 ± 9</td>
<td>33 ± 7</td>
<td>18 ± 5</td>
<td>18 ± 5</td>
</tr>
<tr>
<td><strong>ANOVA</strong></td>
<td><strong>ANOVA</strong></td>
<td><strong>ANOVA</strong></td>
<td><strong>ANOVA</strong></td>
<td><strong>ANOVA</strong></td>
</tr>
<tr>
<td>1, II, III</td>
<td>1, II, III</td>
<td>1, II, III</td>
<td>1, II, III</td>
<td>1, II, III</td>
</tr>
</tbody>
</table>

**Figure 1** Data from a representative experiment showing the increases in cardiac output and pulmonary minute ventilation after tissue metabolism increased in the cross-perfused hindlimb by 2,4-dinitrophenol (DNP). Denervation of the hindlimb was followed by a return of cardiac output and pulmonary minute ventilation to control values, although the local hypermetabolism persisted.

Oxygen consumption increased in the upper half-body of the recipient dog after infusions of DNP into the perfusion circuit (Table 2). The oxygen difference between arterial blood and mixed venous blood, however, did not change significantly after DNP infusion in both cross-perfused hindlimb and lower half-body preparations. There was a significant correlation between cardiac output and oxygen consumption in the recipient dog for both preparations after DNP infusion (Fig. 2); however, the regression coefficient for the cross-perfusion experiments was much larger than

**Values** are mean ± se. The number of experiments (n) is given in parentheses after each subheading. Analysis of variance (ANOVA) was used to determine the statistical significance of differences attributable to the sources of variation, i.e., measures (I), groups (II), and the group x measure interaction (III), at \( P < 0.05 \). Dunnett's test** was used to determine the statistical significance of differences between control values and experimental values after each normal saline or DNP infusion. 

**\*P < 0.05.**
TABLE 2  Effects in Recipient Dogs of Infusion of 2,4-Dinitrophenol (DNP) into the Perfusion Circuit in Two Cross-perfusion Preparations

|                | \( \dot{V_O_2} \) (mI/min) | \( \dot{Q} \) (liters/min) | HR (beats/min) | SV (ml) | \( P_a \) (mm Hg) | \( P_e \) (mm Hg) | pH | \( P_{CO_2} \) (mm Hg) | \( V_e \) (liters/min) | RR (per min) | \( [L] \) (mmol/liter) | \( [P] \) (mmol/liter) | L/P |  
|----------------|----------------------------|-----------------------------|----------------|--------|----------------|----------------|----|----------------|----------------|--------------|----------------|----------------|--------|-----|
| **C**          | 114 ± 10*                  | 148 ± 15                    | 20 ± 3         | 130 ± 10 | 44 ± 8        | 5.3 ± 0.5      | 7.37 ± 0.01 | 40.7 ± 2.9 | 5.58 ± 0.15 | 22.0 ± 8.6  | 2.97 ± 0.78 | 0.29 ± 0.06 | 9.72 ± 0.72 |
| NS 1           | 120 ± 13                   | 141 ± 13                    | 18 ± 3         | 132 ± 10 | 54 ± 8        | 5.2 ± 0.6      | 7.37 ± 0.01 | 40.9 ± 3.6 | 5.66 ± 1.36 | 22.0 ± 8.6  | 2.88 ± 0.78 | 0.28 ± 0.06 | 9.67 ± 0.74 |
| NS 2           | 112 ± 22                   | 148 ± 11                    | 16 ± 3         | 131 ± 9  | 54 ± 8        | 5.0 ± 0.7      | 7.35 ± 0.01 | 41.6 ± 3.5 | 6.05 ± 1.28 | 21.1 ± 7.7  | 3.25 ± 1.02 | 0.28 ± 0.06 | 10.58 ± 1.12 |
| D              | 140 ± 26                   | 148 ± 15                    | 17 ± 2         | 137 ± 8  | 54 ± 11       | 5.0 ± 0.8      | 7.36 ± 0.01 | 39.1 ± 2.7 | 6.19 ± 1.57 | 20.2 ± 10.3 | 2.68 ± 0.66 | 0.25 ± 0.05 | 10.29 ± 0.70 |
| **DNP infusions** (n = 7; 24.7 ± 1.2 kg) |                       |                            |                |         |               |               |    |               |               |              |               |               |        |
| C              | 140 ± 14                   | 156 ± 13                    | 17 ± 3         | 148 ± 10 | 56 ± 12       | 7.7 ± 0.8      | 7.33 ± 0.02 | 40.7 ± 2.3 | 4.52 ± 0.42 | 12.7 ± 2.4  | 2.45 ± 0.36 | 0.25 ± 0.03 | 9.73 ± 0.39 |
| DNP 1          | 160 ± 17                   | 157 ± 14                    | 20 ± 3         | 153 ± 10 | 50 ± 10       | 7.8 ± 1.2      | 7.35 ± 0.02* | 38.4 ± 2.2 | 5.86 ± 0.60 | 15.5 ± 2.6  | 2.50 ± 0.42 | 0.25 ± 0.03 | 9.89 ± 0.45 |
| DNP 2          | 184 ± 24                   | 181 ± 14                    | 22 ± 4*        | 152 ± 8  | 46 ± 8*       | 7.5 ± 1.1      | 7.38 ± 0.02* | 34.3 ± 2.2* | 8.64 ± 1.57*| 22.9 ± 6.0* | 2.85 ± 0.54 | 0.26 ± 0.04 | 10.66 ± 0.71 |
| D              | 172 ± 39                   | 148 ± 16                    | 18 ± 3         | 140 ± 6  | 52 ± 9        | 6.8 ± 0.8      | 7.33 ± 0.01 | 38.6 ± 1.7 | 5.97 ± 0.76 | 14.0 ± 2.3  | 2.52 ± 0.65 | 0.23 ± 0.04 | 10.33 ± 1.08 |
| **ANOVA**      |                           |                            |                |         |               |               |    |               |               |              |               |               |        |

1. Hindlimb cross-perfusion preparation
2. Lower half-body cross-perfusion preparation (n = 6; 21.2 ± 1.3 kg)

1. Hindlimb cross-perfusion preparation
2. Lower half-body cross-perfusion preparation

**ANOVA**

- \( \dot{V}_O_2 \) = oxygen consumption; \( Q \) = cardiac output; HR = heart rate; SV = stroke volume; \( P_a \) = mean systemic arterial blood pressure; TPVR = total peripheral vascular resistance; \( P_e \) = mean pulmonary artery wedge pressure; \( pH \) = arterial blood pH; \( P_{CO_2} \) = arterial blood carbon dioxide tension; \( V_e \) = pulmonary minute ventilation; RR = respiratory rate; [L] = lactate concentration in arterial blood water; [P] = pyruvate concentration in arterial blood water; L/P = lactate-pyruvate ratio; C = control; NS 1, NS 2 = after the first and second infusions of normal saline (2 ml/kg); D = after denervation of the cross-perfused hindlimb; DNP 1, DNP 2 = after the first and second infusions of DNP (4 mg/kg); NS = after infusion of normal saline (2 ml/kg) (doses based on the weight of the donor dog).

Values are mean ± SE. The number of experiments (n) and body weights of the recipient dogs are given in parentheses after each subheading. Analysis of variance (ANOVA) was used to determine the statistical significance of differences attributable to the sources of variation, i.e., measures (I), groups (II), and the group x measure interaction (III), at \( P < 0.05 \). No roman numerals are given if there was no statistically significant difference. Dunnett's test* was used to determine the statistical significance of differences between control values and experimental values after each normal saline or DNP infusion.

* \( P < 0.05 \).
Consequently, the increase in blood pH and decrease in cardiac output, stroke volume, and systemic arterial blood pressure toward preinfusion control values. Figure 1 and Table 2 show that surgical denervation after the second DNP infusion promptly lowered pulmonary minute ventilation and respiratory rate toward preinfusion control values. Consequently, the increase in blood pH and decrease in Pco₂ which had been produced by DNP infusion were reversed. Denervation of the perfused hindlimb also reduced cardiac output, stroke volume, and systemic arterial blood pressure (Fig. 1, Table 2).

In contrast to DNP, normal saline, when similarly administered, produced no effect in the recipient dog (Table 2). Cutting the femoral and sciatic nerves without previous DNP infusions also did not produce any hemodynamic or respiratory changes in the recipient dog (Table 2).

### Discussion

Separation of the circulation between the cross-perfused hindlimb and its parent body was complete in our cross-perfused hindlimb preparation. It was also adequate in the cross-perfused lower half-body preparation; 20 minutes after the inert, highly diffusible indicator 4-aminoantipyrine had been infused into the cross-perfusion circuit, the plasma concentrations of 4-aminoantipyrine in recipient dogs were less than 5% of those in donor dogs. It was estimated that the maximal amount of DNP that could have leaked into the recipient's body was 0.4 mg/kg. This leakage of DNP is not likely to be responsible for the circulatory and respiratory changes in our experiments, because this dose of DNP was too small to produce any significant increase in cardiac output and because a dose of DNP of more than 2 mg/kg would have to be infused into intact dogs to produce increases in cardiac output and pulmonary ventilation of the magnitude reported for our present experiments. Furthermore, unlike the findings for intact dogs, in the cross-perfusion experiments the increase in cardiac output after DNP infusion was not accompanied by an increase in arteriovenous oxygen difference. In these cross-perfusion experiments the ratios of the increases in cardiac output and pulmonary ventilation to the increases in oxygen consumption were 4 to 5 times those found for intact dogs. Therefore, it seems likely that the increased cardiac output and pulmonary ventilation in the present experiments were not caused by tissue hypermetabolism in the recipient dog; this again confirms the absence of significant leakage of DNP into the recipient dog.

As expected, infusion of DNP increased oxygen consumption and blood flow in the cross-perfused area (Table 1). It also caused increases in tissue lactate production and lactate to pyruvate ratio, a finding which probably indicates relative tissue hypoxia. Table 2 shows that, in the cross-perfused lower half-body preparation, oxygen consumption increased slightly in the recipient dog after DNP infusion. This increase in the oxygen consumption in the recipient probably was caused by the cardiac and respiratory stimulation produced by local DNP infusion.

Control values for hemodynamic and metabolic parameters in the two groups of animals with cross-perfused hindlimbs were similar to those obtained for intact anesthetized dogs. However, in the cross-perfused lower half-body preparation, control values for cardiac output, stroke volume, oxygen consumption, and pulmonary ventilation were lower than those found for intact dogs; this probably was due to the fact that the recipient dogs, excluding cross-perfused areas, had smaller body masses. Both hindlimb and lower half-body preparations appeared stable during the experimental period because none of the variables measured changed significantly after infusion of normal saline (Table 2).

Our results show that cardiac output increased in the recipient dog after DNP was infused into the cross-perfused area which was connected to the body of the recipient dog only by nerves (Fig. 1, Table 2). This circulatory stimulation, which was correlated with the doses of DNP infused, was abolished when the cross-perfused area was denervated. Respiratory stimulation also occurred in the recipient dog after infusion of DNP into the perfusion circuit. Table 2 and Figure 1 show that pulmonary minute ventilation and respiratory rate increased in the recipient dog after infusion of DNP. Concomitantly, arterial Pco₂ fell and pH rose. These respiratory changes, like the circulatory changes, were reversed after the nerve connections to the cross-perfused hindlimb had been cut.

The neural mechanism for respiratory stimulation after local DNP infusion was first reported by Ramsay, who used a cross-circulated hindlimb technique similar to ours, except that the vascular connections between the hindlimb...
and body were interrupted by tourniquet rather than by surgery. His results, however, were not confirmed by Bainen and Horvath,4 who produced vascular isolation of the hindlimb from the body by surgical resection of muscle bundles and the femur. They suggested that the increase in pulmonary minute ventilation in Ramsay’s experiments was caused by the stimulatory action of DNP that reached the body of the recipient dog through the blood supply of the femur. However, the latter investigators infused a dose of DNP of only 3 mg/kg into the donor dog, whereas Ramsay infused 5 mg/kg; this difference in doses might be responsible, at least in part, for their discrepant results. Our present study provides evidence that supports this hypothesis and reconciles both reports. In our hindlimb preparation, the limb was completely separated from the body, the only connection being the intact femoral and sciatic nerves. DNP, 4 mg/kg, was infused twice into the perfusion circuit. The amount of our first dose of DNP was between those used by the previous two groups of investigators,5 6 whereas the total amount which had been given after the second infusion exceeded that in the prior reports. Figure 1 and Table 2 show that infusion of DNP produced an increase in pulmonary minute ventilation, which, however, was not statistically significant until the second dose had been administered. Although the increase in pulmonary minute ventilation after the first infusion in our experiments and in the experiments of Bainen and Horvath was not statistically significant, the same directional changes were observed. In addition, we studied a lower half-body preparation in which larger tissue masses were rendered hypermetabolic by infusion of DNP. In this preparation, both doses of DNP caused a significant increase in pulmonary minute ventilation (Table 2). Our results clearly confirm Ramsay’s earlier findings8 that DNP-induced metabolic changes can initiate a neurogenic reflex which is responsible for respiratory stimulation.

The neurogenic reflex originating from the hypermetabolic tissue undoubtedly plays an important role in the circulatory and respiratory responses to infusion of DNP. A similar neural reflex affecting respiration and circulation was demonstrated by Kao and Ray8 to arise from exercising limbs. It has been suggested that, during exercise, the stimulus for this reflex is chemical rather than mechanical in nature because the reflex responses are potentiated when circulation through the working muscle is blocked.13 19 Our experiments with DNP provide direct evidence that this neural reflex could, indeed, be brought about by the metabolic effects of exercise, independently of any increase in muscle movement. The “metabolic receptors” for this reflex are the free endings of small myelinated and unmyelinated fibers (groups III and IV).19 21

Electrical stimulation of these afferent fibers from skeletal muscle produced hemodynamic changes similar to those that occur during exercise.22-24 These fibers enter the spinal cord and probably travel in the lateral spinal column, because the neurogenic hyperventilation caused by exercise in Kao’s cross-circulation experiments may be abolished selectively by lateral chordotomy.28

In summary, we have shown that an afferent neural mechanism plays an important role in the regulation of cardiopulmonary responses to tissue hypermetabolism. Our experiments, however, do not preclude a humoral mechanism, as in the work of Kao and Ray,14 15 nor do they contradict the possibility of cortical influences on the circulatory and respiratory responses in awake subjects, as in other studies.16 17

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