The Effects of Sympathetic Nerves and Catecholamines on the Myocardial Reactive Hyperemia

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The effects of sympathetic nerves and catecholamines on the characteristics of the myocardial reactive hyperemia were studied in anesthetized open-chest dogs. The flow repayment, the ratio of the reactive hyperemic blood flow to the flow debt, averaged 166 per cent.

The calculated oxygen debt was also overpaid, the average repayment being of 118 per cent. The occlusion of the left coronary artery up to 40 sec. did not affect the flow repayment; a constant correlation was observed between flow debt and reactive hyperemic flow.

To study the sympathetic effect on the reactive hyperemia characteristics, acute cardiac sympathectomy, intracoronary infusion of propranolol and deprivation of catecholamines by reserpine were performed. These procedures did not affect the repayment of flow and oxygen debt.

From these experimental results the sympathetic nervous control was not observed in the response of the myocardial reactive hyperemia indicating that reactive hyperemia was primarily a metabolic response induced by anoxia. It was also suggested that catecholamines in the heart did not play any significant metabolic role in the regulation of the myocardial reactive hyperemia.

A n immediate increase in coronary blood flow after the release of occlusion of the coronary artery has been called myocardial reactive hyperemia. The underlying mechanism for this response is not clear, but there has been an increasing accumulation of evidences in support of the idea that the myocardial reactive hyperemia is primarily a metabolic response to metabolites produced by anoxia. On the other hand, the rich adrenergic supply and high catecholamine contents in the myocardium have been demonstrated. Acute myocardial ischemia causes a release of these cardiac catecholamines which increase the myocardial oxygen consumption and activate the anaerobic myocardial metabolism.

It is of interest to know the role of sympathetic nerves and catecholamines on the characteristics of the myocardial reactive hyperemia. This study was designed to investigate the effect of sympathetic nerves and catecholamines in the heart on the coronary blood flow and myocardial oxygen consumption during reactive hyperemia.

METHODS

The total of 36 experiments in 26 dogs were carried out. All of the experimental animals, weighing 10 to 17 kg, were anesthetized with intravenous injection of sodium thiopental (30 mg/kg). Under positive pressure respiration with a constant volume respirator, bilateral thoracotomy was performed. After administration of heparine (5 mg/kg), a modified Gregg type cannula with convoluted tip was inserted securely into the left coronary ostium via the right subclavian artery. The left coronary artery was perfused with dog's own blood from the left subclavian artery, and the left coronary inflow was measured by means

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of an electromagnetic flowmeter inserted in the perfusion circuit (Fig.1).

To produce the reactive hyperemia, coronary circuit was clamped. The clamp for occlusion of coronary blood flow was placed distal to the flowmeter. During clamping of the coronary circuit, the coronary venous outflow was decreased and almost disappeared. We usually clamped the coronary circuit for 20 seconds, because cessation of the perfusion for this period revealed little effect on the hemodynamics with marked reactive hyperemic response. Following each experiment, a ten to twenty-minute-period was elapsed prior to next experiment in order to insure a steady state.

Cardiac output was obtained by means of an electromagnetic flowmeter, the probe being seted at the portion of the descending aorta. Carotid arteries were perfused through the left femoral artery. Blood pressure was recorded in the coronary circuit. Polyethylene sampling catheters were introduced into the coronary sinus via the right atrium and into the femoral artery. Simultaneous blood samples were taken for determination of arteriovenous differences of oxygen content. Blood from the donor animal was used for blood replacement after each sampling. This procedure had no effect on the substrate concentration. Blood gas was analyzed by the method of Van Slyke and Neill. The hematocrit was measured by the glass capillary method and ranged from 38 to 56 per cent (avg. 42%). Arterial oxygen saturation averaged 92.6 per cent.

Five animals were sympathectomized by the removal of the bilateral stellite ganglia. In 6 animals adrenergic beta receptor was blocked with intracoronary infusion of propranolol (2-4 mg). To deplete catecholamines from the heart, reserpine was administered intramuscularly in a daily dose of 0.5 mg/kg body weight for two days prior to the experiment in 5 animals.18–20

The reactive hyperemic flow was considered to be the total flow following occlusion less the control flow that would have occurred during the reactive hyperemia. The flow debt was calculated by multiplying the duration of coronary artery occlusion by the control flow rate. Calculation of repayment of flow debt was made as described by Coffman and Gregg.

Repayment of flow debt = (reactive hyperemic flow/flow debt) x 100% Calculation of control oxygen consumption, oxygen debt, reactive hyperemic oxygen consumption and repayment of oxygen debt was made as follows:

1) control oxygen consumption = (control coronary flow) x (control A-V oxygen difference)
2) oxygen debt = (control oxygen consumption rate) x (duration of occlusion)
3) reactive hyperemic oxygen consumption = (total coronary flow during reactive hyperemia x A-V difference of integrated sample) - (control oxygen consumption rate x duration of reactive hyperemia)
4) repayment of oxygen debt = (reactive hyperemic oxygen consumption/oxygen debt) x 100%

RESULTS

I. Reactive Hyperemia Characteristics in the Control State.

A section of records taken from a typical experiment is illustrated in Figure 2. Coronary blood flow increased rapidly upon the release of left coronary artery occlusion. Peak reactive hyperemic flow rate was usually attained 8 to 12 sec. after the release. The increased coronary blood flow returned gradually to the control level within 2 or 3 minutes. Cessation of the coronary flow for 20 seconds did not alter the hemodynamics during the occlusion and following reactive hyperemic period. The heart rate ranged from 130 to 170 beats per minute and varied by no more than 15 beats per minute during reactive hyperemia. Blood pressure and

![Diagram of the coronary circuit](image-url)
TABLE I  FLOW AND OXYGEN DEBT REPAYMENT DURING MYOCARDIAL REACTIVE HYPEREMIA

| Animal No. | Control Flow Rate ml/min | Flow Debt ml | RH Flow ml | Flow Repay % | Control A-V O₂ ml/100 ml | Control O₂ ml/min | Oxygen Debt ml | RH O₂ ml | O₂ Repay % |
|------------|--------------------------|--------------|------------|--------------|--------------------------|-----------------|---------------|-------------|-----------|------------|
| 11         | 46.0                     | 15.3         | 34.9       | 227         | 17.7                     | 8.13            | 2.71          | 4.70       | 173       |
| 12         | 64.2                     | 21.4         | 32.8       | 154         | 11.5                     | 7.37            | 2.47          | 2.20       | 89        |
| 13         | 32.1                     | 10.7         | 18.6       | 174         | 10.0                     | 3.21            | 1.08          | 1.55       | 143       |
| 14         | 61.8                     | 20.6         | 22.7       | 109         | 15.9                     | 9.83            | 3.27          | 3.47       | 106       |
| 15         | 30.0                     | 10.0         | 15.9       | 159         | 10.4                     | 3.13            | 1.04          | 0.84       | 81        |
| 18         | 66.3                     | 22.1         | 26.5       | 121         | 14.8                     | 9.83            | 3.27          | 3.41       | 105       |
| 19         | 30.3                     | 10.1         | 18.8       | 188         | 14.7                     | 4.46            | 1.48          | 1.73       | 117       |
| 20         | 60.6                     | 20.2         | 32.8       | 163         | 10.2                     | 6.19            | 2.02          | 2.64       | 128       |
| 21         | 37.2                     | 12.4         | 17.2       | 139         | 8.2                      | 3.13            | 1.04          | 0.84       | 81        |
| 22         | 36.0                     | 13.0         | 14.7       | 113         | 8.2                      | 3.13            | 1.04          | 0.84       | 81        |
| 25         | 28.4                     | 9.5          | 18.2       | 191         | 8.2                      | 3.13            | 1.04          | 0.84       | 81        |
| 26         | 44.1                     | 14.7         | 38.2       | 260         | 14.7                     | 4.46            | 1.48          | 1.73       | 117       |
| ±14.1      | ±4.6                     | ±8.0         | ±44        | ±2.8        | ±2.6                      | ±0.85           | ±1.18        | ±28        |

TABLE II  REACTIVE HYPEREMIA CHARACTERISTICS FROM INCREASING LENGTH OF OCCLUSION

<table>
<thead>
<tr>
<th>Animal No.</th>
<th>Occlusion Time sec.</th>
<th>Control Flow Rate ml/min</th>
<th>Flow Debt ml</th>
<th>RH Flow ml</th>
<th>Flow Repay %</th>
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Cardiac output ranged from 86 to 118 mmHg and from 450 to 970 ml/min respectively, and these were maintained constantly in each animal during the experiments.

Table I gives the data from 12 left coronary artery occlusions for 20 seconds. The control flow rate before occlusion averaged 44.8 ± 14.1 (S.D.) ml/min, and flow debt averaged 15.0 ± 4.6 ml and reactive hyperemic flow averaged 24.3 ± 8.0 ml. The flow debt was overpaid with repayment of 166 ± 44%. Oxygen debt and reactive hyperemic oxygen consumption averaged 2.17 ± 0.85 and 2.56 ± 1.18 ml, respectively. Oxygen debt was also overpaid with repayment of 118 ± 28%. But the repayment of oxygen debt was less than that of flow debt, and in two instances oxygen debt.

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Fig. 2. Myocardial reactive hyperemia. Electrocardiogram (ECG), left ventricular pressure (LVP), dP/dt, blood pressure (BP), left coronary blood flow (CBF), and cardiac output (CO) changes produced by 20-sec. occlusion of left coronary artery. Blood pressure tracing is artificially affected with clamping of the coronary circuit due to measurement of blood pressure at the circuit.

Fig. 3. A consistent correlation between the flow repayment and the duration of coronary artery occlusion.

was not overpaid.

The reactive hyperemia responses following left coronary artery occlusion for 10, 20, 30 and 40 seconds were studied. Each experiment was accomplished at the same level of blood pressure and heart rate. The repayment of the flow debt against the duration of occlusion is shown in Table II. The longer occlusion period up to 40 seconds produced the larger reactive hyperemia, so that repayment of flow debt was almost constant in a series of experiments (Fig. 3).

2. Reactive Hyperemia Characteristics after Acute Sympathectomy.

In 5 dogs the effect of acute cardiac sympathectomy on reactive hyperemia was examined. Even under sympathectomized state the characteristic pattern was preserved. The coronary blood flow was increased immediately after the release of coronary artery occlusion, and returned to the control level in about two minutes. Table III gives the results. After sympathectomy, both the control flow and reactive hyperemic flow decreased significantly, but repayment of flow debt was not varied because of proportional decreases. On the other hand, there was no consistent tendency in repayment of oxygen debt.


In 6 dogs the reactive hyperemia responses to the control 20-second occlusion were compared before and after the intracoronary infusion of propranolol (2–4 mg). The results are given in Table III. In general, after infusion of propranolol, both the control flow and reactive hyperemic
Table III  Flow and Oxygen Debt Repayment during Reactive Hyperemia

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flow decreased, but repayment of flow debt was maintained. In the same dog oxygen consump-
tions in control and in reactive hyperemia were 
measured before and after infusion of propranolol. 
After infusion of propranolol reactive hyperemic
oxygen consumption decreased but repayment 
of oxygen debt did not change due to propor-
tional decrease in oxygen debt.

4. Rective Hyperemia Characteristics after Reser-
pine Pretreatment.

In 5 dogs the effect of depletion of catechol-
aminas in the heart on reactive hyperemia response 
was investigated. Reserpine (0.5 mg/kg) was given 
for two days prior to the experiment. Reactive 
hyperemia was not able to be examined in the 
control state before the reserpinization because 
of the operative procedures for the experiment. 
Therefore it is impossible that reactive hyperemia 
responses are compared before and after the 
reserpinization. The results are shown in Table III. 
The repayments of flow and oxygen debt were 
larger after reserpine treatment compared with 
the control state in other dogs, but the difference 
was not significant.

DISCUSSION

Markedly increased blood flow following oc-
closure of an artery has been observed at first in 
skeletal muscles. Recently the characteristics 
of reactive hyperemia of the heart were described 
1—4.6. The present results indicated that the re-
active hyperemic flow following repeated coro-
nary artery occlusion reproduced the uniform 
response and that repayment of flow debt was 
almost constant with an average of 166 per cent. 
The flow debt repayment was overpaid but less 
than those of 219 per cent reported by COFFMAN 
and GREGG. Their different results could be 
explained by the area of occlusion. The circumflex 
artery was clamped in their report but the left 
coronary artery in this report to produce reactive 
hyperemia. The reactive hyperemic flow was 
increased proportionally to the lengthening of 
occlusion time, and repayment of flow debt was 
not varied by changing occlusion time. There 
was a constant correlation between flow debt and 
reactive hyperemic flow following the occlusion 
up to 40 sec. The coronary artery occlusion longer 
than 40 sec. reduced blood pressure and ventri-
cular contractility and induced premature beats. 
Under these conditions the repayment of flow 
debt was inclined to decrease. The characteristics 
of reactive hyperemic oxygen consumption were 
similar to those of reactive hyperemic flow de-
scribed above. Oxygen debt was also overpaid 
with an average of 118 per cent.

It is well known that sympathetic nerves in-
ervate abundantly the heart muscle and large 
amounts of catecholamines are contained. Acute 
myocardial ischemia may release these cardiac 
catecholamines which increase myocardial oxygen 
consumption, activating the anaerobic myocardial 
metabolism. BERNE et al. observed that the 
increase in coronary blood flow with hypoxia 
was roughly proportional to the sum of adenosine, 
inosine and hypoxanthine released from the heart, 
and addition of epinephrine to oxygenated perfu-
sion medium yielded the results similar to those 
obtained with hypoxia. OLSON and GREGG 
found that the reactive hyperemic flow was increased after the acute 
administration of atropine and guanethidine by 
an amount that could be explained solely by the 
increase in control flow rate. COFFMAN and 
GREGG also found that intracoronary infusion 
of isoproterenol, levarterenol and epinephrine 
produced no change, an increase or a decrease in 
reactive hyperemic flow. Since their data indicated 
the variable change in control flow rate, the effect 
of these drugs was not understood quantitatively. 
The control flow rate is one of the most important 
factors to determine the volume of reactive 
hyperemic flow for a given duration of occlusion. 
The present study was intended to compare the 
characteristics of reactive hyperemia on the pre-
ABSE or absence of the sympathetic effect quanti-
tatively.

Acute cardiac sympathectomy did not affect 
the characteristics of reactive hyperemia. Even 
under these circumstances, flow and oxygen debts 
were overpaid, and repayments were not signifi-
cantly changed compared with the control state 
in the same dog. In infusion of propranolol, in 
spite of decreases in both the control and reactive 
hyperemic blood flow and oxygen consumption, 
there was little change in repayments of flow and 
oxygen debt. Depletion of myocardial catechol-
amines by reserpinization did not affect reactive 
hyperemic response of the heart significantly. 
These facts indicated that the endogenous 
catecholamines revealed little affect on the repay-
ment of flow and oxygen debt.

From these experimental results the sympathetic nervous mechanism played little role on the regulation of reactive hyperemia of the heart. Although the underlying mechanism of the reactive hyperemia was uncertain, it was supported the idea that reactive hyperemia was primarily a metabolic response to metabolites produced by anoxia and that the excess flow during reactive hyperemia was necessary for the delivery of oxygen and other substances to the previously anoxic heart muscle for repayment of those used during the occlusion. Further it was suggested that catecholamines did not play any significant metabolic role in regulation of the myocardial reactive hyperemia.

Acknowledgement

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REFERENCES