Limitation of the Coronary Vascular Response to Ischemia in the Awake Dog

By Robert J. Bache, Frederick R. Cobb, and Joseph C. Greenfield, Jr.

ABSTRACT
During reactive hyperemia following a brief coronary artery occlusion, excess arterial inflow exceeds the blood flow debt incurred during occlusion by 300-600%. The present study was performed to determine whether this marked reactive hyperemia is essential for restoration of coronary vascular tone. Coronary blood flow was measured in unanesthetized dogs with electromagnetic flowmeters and hydraulic occluders chronically implanted on their left circumflex coronary arteries. When 10-second coronary artery occlusions were performed in pairs separated by a brief interval during which excess arterial inflow equaled the blood flow debt incurred during the first occlusion, reactive hyperemia following the second occlusion was no greater than that following an isolated control occlusion. Thus, approximately 100% repayment of the blood flow debt resulted in restoration of normal reactivity to a second occlusion. To further ascertain whether coronary vascular tone could be regained without the usual excess inflow, the reactive hyperemia following a 10-second occlusion was mechanically limited by partial inflation of the occluder. When reactive hyperemia equal to 115 ± 10% repayment of the blood flow debt was allowed, final complete release of the occluder was followed by no additional hyperemia. These studies demonstrated that the markedly excess arterial inflow which occurs during coronary reactive hyperemia is not essential for restoration of coronary vascular tone.

KEY WORDS coronary artery occlusion electromagnetic flowmeter blood flow debt repayment myogenic hypothesis autoregulation reactive hyperemia myocardial blood flow coronary vasodilation

Temporary interruption of arterial inflow to many organs and tissues results in vasodilation with a subsequent reactive hyperemic response. Freeman (1) has proposed that during transient arterial occlusion a cumulative local metabolic disturbance occurs resulting in a blood flow debt and that quantitative repayment of this debt during the subsequent reactive hyperemia restores metabolic equilibrium and allows normal vascular tone to be regained. Although in some tissues the excess arterial inflow during reactive hyperemia does result in quantitative repayment of the blood flow debt (1, 2), excess arterial inflow in the heart is regularly markedly greater than the deficit, resulting in debt repayments of 300-600% (3–5). It is unclear whether this large volume of arterial inflow characteristic of reactive hyperemia in the coronary vascular system is in fact necessary for restoration of vascular tone or whether it represents vasodilation occurring in excess of the actual requirement for arterial blood. Consequently, the present study was designed to determine whether coronary vascular tone and coronary reactivity to a second arterial occlusion could be regained without the usual excess volume of reactive hyperemic flow. All studies were carried out in unanesthetized dogs to eliminate possible interference from general anesthesia or acute surgical trauma.

Methods
A total of 24 adult mongrel dogs weighing 21–32 kg were anesthetized with sodium thiopental (40–50 mg/kg, iv) and underwent left thoracotomy. The proximal 1.5 cm of the circumflex branch of the left coronary artery was dissected free, and a Statham ST-type electromagnetic flowmeter probe was positioned around the vessel proximal to any branches (6). Care was taken to attain mechanical stability of the flow probe on the coronary artery to ensure a consistently stable base line during subsequent coronary flow measurements. A hydraulic occluder made of polyvinyl chloride tubing (2.7 mm, o.d.) was placed around the circumflex coronary artery distal to the electromagnetic flow probe (7). A polyvinyl chloride, heparin-filled catheter (3 mm, o.d.) was introduced into the left internal mammary artery and ad-
advanced into the arch of the aorta. The flowmeter leads, the hydraulic occluder tube, and the aortic catheter were tunneled dorsally into a subcutaneous pouch at the base of the neck but were not exteriorized prior to the experiment to protect them from damage. On the morning of the study, the flowmeter leads, the hydraulic occluder tube, and the aortic catheter were exteriorized through a 1-cm skin incision using 2% lidocaine infiltration anesthesia.

Throughout the present report, coronary flow denotes measurements of blood flow through the circumflex branch of the left coronary artery. Coronary flow was measured using a Statham model M-4000 electromagnetic flowmeter. Flowmeter calibrations performed by passing measured flows of normal saline through the flowmeter probes remained within a standard deviation of no more than ±7% for all probes during the study. Aortic pressure was measured using a Statham P23Db pressure transducer. Lead II of a standard electrocardiogram was obtained. Data were recorded on an eight-channel magnetic tape recorder (Hewlett-Packard 8800) and an eight-channel direct-writing oscillograph (Hewlett-Packard 8800).

Studies were carried out 10–35 days after the initial surgery. All dogs were active and fully recovered from the effects of surgery: they were without fever, anemia, or other evidence of ill health. The dogs were trained to lie quietly on their right sides during the study; the laboratory was dimly illuminated and kept free from noise or other activity which might disturb the dog. After all recording instruments were connected, a 45–60-minute interval was allowed for the dog to adjust to the laboratory conditions. During this time, data were sampled continuously to ensure that a control steady state had been achieved. Coronary artery occlusions were performed by abruptly injecting and holding 1–2 ml of water in the occluder tube with a hand-held syringe. Examination of recordings of coronary blood flow made at a paper speed of 100 mm/sec demonstrated that with this technique total or subtotal coronary artery occlusion could be produced or released within less than 0.1 seconds. The reactive hyperemic response following a 10-second coronary artery occlusion was observed. Each response was observed in duplicate. A minimum of 3 minutes was allowed between each occlusion. The dogs were divided into three groups for subsequent studies.

GROUP 1

Group 1 consisted of ten dogs in which 10-second coronary artery occlusions were produced in pairs separated by a brief interval: during this interval the occluder was completely deflated to permit unimpeded arterial inflow between occlusions. This study was performed to determine the quantity of reactive hyperemic flow following an initial occlusion required to restore normal vasomotor reactivity to a second test occlusion. A 10-second coronary artery occlusion was produced and then completely released for intervals of 1, 2, 3, 4, 5, 7, 10, 20, 40, and 60 seconds; a second 10-second occlusion was then produced and the subsequent reactive hyperemia was observed. Each study was performed in duplicate, and a minimum of 3 minutes was allowed between pairs of occlusions. The response to a single 10-second control coronary artery occlusion was observed in duplicate at the beginning, the middle, and the end of each study, and the response to a single 20-second coronary artery occlusion was observed at the beginning and the end of each study.

GROUP 2

Since the reactive hyperemia following the second occlusion of a pair of 10-second occlusions was sometimes less than the control value for an isolated 10-second occlusion, an attempt was made to quantify the reduction in the reactive hyperemic response to the second occlusion. In five dogs control reactive hyperemic responses to coronary artery occlusions of 2, 3, 5, 7, and 10 seconds were observed in duplicate. A minimum of 3 minutes was allowed between the occlusions. Coronary artery occlusions were then performed in pairs; the first occlusion of each pair lasted 10 seconds. The occluder was then completely released to allow the initial portion of the reactive hyperemic response; 15 seconds later, an occlusion lasting 2, 3, 5, or 7 seconds was performed and the subsequent reactive hyperemic response was observed. Each response was observed in duplicate.

GROUP 3

To quantify the volume of reactive hyperemic flow necessary for restoration of coronary vascular tone, nine dogs in group 3 were subjected to 10-second total coronary artery occlusions; the occluder was subsequently completely released for 2, 3, 4, 5, or 6 seconds to allow the onset of a normal reactive hyperemic response. Next, the occluder was partially reinflated to restrict coronary flow to the preocclusion control level for a duration equal to that of the reactive hyperemia observed following a control 10-second coronary artery occlusion and then completely released.

Mean and phasic aortic blood pressure and mean coronary blood flow were measured directly from the recordings. The volume of flow occurring during the reactive hyperemia following a coronary artery occlusion was integrated using a Donner-Systrom model 3400 analog computer. The duration of the hyperemic period was taken as the time required for flow to fall to within 5% of the control measurement. Studies were discarded in which arterial blood pressure differed by more than 5% from the control value during the occlusion and to the end of the reactive hyperemic response. Calculations of blood flow debt incurred during coronary artery occlusion, reactive hyperemic flow, and blood flow debt repayment were made as described by Freeman (1).

Blood flow debt (ml) = control flow rate (ml/sec) × duration of occlusion (seconds).

Excess reactive hyperemic flow (ml) = [total flow during the reactive hyperemia (ml)] – [control flow rate (ml/sec) × duration of reactive hyperemia (seconds)].

Blood flow debt repayment (%) = (excess reactive hyperemic flow/blood flow debt) × 100.

Data were analyzed using Student’s t-test for paired data. All computations were carried out on an IBM model 1130 digital computer.

Results

GROUP 1

The mean heart rate for the ten dogs in group 1 was 64 ± 6 (SE) beats/min (range 48 to 100 beats/min) during the reactive hyperemia.
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Results from Group I

Table 1

<table>
<thead>
<tr>
<th>Control coronary blood flow (ml/min)</th>
<th>First occlusion</th>
<th>Release after first occlusion</th>
<th>Second occlusion</th>
<th>Reactive hyperemia after second occlusion</th>
<th>Total excess flow (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Duration (sec)</td>
<td>Flow debt (ml)</td>
<td>Duration (sec)</td>
<td>Excess flow (ml)</td>
<td>Duration (sec)</td>
</tr>
<tr>
<td>Control 10-second occlusion</td>
<td>32.0 ± 2.4</td>
<td>10.0 ± 0.1</td>
<td>5.4 ± 0.5</td>
<td>46 ± 4</td>
<td>23.4 ± 1.9</td>
</tr>
<tr>
<td></td>
<td>37.0 ± 3.4</td>
<td>9.9 ± 0.1</td>
<td>6.2 ± 0.6</td>
<td>52 ± 2</td>
<td>25.6 ± 3.2</td>
</tr>
<tr>
<td></td>
<td>33.5 ± 2.4</td>
<td>9.8 ± 0.1</td>
<td>5.5 ± 0.1</td>
<td>51 ± 3</td>
<td>27.2 ± 4.3</td>
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<tr>
<td></td>
<td>33.5 ± 2.2</td>
<td>10.0 ± 0.1</td>
<td>5.6 ± 0.4</td>
<td>51 ± 3</td>
<td>30.4 ± 4.3</td>
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<td>32.5 ± 2.5</td>
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<td>5.4 ± 0.4</td>
<td>51 ± 3</td>
<td>33.6 ± 4.4</td>
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<td>5.4 ± 0.4</td>
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<td>36.5 ± 4.5</td>
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<td>35.5 ± 3.3</td>
<td>9.8 ± 0.1</td>
<td>5.8 ± 0.6</td>
<td>51 ± 3</td>
<td>39.4 ± 4.6</td>
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<tr>
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<td>31.0 ± 3.0</td>
<td>9.8 ± 0.1</td>
<td>5.1 ± 0.5</td>
<td>51 ± 3</td>
<td>42.1 ± 4.7</td>
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<tr>
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<td>33.0 ± 2.2</td>
<td>9.9 ± 0.3</td>
<td>5.4 ± 0.4</td>
<td>51 ± 3</td>
<td>45.5 ± 4.9</td>
</tr>
<tr>
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<td>29.5 ± 2.7</td>
<td>9.9 ± 0.1</td>
<td>4.9 ± 0.4</td>
<td>51 ± 3</td>
<td>48.8 ± 5.2</td>
</tr>
<tr>
<td></td>
<td>32.5 ± 2.4</td>
<td>9.9 ± 0.1</td>
<td>5.4 ± 0.4</td>
<td>51 ± 3</td>
<td>51.9 ± 5.4</td>
</tr>
<tr>
<td>Control 20-second occlusion</td>
<td>32.0 ± 2.7</td>
<td>19.8 ± 0.1</td>
<td>10.6 ± 0.9</td>
<td>47 ± 5</td>
<td>46.5 ± 4.2</td>
</tr>
</tbody>
</table>

Values are means ± SE. Pairs of left circumflex coronary artery occlusions 10 seconds in duration, separated by complete release of occlusion with intervals ranging from 1 to 60 seconds are shown in Table 1 and Figure 2. With intervals of 1 and 2 seconds between occlusions, excess inflow during these intervals resulted in blood flow debt repayments of 35 ± 5% and 65 ± 10%, respectively. In both cases, the reactive hyperemia following the second 10-second coronary artery occlusion was significantly augmented above the control reactive hyperemic response so that excess arterial inflow following the second coronary artery occlusion resulted in blood flow debt repayments for the second occlusion of 625 ± 45% and 540 ± 75%, respectively (P < 0.01). Although intervals between occlusions of 3, 4, and 5 seconds resulted in mean blood flow debt repayments of only 90 ± 10%, 130 ± 20%, and 160 ± 25%, respectively, reactive hyperemia following the second occlusion was not augmented above that following an isolated 10-second coronary artery occlusion (Table 1). Thus arterial inflow yielding blood flow debt repayments of only 90-160% resulted in restoration of normal coronary reactivity to a subsequent 10-second coronary artery occlusion.

With intervals between occlusions of 7-40 seconds, blood flow debt repayments following the first occlusion ranged from 190 ± 30 to 360 ± 30%. The subsequent reactive hyperemia following the second occlusion was significantly briefer and resulted in significantly less blood flow debt repayment than those following isolated 10-second coronary artery occlusions (P < 0.01) (Table 1, Fig. 2).
When a 60-second interval was allowed between occlusions, the reactive hyperemias following both the first and the second 10-second occlusion were not significantly different from the control reactive hyperemic response.

**GROUP 2**

The mean heart rate for the five dogs in group 2 was 74 ± 6 beats/min; mean arterial blood pressure was 98 ± 6 mm Hg. Mean resting coronary blood flow was 28.5 ± 1.8 ml/min. A 10-second control coronary artery occlusion resulted in a reactive hyperemia lasting 52 ± 4 seconds with excess arterial inflow resulting in 485 ± 90% repayment of the blood flow debt. Table 2 and Figure 3 demonstrate that coronary artery occlusions lasting 2, 3, or 5 seconds performed 15 seconds after the release of a 10-second coronary artery occlusion did not result in significant augmentation of the reactive hyperemic response above that following an isolated single 10-second occlusion. Thus, these 2-5-second occlusions did not result in a reactive hyperemic response of their own and did not significantly alter the reactive hyperemic response following the preceding 10-second coronary artery occlusion.

When the second coronary artery occlusion lasted 7 or 10 seconds, the combined excess arterial inflow during the reactive hyperemic responses after the first and second coronary occlusions was significantly greater than that following a single isolated 10-second occlusion ($P < 0.01$) (Table 2). However, augmentation of the reactive hyperemia by a 7- or 10-second occlusion 15 seconds after the initial 10-second occlusion was significantly less than the reactive hyperemia that followed an isolated 7- or 10-second coronary artery occlusion. Thus, a 7-second coronary artery occlusion resulted in a blood flow debt of 3.48 ± 0.29 ml, but augmentation of the reactive hyperemia was only 5.2 ± 1.4 ml. This augmentation accounted for only 150 ± 35% repayment of the blood flow debt.
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Blood flow debt repayments observed when pairs of 10-second coronary artery occlusions were applied with various intervals of unimpeded arterial inflow between the first and second occlusions. The solid line indicates the percent repayment of the blood flow debt incurred by the first occlusion; this repayment occurred during the interval between occlusions. The broken line indicates the percent repayment of the blood flow debt incurred by the second arterial occlusion; this repayment occurred during the reactive hyperemia following the second occlusion. The stippled area indicates the blood flow debt repayment ± 1 SE observed during the control reactive hyperemia which followed a single isolated 10-second coronary artery occlusion. Brackets indicate ± 1 SE.

incurred during the 7-second occlusion compared with a 460 ± 55% debt repayment resulting from a control 7-second occlusion (P < 0.01). Similarly, a second 10-second occlusion 15 seconds after the initial occlusion resulted in a blood flow debt of 4.82 ± 0.33 ml, although augmentation of the reactive hyperemia by this second 10-second occlusion was only 7.9 ± 3.2 ml. This additional arterial inflow during the reactive hyperemia resulted in only 165 ± 80% repayment of the blood flow debt incurred by the second 10-second occlusion, which was significantly less than the 485 ± 90% debt repayment following an isolated 10-second coronary artery occlusion (P < 0.01).

GROUP 3

The mean heart rate for the nine dogs in group 3 was 60 ± 5 beats/min; mean arterial blood pressure was 105 ± 6 mm Hg. Resting control coronary blood flow was 32.5 ± 2.5 ml/min. A control 10-second coronary artery occlusion resulted in a reactive hyperemic response lasting 48 ± 4 seconds during which excess arterial inflow resulted in 425 ± 357 repayment of the blood flow debt. Figure 4 and Table 3 demonstrate results obtained following 10-second coronary artery occlusions when the occluder was briefly completely released and then partially reinflated to return arterial inflow to the control rate for an interval equal to the duration of reactive hyperemia following the control 10-second occlusion. When the occluder was totally released for intervals of 1.4 seconds to 5.0 seconds, the excess arterial inflow during this initial release ranged from 1.72 ± 0.17 to 5.82 ± 0.45 ml. When the subsequent partial occlusion which restricted arterial inflow to the control level was finally released, significant additional hyperemia occurred, resulting in additional excess inflow of 6.69 ± 2.75 to 1.83 ± 0.92 ml, respectively. The sum of the initial and the terminal hyperemia resulted in blood flow debt repayments ranging from 115 ± 16% to 145 ± 52%. These debt repayments were markedly less than that following a control 10-second coronary artery occlusion (P < 0.01). When the occluder was completely released for an average of 6.1 seconds, excess arterial inflow during this interval resulted in 115 ± 107% repayment of the blood flow debt, and no significant further hyper-
## Results from Group 2

<table>
<thead>
<tr>
<th>Control coronary blood flow (ml/min)</th>
<th>Duration of first occlusion</th>
<th>Flow debit (ml)</th>
<th>Duration of first release (sec)</th>
<th>Flow debit (ml)</th>
<th>Duration of second release (sec)</th>
<th>Excess flow (first plus second release) (ml)</th>
<th>Difference in excess flow from control occlusion (ml)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>28.5 ± 1.8</td>
<td>10.0 ± 0.1</td>
<td>4.78 ± 0.31</td>
<td>52 ± 4</td>
<td>23.3 ± 5.2</td>
<td>5.2 ± 1.9</td>
<td>32 ± 6</td>
<td>-17 ± 1.9</td>
<td>NS</td>
</tr>
<tr>
<td>28.0 ± 1.9</td>
<td>10.0 ± 0.1</td>
<td>4.66 ± 0.32</td>
<td>47 ± 6</td>
<td>21.3 ± 5.4</td>
<td>3.3 ± 2.3</td>
<td>37 ± 6</td>
<td>-10.0 ± 1.3</td>
<td>NS</td>
</tr>
<tr>
<td>28.0 ± 2.1</td>
<td>9.8 ± 0.1</td>
<td>4.56 ± 0.36</td>
<td>52 ± 5</td>
<td>20.0 ± 3.6</td>
<td>5.2 ± 1.4</td>
<td>37 ± 6</td>
<td>-3.3 ± 2.3</td>
<td>NS</td>
</tr>
<tr>
<td>29.0 ± 2.3</td>
<td>9.9 ± 0.1</td>
<td>4.79 ± 0.37</td>
<td>54 ± 7</td>
<td>22.3 ± 6.1</td>
<td>5.2 ± 1.4</td>
<td>39 ± 8</td>
<td>-10.0 ± 1.3</td>
<td>NS</td>
</tr>
<tr>
<td>30.0 ± 1.9</td>
<td>10.0 ± 0.1</td>
<td>4.97 ± 0.33</td>
<td>55 ± 8</td>
<td>28.5 ± 2.2</td>
<td>5.2 ± 1.4</td>
<td>40 ± 8</td>
<td>5.2 ± 1.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>29.5 ± 2.3</td>
<td>10.0 ± 0.1</td>
<td>4.92 ± 0.38</td>
<td>55 ± 6</td>
<td>31.2 ± 8.0</td>
<td>7.9 ± 3.2</td>
<td>41 ± 5</td>
<td>&lt;0.01</td>
<td>---</td>
</tr>
</tbody>
</table>

Values are means ± SE; NS = not significant. Reactive hyperemia observed in the five dogs in group 2 when a left circumflex coronary artery occlusion 10 seconds in duration was followed by 15-second complete release of occlusion and then a reocclusion for 2, 3, 5, 7, or 10 seconds with subsequent complete release is illustrated. Total excess reactive hyperemic flow was computed as the volume of flow in excess of the control flow rate which occurred during the initial release added to the volume of excess flow during the reactive hyperemia following the second occlusion.

Emia occurred when the partial occlusion was finally completely released. Intervals of initial complete release of the occlusion longer than 6 seconds resulted in greater initial blood flow debt repayments and completely eliminated additional excess hyperemic flow following final release of the partial occlusion. However, if the partial occlusion was released prior to the time a control reactive hyperemia would have ended, a period of additional hyperemia occurred which corresponded to the interval between premature complete release of the occluder and the end of a control reactive hyperemia.

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**FIGURE 3**

Left circumflex coronary artery blood flow recorded in an awake dog. A: Reactive hyperemia following a control 10-second coronary artery occlusion resulted in 485% repayment of the blood flow debt incurred during occlusion. B: Coronary blood flow response to a 10-second occlusion followed by a 15-second release of the occluder and then a 5-second occlusion. The combined excess arterial inflow during reactive hyperemia following the 10-second and the 5-second occlusion resulted in 455% repayment of the blood flow debt incurred during the 10-second occlusion.

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S. A. 10 sec. Occlusion. Debt repayment = 355%

B. 10 sec. Occlusion followed by 2.0 sec. complete release.
Debt repayment = 40% + 95% = 135%

Left circumflex coronary artery blood flow recorded in an awake dog. A: Reactive hyperemia following a control 10-second coronary artery occlusion resulted in 355% repayment of the blood flow debt incurred during occlusion. B: Following a 10-second coronary artery occlusion, the hydraulic occluder was totally released for 2.0 seconds. During this interval, inflow of arterial blood resulted in 40% repayment of the blood flow debt incurred during coronary artery occlusion. Subsequently, the occluder was partially reinflated to limit the mean rate of arterial inflow to the preocclusion control level for an interval equal to the duration of the control reactive hyperemic response. Subsequent total release of the occluder resulted in a modest additional hyperemia producing an additional 95% repayment of the blood flow debt. Total repayment of the blood flow debt was thus 135%.

Discussion

Some previous data have suggested that arterial inflow during coronary reactive hyperemia does in

TABLE 3

Results from Group 3

<table>
<thead>
<tr>
<th>Control</th>
<th>Duration of</th>
<th>Blood flow</th>
<th>Duration of</th>
<th>Excess inflow</th>
<th>Excess inflow</th>
<th>Total excess</th>
<th>Total combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>coronary</td>
<td>occlusion</td>
<td>debt</td>
<td>initial total</td>
<td>during initial release</td>
<td>during final release</td>
<td>inflow during</td>
<td>blood flow debt</td>
</tr>
<tr>
<td>blood flow</td>
<td>(sec)</td>
<td>(ml)</td>
<td>release</td>
<td>release</td>
<td>release</td>
<td>initial and</td>
<td>repayment during initial and final releases</td>
</tr>
<tr>
<td>(ml/min)</td>
<td></td>
<td></td>
<td>(sec)</td>
<td>(ml)</td>
<td>(ml)</td>
<td>final releases</td>
<td>(ml) (%)</td>
</tr>
<tr>
<td>Control</td>
<td>32.5 ± 2.5</td>
<td>5.14 ± 0.40</td>
<td>1.72 ± 0.00</td>
<td>21.72 ± 2.00</td>
<td>21.72 ± 2.00</td>
<td>425 ± 35</td>
<td></td>
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<td>1</td>
<td>36.5 ± 3.6</td>
<td>5.78 ± 0.62</td>
<td>1.4 ± 0.1</td>
<td>1.72 ± 0.17</td>
<td>6.69 ± 2.75</td>
<td>8.41 ± 2.83</td>
<td>145 ± 52</td>
</tr>
<tr>
<td>2</td>
<td>36.5 ± 3.0</td>
<td>5.80 ± 0.53</td>
<td>2.3 ± 0.1</td>
<td>2.57 ± 0.27</td>
<td>4.15 ± 0.93</td>
<td>6.72 ± 1.15</td>
<td>115 ± 16</td>
</tr>
<tr>
<td>3</td>
<td>34.0 ± 3.3</td>
<td>5.48 ± 0.62</td>
<td>3.1 ± 0.1</td>
<td>3.84 ± 0.38</td>
<td>3.08 ± 0.87</td>
<td>6.92 ± 1.18</td>
<td>120 ± 15</td>
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<td>4</td>
<td>32.0 ± 3.4</td>
<td>5.15 ± 0.65</td>
<td>3.9 ± 0.1</td>
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<td>1.93 ± 0.67</td>
<td>6.39 ± 0.94</td>
<td>125 ± 13</td>
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<td>5</td>
<td>32.5 ± 4.1</td>
<td>5.26 ± 0.65</td>
<td>5.0 ± 0.1</td>
<td>5.82 ± 0.45</td>
<td>1.83 ± 0.92</td>
<td>7.65 ± 1.32</td>
<td>145 ± 13</td>
</tr>
<tr>
<td>6</td>
<td>38.5 ± 4.7</td>
<td>6.35 ± 0.78</td>
<td>6.1 ± 0.1</td>
<td>7.29 ± 0.79</td>
<td>0.55 ± 0.37</td>
<td>7.84 ± 0.74</td>
<td>125 ± 10</td>
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Values are means ± se. Blood flow debt repayment was observed in nine dogs in group 3 when 10-second left circumflex coronary artery occlusion was followed by a brief total release of the occlusion and a subsequent partial reocclusion to limit arterial inflow to the control level for an interval equal to the reactive hyperemia following a control 10-second occlusion. The total excess inflow of arterial blood was computed as the sum of the excess inflow which occurred during the initial brief complete release of the occluder and any excess inflow subsequent to complete release of the occluder after the period of restriction in inflow to the control level.

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fact exceed the myocardial requirement for blood. Using a polarographic technique to estimate myocardial tissue oxygen, Sayen and his associates (8) observed that, during reactive hyperemia following coronary artery occlusions lasting 15-40 seconds, myocardial oxygen tension exceeded the preocclusion control level for intervals of 30 seconds to several minutes following release of the occlusion. Coffman and Gregg (9) in open-chest dogs and Olsson and Gregg (10) in unanesthetized dogs studied coronary sinus oxygen content following release of a brief coronary artery occlusion. Following an initial brief interval of marked oxygen desaturation, coronary sinus oxygen rapidly rose to values considerably above the control level and only gradually returned to the control level as the hyperemia subsided. Myocardial oxygen uptake did not appear to be impaired during the reactive hyperemic response, since uptake during the initial part of the reactive hyperemia was sufficient to result in prompt repayment of the oxygen debt incurred during the preceding occlusion. Since the oxygen debt was rapidly repaid during the early part of the reactive hyperemic response, it was not clear why coronary blood flow remained elevated during the subsequent portion of the reactive hyperemia.

In a recent study, Eikens and Wilcken (12) observed that in awake greyhounds the reactive hyperemic response in the left circumflex coronary artery bed was reduced for 1-2 minutes after an 8-second coronary artery occlusion. These authors suggested that this reduction resulted from a nonspecific depression of coronary reactivity during the immediate posthyperemic period. The present study extended this finding by showing that, when two 10-second coronary artery occlusions were performed sequentially with a 7-40-second interval between them, the reactive hyperemia following the second occlusion was smaller than that following a control 10-second occlusion, even though reactive hyperemia following the first occlusion was incomplete at the time the second occlusion was applied. In the present study, however, the reactive hyperemic response returned to the control level within 1 minute after the preceding occlusion, but in the study of Eikens and Wilcken (12) the reactive hyperemic response was depressed for 1-2 minutes. This difference in duration of depressed reactivity following a coronary occlusion may have resulted from an intrinsic difference in reactivity of the coronary vasculature of the greyhounds used in that study compared with the mongrel dogs used in the present study. In support of this possibility, the mean blood flow debt repayment during control reactive hyperemia in the dogs studied by Eikens and Wilcken (320 ± 27%) was significantly less than that in the present study (435 ± 30%, P < 0.01), suggesting an innate difference in reactivity of the coronary vasculature between these two groups of dogs.

The reduction in the reactive hyperemic response following a second occlusion was further investigated in the present study by varying the duration of the second occlusion. When occlusions lasting 2, 3, or 5 seconds were applied during the reactive hyperemia of a preceding 10-second occlusion, no augmentation of the reactive hyperemia following the initial 10-second occlusion occurred. However, when the second occlusion lasted 7 or 10 seconds, the reactive hyperemic response was augmented approximately in proportion to the amount by which the second occlusion exceeded a 5-second occlusion. Thus, reduction in the reactive hyperemic response did not occur as a uniform proportionate depression of coronary vascular reactivity which would have caused the reactive hyperemia following the second occlusion to be reduced by a constant fraction; instead, the conditions produced by the reactive hyperemia following the first occlusion allowed a subsequent occlusion up to 5 seconds in duration to be completely absorbed by the reactive hyperemia in progress. Only when the second occlusion exceeded 5 seconds did a demonstrable additional vasodilation occur. It is possible that the increased myocardial oxygen tension (PO₂) which occurred during the reactive hyperemia following the first occlusion may have resulted in a sufficient increase in myocardial myoglobin saturation to absorb an occlusion up to 5 seconds in duration without resulting in additional coronary vasodilation. This possibility agrees with the computation of Olsson (13) that the myocardial content of myoglobin, if fully saturated with oxygen, is sufficient to sustain aerobic myocardial metabolism in the absence of arterial inflow for approximately 6 seconds. Although precise measurement of myocardial PO₂ presents technical difficulties, it appears likely that the markedly elevated tissue and coronary venous blood PO₂ levels observed during reactive hyperemia would ensure a myocardial myoglobin saturation approaching 100% (8, 10, 14).

In the present study, when a brief interval of reactive hyperemia resulting in approximately 100% repayment of the blood flow debt incurred during the previous occlusion was followed by restriction of arterial inflow to the preocclusion...
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...complete release of the occluder after an interval corresponding to the duration of a control reactive hyperemia revealed complete restoration of normal coronary vascular tone. If, however, the occluder was completely released prior to the time at which a control reactive hyperemic response would have ended, a period of additional hyperemia resulted corresponding to the interval between the premature complete release of the occluder and the end of a control reactive hyperemic response. Thus, although the usual large volume of excess arterial inflow during coronary reactive hyperemia was not essential to deliver oxygen or other arterial substrates (15, 16), restoration of vascular tone did require a specific amount of time that corresponded to the duration of the control reactive hyperemic response. These data may be interpreted to indicate that the reactive hyperemic response consists of separate flow and time components. The flow component may be satisfied by a volume of inflow approximately equal to the blood flow debt incurred during occlusion. In contrast to this situation, the time component, which represents the interval necessary for restoration of vascular tone, was not altered by any maneuver in the present study. It is possible that this interval corresponds to the time required for movement of a slowly diffusible vasodilator metabolite into the vascular space to be washed out of the ischemic tissue or for a local metabolic process to inactivate a vasodilator substance accumulated during ischemia (17, 18). Alternatively, the time course of restoration of coronary vascular tone after ischemic vasodilation may represent a fundamental myogenic characteristic of coronary vascular smooth muscle (19). Unfortunately, the data obtained in the present study do not allow a clear choice between these alternatives.

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