Reactive Hyperemia in the Dog Heart

EFFECTS OF TEMPORARILY RESTRICTING ARTERIAL INFLOW AND OF CORONARY OCCLUSIONS LASTING ONE AND TWO CARDIAC CYCLES

By Eduards Eikens and David E. L. Wilcken

ABSTRACT

With electromagnetic flow transducers and pneumatic cuff occluders on the circumflex branch of the left coronary artery in conscious and in anesthetized dogs, we examined the effects of both a temporary reduction in postocclusion hyperemia and one- and two-cardiac cycle occlusions of the artery on the size and the duration of the hyperemic response. After release of 8-second occlusions, flow was prevented from rising to more than 10–20% above the preocclusion value for the expected duration of the hyperemia. Peripheral coronary arterial pressure measurements established that this maneuver produced a pressure gradient. Temporary restriction of arterial inflow markedly reduced the percent repayment of the flow deficit from 618 ± 34% to 213 ± 17% (mean ± SE) and moderately prolonged the duration of the response from 95 ± 4 seconds to 129 ± 5 seconds (P < 0.0005 for both). In conscious dogs, the mean percent repayment after a one-cycle (0.7-second) occlusion was 227%. Much larger and longer-lasting responses were obtained with one-cycle (0.4-second) occlusions in anesthetized dogs in which heart rate and blood pressure were considerably higher. Since restricting arterial inflow resulted in a large reduction in reactive hyperemia with only a small increase in its duration, local mechanisms acting in the interstitial space and possibly in the vascular smooth muscle may be relatively more important for the hyperemia that occurs after short occlusions than is the myocardial release of freely diffusible metabolites that are removed by the blood stream. The results with one- and two-cycle occlusions suggest that myogenic responses contribute to the hyperemia, since it is unlikely that such brief occlusions produce myocardial hypoxia under resting conditions.

KEY WORDS regulation of coronary blood flow myogenic responses coronary vasodilator metabolites

Reactive hyperemia in the heart is thought to result from either hypoxia-induced release of vasodilator metabolites from the myocardium (1) or the effects, direct or indirect, of reduced oxygen tension (Po2) on the vascular smooth muscle of the coronary resistance vessels (2, 3). In the heart, there is a close positive relationship between the period of circulatory arrest and the size of the subsequent hyperemic response (4). Moreover, a feature of the reactive hyperemia is a great overpayment of the flow deficit. It has been suggested that this overpayment is necessary to correct the metabolic abnormality induced during the ischemia (5). In the present experiments, we reduced postocclusion hyperemia by temporarily restricting arterial inflow after the occlusion had been released; we then measured the effect of this maneuver on the magnitude and the duration of the hyperemic response.

The results of our experiments suggested that myogenic responses partially accounted for the postocclusion hyperemia. Since earlier studies have also indicated that intrinsic mechanisms in vascular smooth muscle are important for the response (6), we extended the investigation in an attempt to show that mechanisms unrelated to the effects of myocardial hypoxia contribute to the hyperemia. We measured the changes produced by coronary artery occlusions lasting only one or two cardiac cycles in conscious and anesthetized dogs, reasoning that such brief interruptions of the circulation probably do not reduce the Po2 of heart muscle cells.

Methods

EXPERIMENTAL MODEL

The healthy conscious dog and open-chest dog preparations used in this study have been fully described in previous publications (6–8) and will be discussed only briefly. Electromagnetic flow probes of appropriate size

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and then rapidly deflating it after 8 seconds. Changes in blood flow could only rise 10-20% above the preocclusion value. We chose this level because it was important not to maintain flow below preocclusion level which produced zero flow. The occlusion was continued only for the duration of the hyperemia and blood pressure showed no significant change (±10%) for at least 1 minute before the occlusion and during the period of reactive hyperemia. In some experiments, there was a brief reduction in blood pressure during the occlusion (Fig. 1). Such experiments were only accepted for analysis if the reduction during all three occlusions (one with restricted arterial inflow, and one before and one after with unrestricted arterial inflow) did not vary by more than ±10%. Experiments were rejected if the duration of occlusion varied more than ±1.2 seconds. Nineteen successful experiments were performed in these five dogs.

To assess changes in peripheral coronary arterial pressure during responses, we measured this parameter in a steady state, and a 10-minute recovery period was allowed between experiments. The occlusions caused no apparent distress in the conscious dogs; they frequently fell asleep during the studies.

In the analysis of the responses, we measured the total stroke coronary flow and the systolic and diastolic stroke coronary flows for beats before and after the occlusions, using methods similar to those described by Olsson and Gregg (4). Total stroke coronary flow was obtained by planimetry of the area described by the phasic coronary blood flow tracing during the cardiac cycle. Diastolic stroke coronary flow was calculated as the area under the flow curve from the end of the T wave of the electrocardiogram to the peak of the R wave of the subsequent cycle. Systolic stroke coronary flow was the difference between flow debt, reactive hyperemic flow, and repayment of flow debt were calculated as described by Coffman and Gregg (5) according to the following formulas.

Flow debt

= (control flow rate) x (duration of occlusion). (1)

Reactive hyperemic flow

= (integral of flow curve during reactive hyperemia) - flow debt. (2)

Percent repayment of flow debt

= (reactive hyperemic flow/flow debt) x 100. (3)

Records were accepted for analysis only if heart rate and blood pressure showed no significant change (±10%) for at least 1 minute before the occlusion and during the period of reactive hyperemia. In some experiments, there was a brief reduction in blood pressure during the occlusion (Fig. 1). Such experiments were only accepted for analysis if the reduction during all three occlusions (one with restricted arterial inflow, and one before and one after with unrestricted arterial inflow) did not vary by more than ±10%. Experiments were rejected if the duration of occlusion varied more than ±1.2 seconds. Nineteen successful experiments were performed in these five dogs.

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total stroke coronary flow and diastolic stroke coronary
flow.

In all conscious dogs, there was considerable variation
in stroke coronary flow because of sinus arrhythmia (Fig.
2). Nevertheless, mean pre- and postocclusion heart
rates were the same (±10%) in all experiments accepted
for analysis. To obtain a representative value for the flow
deficit resulting from one-cycle occlusions, we measured
the systolic and diastolic flows during the five beats
before each coronary artery occlusion and calculated the
mean systolic and diastolic stroke coronary flows. We
assumed that these mean flows were the systolic and
diastolic flow deficits produced by the subsequent occlu-
sion. For occlusions lasting two cardiac cycles, we used
twice the mean systolic and diastolic flows. Occlusions
were performed during both the slow and the faster
phases of sinus arrhythmia. Responses to individual
occlusions lasting one cardiac cycle were included in the
analysis only if the duration of the occlusion was the
same (±15%) as the mean cycle length of the beats
measured in each experiment. Two-cycle occlusions were
treated similarly. Thus, the mean occlusion time for the
series was the same as the mean cycle length or twice this
value in the case of the two-cycle occlusions. We mea-
sured systolic and diastolic flows to obtain an index of
the distribution of flow through the myocardium (10).

Using mean values for flow deficit calculated in this
way, reactive hyperemic flow and repayment of flow debt
were determined as follows. Mean preocclusion systolic
and diastolic flows were subtracted from the correspond-
ing flows during each postocclusion beat. The t-test was
used to determine whether, on release, flow was in-
creased during postocclusion beats. The values for the
five preocclusion (control) beats for both systole and
diastole were compared with the corresponding values
for the individual postocclusion beats. Differences were
considered significant at the P < 0.05 level. The cumula-
tive significant differences were, respectively, the sys-
tolic and the diastolic reactive hyperemic flow. Percent
repayments were calculated by dividing the cumulative
reactive hyperemic systolic and diastolic flows by their
respective flow deficits and multiplying by 100. The
percent repayment for the whole occlusion was 100 times
the sum of the significant systolic and diastolic reactive
hyperemic flows divided by the total flow deficit.

In the anesthetized dogs, the same methods were used
even though heart rates were relatively constant and
much faster than they were in the conscious dogs so that
there was little or no beat-to-beat variation.

Results are expressed as means ± se. There were 17
one-cardiac cycle and 19 two-cardiac cycle experiments
in the five conscious dogs and 10 one-cycle and 9
two-cycle experiments in the six anesthetized dogs.

Results

OCCUSIONS WITH RESTRICTED ARTERIAL INFLOW

Figure 1A–C shows the effect of restricting arte-
rial inflow in one dog. In Figure 1A the artery was
occluded for 8 seconds and the arterial inflow was
not restricted on release. After release there was a
rapid increase in coronary blood flow; the peak
value of 151 ml/min occurred in 6 seconds. Subse-
quently, flow gradually decreased and returned to
the preocclusion value in 86 seconds.

In Figure 1B the artery was occluded for 9.2
seconds; then the cuff was partially deflated to
restrict arterial inflow. This controlled coronary
blood flow was allowed to increase only to about
15% above the preocclusion level. It was main-
tained at that level for the expected duration of the
hyperemia as judged by the control response shown
in A. The period of restricted inflow is indicated in
B by the black bar. This period was actually
slightly longer than the duration of the response
in A, since the occlusion period in B was a little longer
(9.2 compared with 8.0 seconds). Restricting arte-
rial inflow reduced the percent repayment from
500% to 141%. Complete release of the cuff, which
is indicated by the end of the black bar, was
followed by a small transient increase in flow which
prolonged the duration of the response from the
control value of 86 seconds (Fig. 1A) to 140 seconds
(Fig. 1B). Preocclusion coronary blood flow, blood
pressure, and heart rate were virtually the same as
they were in Figure 1A.

When another coronary artery occlusion was
performed without restricting arterial inflow, the
full reactive hyperemic response was again ob-
tained on release of the occlusion (Fig. 1C). Peak
flow was 135 ml/min, percent repayment was 469%,
and the duration of the response was 99 seconds.
Preocclusion coronary blood flow, blood pressure,
and heart rate were the same as they were in A and
B. These occlusions were performed in the same
dog with an interval of 10 minutes between each
occlusion.

The results obtained in 19 experiments like that
in Figure 1 performed on five dogs are summarized
in Table 1. Restricting arterial inflow reduced the
percent repayment of the flow debt from 618 ± 34%
to 213 ± 17% and prolonged the duration of the
response from 95 ± 4 seconds to 129 ± 5 seconds (P
< 0.0005 for both). The reduction in reactive
hyperemia occurred without any change in preoc-
closure coronary blood flow, blood pressure, or
heart rate. When the coronary artery was occluded
again 10 minutes later for 8 seconds and released
without restricting arterial inflow (Fig. 1C), the
responses were the same as those obtained in
control occlusions.

When these experiments were repeated with
peripheral coronary arterial pressure measure-
ments in two additional dogs, the results were the
same. In the five experiments performed, reactive
hyperemic flow was reduced from 561 ± 86% to 352
± 35% during restricted inflow and responses were
Effects of an 8-second occlusion on coronary blood flow (CBF) and systemic arterial blood pressure (BP) without restriction of arterial inflow (A and C) and with restriction of arterial inflow (B) in an anesthetized dog. The black bar indicates the period when arterial inflow was restricted. Reactive hyperemic flow is greatly reduced in B, and the duration of the response is prolonged. There was an interval of 10 minutes between coronary artery occlusions. ECG = electrocardiogram.

prolonged from $60 \pm 6$ seconds to $102 \pm 11.5$ seconds. The occlusions immediately reduced mean peripheral coronary arterial pressure (which with the recording system used was not different from mean systemic pressure) from $122 \pm 3$ mm Hg to $27.5 \pm 2$ mm Hg. On release of control occlusions, peripheral coronary arterial pressure always returned to systemic levels within 12 seconds (mean $10 \pm 1$ seconds; range 6 to 12 seconds). But during restricted inflow there was a substantial gradient between systemic and peripheral coronary arterial pressures in every experiment; this gradient was still present at the time of final release. The mean gradient during restricted inflow was $37.9 \pm 4.6$ mm Hg (range 55 to 26.5 mm Hg); immediately before final release it was $17.8 \pm 6.8$ mm Hg (range 42 to 5 mm Hg). Final release was always associated with a transient increase in coronary blood flow; the smallest increase occurred in the experiment in which there was the smallest
TABLE 1
Reactive Hyperemic Responses after 8-Second Coronary Artery Occlusions without and with Temporary Restriction of Arterial Inflow during Hyperemia: 19 Experiments in Five Dogs

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Restricted</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactive hyperemic flow (ml)</td>
<td>36 ± 2</td>
<td>13 ± 1*</td>
<td>34 ± 3</td>
</tr>
<tr>
<td>% Repayment</td>
<td>618 ± 34</td>
<td>213 ± 17*</td>
<td>620 ± 38</td>
</tr>
<tr>
<td>Preocclusion coronary blood flow (ml/min)</td>
<td>46 ± 2</td>
<td>45 ± 2</td>
<td>45 ± 2</td>
</tr>
<tr>
<td>Duration of reactive hyperemic flow (seconds)</td>
<td>96 ± 4</td>
<td>129 ± 5*</td>
<td>94 ± 4</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>121 ± 3</td>
<td>119 ± 3</td>
<td>119 ± 3</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>161 ± 8</td>
<td>162 ± 8</td>
<td>161 ± 8</td>
</tr>
</tbody>
</table>

Values are means ± se.
* Differences significant at the P < 0.0005 level.

mean pressure gradient at that time (5 mm Hg). In each of these experiments, the flow debt was fully repaid during the period of restricted inflow and before final release. Immediately before final release, percent repayment was already 176 ± 29% (range 107 to 257%).

ONE- AND TWO-CARDIAC CYCLE OCCLUSIONS

Conscious Dogs.—Figure 2 shows three separate records of phasic coronary blood flow, blood pressure, and the electrocardiogram taken 10 minutes apart in one resting dog. Sinus arrhythmia was well marked, and the relative proportion of systolic and

FIGURE 2
Representative tracings of coronary blood flow (CBF) and blood pressure (BP) obtained in one resting conscious dog before and after one- and two-cardiac cycle occlusions. Marked sinus arrhythmia is evident. A: Zero flow. B: Coronary artery occlusion for one cardiac cycle (indicated by the gray bar). C: Coronary artery occlusion for two cardiac cycles (indicated by the black bar). Stroke coronary flow was increased in the postocclusion beats. Calibrations in A and C are the same as those in B. ECG = electrocardiogram.
diastolic flow in each beat changed with the heart rate. During periods of bradycardia, clearly visible in beats 1 and 2 of Figure 2A, flow was largely diastolic. But as the heart rate increased the flow pattern changed and systolic flow became proportionately larger, as shown in beats 5 and 6 of A: in beat 1 systolic flow was only 10% of stroke coronary flow, but in beat 6 it was 32%.

Figure 2B shows a one-cardiac cycle occlusion. The duration of the occlusion is indicated by the gray bar. After release of the occlusion, flow increased immediately and was higher than stroke coronary flow during preocclusion cardiac cycles with similar heart rates and blood pressures. Significant increases in systolic and diastolic stroke coronary flows \( (P < 0.05) \) were maintained for three and five beats, respectively, compared with the corresponding values during the five beats preceding the occlusion. Using these beats for the calculation of percent repayment, the flow debt was greatly overpaid. The values for systolic and diastolic stroke flows were 180% and 230%, respectively.

Figure 2C shows a two-cycle occlusion performed 10 minutes later. The duration of this occlusion is indicated by the black bar. On release of the occlusion, stroke coronary flow increased immediately to levels far in excess of preocclusion values. Compared with the values for systolic and diastolic stroke flow during the five beats before the occlusion, flows were significantly increased for six and eight beats, respectively. The flow debt was greatly overpaid. Systolic and diastolic stroke percent repayments calculated on those beats with significantly increased flows were 165% and 240%, respectively.

The data obtained in all one- and two-cardiac cycle occlusions performed in the five conscious dogs are summarized in Figure 3. The flow debt resulting from an interruption of the coronary circulation for only one cardiac cycle was overpaid in all 17 experiments performed in the five conscious dogs. The mean percent repayment was 227% and of this the systolic and diastolic repayments were 280% and 173%, respectively. Significant increases in diastolic flow, determined by Student's \( t \)-test, occurred for four beats and significant increases in diastolic flow occurred for three beats, although the response undoubtedly lasted longer than that, as the figure indicates. The heart rate during one-cycle occlusions was 85 ± 3.9 beats/min so that the mean duration of the occlusions was only 0.7 seconds. Blood pressure was 92 ± 1.3 mm Hg. There were no differences in heart rate or blood pressure before and after the occlusions.

The group responses to two-cycle occlusions were similar but lasted longer; they are also shown in Figure 3. Both systolic and diastolic stroke coronary flow were significantly increased \( (P < 0.05) \) for five beats in the 19 experiments performed in the five conscious dogs. Mean percent repayment calculated from these significantly increased beats was 172%, the systolic and diastolic repayments being 173% and 171%, respectively. But as Figure 3B shows, the response clearly lasted longer than the five-cardiac cycle period during which statistically significant differences could be obtained for individual beats. Heart rate and blood pressure were 84 ± 4.3 beats/min and 92 ± 2.2 mm Hg and were not different before and after the occlusion. The mean duration of occlusion was 1.4 seconds.

Figure 3 also shows the relative proportions of stroke coronary flow occurring in systole and diastole during cardiac cycles before and after the occlusions. These data provide an index of the evenness of distribution of myocardial blood flow (10) before and after occlusions. As indicated in Figure 3, a high proportion of stroke flow occurred in diastole and this situation did not change during the responses. Before both one- and two-cycle occlusions, diastolic flow was 83 ± 0.4% (range 82 to 84%) of stroke coronary flow. In the beats after one-cycle occlusions, it was 81 ± 0.8% (range 79 to 85%); after two-cycle occlusions, it was 84 ± 0.3% (range 83 to 85%).
Anesthetized Dogs.—Similar but larger and apparently longer-lasting responses were obtained in the anesthetized dogs in which resting heart rate and blood pressure were considerably higher than they were in the conscious dogs. Occlusion times were correspondingly shorter. Mean blood pressures for the one- and two-cycle occlusions were, respectively, 115 ± 5 mm Hg and 119 ± 6 mm Hg; heart rates were 157 ± 9 beats/min and 165 ± 4 beats/min. Thus, the mean occlusion times for the one- and two-cycle occlusions were 0.4 seconds and 0.7 seconds.

The results obtained with the one-cycle occlusions are summarized in Table 2. Despite the brevity of the occlusion times, there were significant increases in systolic stroke flow lasting for 5 beats and in diastolic stroke flow lasting for 14 beats; percent repayments were 225% and 426%, respectively.

The results obtained with the two-cycle occlusions are shown in Table 3. Postocclusion systolic

### Table 2

**Responses to One-Cardiac Cycle Occlusions Ten Experiments in Six Anesthetized Dogs**

<table>
<thead>
<tr>
<th>Beat</th>
<th>Systolic flow (ml/min)</th>
<th>Diastolic flow (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.60 ± 0.07</td>
<td>2.29 ± 0.13</td>
</tr>
<tr>
<td>2</td>
<td>0.58 ± 0.06</td>
<td>2.36 ± 0.13</td>
</tr>
<tr>
<td>3</td>
<td>0.58 ± 0.07</td>
<td>2.37 ± 0.12</td>
</tr>
<tr>
<td>4</td>
<td>0.60 ± 0.07</td>
<td>2.35 ± 0.12</td>
</tr>
<tr>
<td>5</td>
<td>0.58 ± 0.07</td>
<td>2.30 ± 0.12</td>
</tr>
<tr>
<td><strong>GROUP MEAN</strong></td>
<td><strong>0.59 ± 0.07</strong></td>
<td><strong>2.33 ± 0.12</strong></td>
</tr>
</tbody>
</table>

**Values for mean systolic and diastolic stroke coronary flows are means ± se. Mean blood pressure = 115 ± 5 mm Hg, mean heart rate = 157 ± 9 beats/min, and mean occlusion time = 0.4 seconds. The first 5 systolic and the first 14 diastolic postocclusion stroke coronary flows are significantly greater than the preocclusion flows (P < 0.05 or better).**

### Table 3

**Responses to Two-Cardiac Cycle Occlusions: Nine Experiments in Six Anesthetized Dogs**

<table>
<thead>
<tr>
<th>Beats</th>
<th>Systolic flow (ml/min)</th>
<th>Diastolic flow (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preocclusion Beats</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.59 ± 0.09</td>
<td>2.42 ± 0.12</td>
</tr>
<tr>
<td>2</td>
<td>0.63 ± 0.05</td>
<td>2.42 ± 0.11</td>
</tr>
<tr>
<td>3</td>
<td>0.63 ± 0.06</td>
<td>2.42 ± 0.12</td>
</tr>
<tr>
<td>4</td>
<td>0.62 ± 0.07</td>
<td>2.41 ± 0.11</td>
</tr>
<tr>
<td>5</td>
<td>0.62 ± 0.08</td>
<td>2.27 ± 0.13</td>
</tr>
<tr>
<td><strong>GROUP MEAN</strong></td>
<td><strong>0.62 ± 0.07</strong></td>
<td><strong>2.38 ± 0.12</strong></td>
</tr>
</tbody>
</table>

**Postocclusion Beats |
| 1     | 0.91 ± 0.04            | 3.30 ± 0.13             |
| 2     | 0.94 ± 0.06            | 3.31 ± 0.17             |
| 3     | 0.91 ± 0.06            | 3.58 ± 0.17             |
| 4     | 0.97 ± 0.07            | 3.47 ± 0.14             |
| 5     | 0.89 ± 0.07            | 3.40 ± 0.12             |
| 6     | 0.86 ± 0.08            | 3.32 ± 0.12             |
| 7     | 0.87 ± 0.08            | 3.24 ± 0.13             |
| 8     | 0.88 ± 0.11            | 3.25 ± 0.13             |
| 9     | 0.86 ± 0.07            | 3.16 ± 0.13             |
| 10    | 0.87 ± 0.09            | 3.16 ± 0.14             |
| 11    | 0.80 ± 0.08            | 3.16 ± 0.15             |
| 12    | 0.78 ± 0.07            | 3.12 ± 0.14             |
| 13    | 0.75 ± 0.07            | 3.09 ± 0.13             |
| 14    | 0.73 ± 0.09            | 3.02 ± 0.14             |
| 15    | 0.75 ± 0.08            | 3.04 ± 0.16             |
| 16    | 0.69 ± 0.08            | 3.03 ± 0.16             |
| 17    | 0.72 ± 0.08            | 3.01 ± 0.17             |
| 18    | 0.72 ± 0.11            | 2.90 ± 0.16             |
| 19    | 0.69 ± 0.06            | 2.95 ± 0.16             |
| 20    | 0.74 ± 0.11            | 2.92 ± 0.15             |
| 21    | 0.63 ± 0.10            | 2.91 ± 0.16             |
| 22*   |                        | 2.88 ± 0.14             |
| 23    |                        | 2.76 ± 0.14             |
| 24    |                        | 2.79 ± 0.14             |
| 25    |                        | 2.71 ± 0.14             |
| 26    |                        | 2.73 ± 0.17             |

Values for mean systolic and diastolic stroke coronary flows are means ± se. Mean blood pressure = 119 ± 6 mm Hg, mean heart rate = 165 ± 4 beats/min, and mean occlusion time = 0.7 seconds. The first 12 systolic and the first 26 diastolic postocclusion stroke coronary flows are significantly greater than the preocclusion flows (P < 0.05 or better).

* Systolic flows for beats 22-26 were within the control range.

flows were significantly increased for 12 beats, and postocclusion diastolic flows were significantly increased for 26 beats; percent repayments were 249% and 385%, respectively. There were no differences in heart rate or blood pressure before and after either the one- or the two-cardiac cycle occlusions, nor were there any differences in the relative proportions of stroke coronary flow occurring in systole and diastole. Before the one-cycle occlusions, diastolic flow was 79.8 ± 0.2% (range 79.2 to 80.3%) of stroke coronary flow; after the occlusions,
it was 79.7 ± 0.4% (range 76.7 to 80.9%). The corresponding values for the two-cycle occlusions were 79.4 ± 0.3% (range 78.5 to 80.3%) before and 79.6 ± 0.3% (range 76.5 to 82.2%) after the occlusions.

Discussion

OCCULSIONS WITH RESTRICTED ARTERIAL INFLOW

So far as we are aware, there are no published accounts of experiments in the heart similar to those described in this paper, but experiments in the peripheral circulation have been reported. Blair et al. (11) abolished reactive hyperemia in the human forearm after 5-minute brachial artery occlusions by restricting arterial inflow for twice the duration of the normal hyperemia. From similar experiments in the cat leg, Hyman et al. (12) reported increased tissue clearance of iodide during restricted inflow. They suggested that a change in the distribution of the circulation during restricted inflow, so that more of the flow was concerned with exchanges in tissues, explained the findings of Blair et al. (11).

But it is unlikely that redistribution of flow during partial restriction accounts for our results. We know of no evidence for considerable arteriovenous shunting during reactive hyperemia in the heart. Such channels apparently do not exist in the nonischemic dog heart (13, 14). The early studies of Maclean et al. (15) suggested that more than 5% of the coronary blood flow passed through arteriovenous communications 50μ in diameter, but recent definitive work using radioactive microspheres of carefully controlled size contradicts this hypothesis. The extensive studies of Hoffman and his associates (10, 16, 17) have established that arteriovenous shunting of small (9 or 15μ) microspheres under a wide variety of circumstances is usually less than 1%. Opening up of a collateral circulation also cannot explain our findings. The rate at which collaterals develop in the chronically ischemic myocardium and the extent of their formation are well known (13, 18, 19), but in the nonischemic dog heart coronary arteries function as end arteries (14).

In the nonischemic dog heart, the magnitude of the reactive hyperemic response is related closely to the size of the flow debt produced by coronary artery occlusion and is presumed to be a consequence of hypoxia-induced metabolic changes (4, 5). However, by restricting arterial inflow for the duration of the hyperemia found in control observations, we were able to reduce repayment of the flow deficit from 620% with free arterial inflow to 220% with restricted arterial inflow; there was only a modest prolongation of the response (+36%). Since the level of resting coronary blood flow is thought to be metabolically determined (1, 20), these results indicate that the hyperemia is normally greatly in excess of that required to restore the metabolic changes produced during the period of ischemia and that the duration of the response is not greatly affected by large reductions in hyperemic flow. It follows that, if the hyperemia is indeed mediated by the release of vasodilator metabolites from the myocardium, those metabolites principally responsible do not depend critically on blood flow for their removal or inactivation.

Of the many identified diffusible vasodilator metabolites released from ischemic myocardium, only adenosine produces sufficient coronary vasodilation to account for the hyperemia observed (1, 20–23). Adenosine released from the myocardium is mainly rapidly taken up again into heart muscle cells so that only a small proportion actually diffuses into the bloodstream (24). Thus, the removal of released adenosine in our experiments would not depend critically on coronary blood flow rates, which were more than 10–20% above resting levels. Therefore, our observations do not exclude the possibility that adenosine released from ischemic myocardium is an important mediator of reactive hyperemia.

Guyton and his associates (2), from the results of their experiments in dogs, have suggested that Po₂ changes in vascular smooth muscle regulate local blood flow and that it is unnecessary to ascribe a role of overriding importance to released metabolites. But our findings do not favor this hypothesis as an explanation for the hyperemia that occurs after brief coronary artery occlusions. During the period of reduced inflow after release in our experiments, vascular smooth muscle was in contact with arterial blood flowing at rates slightly (10–20%) above preocclusion levels throughout the whole of the period during which coronary vasodilation would be expected to occur. It is hardly likely then that vascular smooth muscle Po₂ was reduced during this time. Yet complete release resulted in a further period of vasodilation extending by 36% the total duration of the response. Since the myocardial oxygen debt should have been fully repaid by then, this latter observation implies that complete release either permitted an augmented washout of residual vasodilator metabolites or uncovered a myogenic response which accounted for the vasodi-
It is known that both adenosine and lactic acid are produced during an 8-second occlusion in the dog, adenosine after approximately eight beats, extrapolating from Olssen’s data (25), or 3 seconds at the heart rates of the anesthetized dogs in our study and lactic acid after 6 seconds (26). So either or both could have contributed to the vasodilation on complete release. But in an earlier study, we have shown that coronary vascular reactivity in the immediate post–reactive hyperemic period is temporarily reduced (6). These latter observations raise the possibility that myogenic responses contribute to reactive hyperemia in the heart.

Vasodilation after release of a coronary artery occlusion could be partly due to the mechanical effects of the reduction in transmural pressure, a suggestion originally proposed by Bayliss (27) for the peripheral circulation and later expanded into a more general hypothesis by Folkow (28). The vasodilation found on complete release in our experiments could be due to the same mechanism.

The findings in the experiments in which peripheral coronary arterial pressure was measured indicate that restricting arterial inflow as we did in this study reduces peripheral pressure, that a pressure gradient is still present at the time of final release, and that after final release flow increases even though the flow debt has already been fully repaid. The conditions necessary for myogenic effects are therefore present. It was in an attempt to obtain other evidence in support of a myogenic contribution to the reactive hyperemic response under more physiological conditions that the one- and two-cardiac cycle experiments were undertaken.

ONE- AND TWO-CARDIAC CYCLE OCCLUSIONS

These experiments established that one- and two-cardiac cycle coronary artery occlusions result in reactive hyperemia with considerable overpayment of the flow debt in both conscious and anesthetized dogs. Mean cycle lengths were 0.7 seconds and 0.4 seconds, respectively. We are not aware of reports of similar observations, although Olsson and Gregg (4) in their studies of reactive hyperemia in conscious dogs commented on finding overpayment of the flow debt after occlusions as short as 1.2 seconds.

We found larger and longer-lasting responses in the anesthetized dogs. Several factors could have contributed to this finding. First, the method of analysis tended to underestimate responses in the conscious dog; reactive hyperemic flow was only calculated from those postocclusion beats that were significantly larger (Student’s t-test) than those in the control period. Because of marked sinus arrhythmia, there was considerable beat-to-beat variation in coronary blood flow so that differences had to be large to be significant. This situation did not exist in the anesthetized dogs, since cycle length and stroke coronary flow were relatively constant. Moreover, in the anesthetized preparations mean blood pressure was much higher and heart rate was approximately double that in the conscious dogs; both of these factors increase hyperemic flow for a given occlusion period.

We have no measurements of the distribution of flow through the myocardium in our experiments, but a high proportion of stroke coronary flow occurred during diastole (>79%) before and after the occlusions in both conscious and anesthetized dogs (Fig. 3, Tables 2 and 3). From the measurements of Buckberg and his associates (10) of endocardial and epicardial flows with small (9-15μ) microspheres in a variety of physiological and pathological states in the dog, this finding would be consistent with uniform myocardial perfusion occurring both before the occlusions and during the reactive hyperemia; thus, ratios of endocardial flow to epicardial flow should have been close to unity throughout, suggesting that the results were not influenced by uneven myocardial flow.

The experiments showed that reactive hyperemia does indeed occur after one- and two-cycle occlusions, but we did not establish whether, under resting conditions, such brief occlusions influence myocardial metabolism through hypoxia. Nevertheless, it seems very unlikely that they would. Olsson (29) has calculated that myocardial oxygen stores should be sufficient for normal cellular metabolism for up to 6 seconds after coronary artery occlusion. There are data that support this calculation. Lactic acid production, which indicates anaerobic metabolism, cannot be detected with occlusions shorter than 6 seconds in conscious dogs (26). Adenosine release is a sensitive indicator of reduced myocardial PO\(_2\), and it has been suggested that adenosine is the principal mechanism responsible for the physiological regulation of coronary blood flow (1, 20–23). It is not known whether myocardial adenosine levels are increased after a one-cycle occlusion lasting only 0.4 seconds. But from the measurements of Olsson (25) beginning 5 seconds after occlusion and showing an apparently linear relationship between the increase in myocardial adenosine and the number of beats during.
occlusion, it seems unlikely that levels at 0.4 seconds are consistently significantly different from control values. Furthermore, inspection of published records of direct measurements of myocardial \( \text{Po}_4 \) during experimental coronary artery occlusions in dogs shows no significant change within 1 second of occlusion (30, 31).

Rayford et al. (32) measured the oxygen supplied to the myocardium by circumflex coronary artery flow in conscious dogs. They found that at rest approximately 0.05 ml of oxygen was taken up by the myocardium per beat. Their preparation was similar to the one that we used, and resting circumflex artery flow, heart rate, blood pressure, and the size of the dogs were all virtually identical in the two studies. A resting circumflex flow of 40 ml/min probably supplies 50–60 g of heart muscle. At rest the conscious dog heart used about two-thirds of the coronary arterial oxygen content (32), but with the increased oxygen demand it is capable of extracting more oxygen so that the coronary arteriovenous oxygen difference widens (33). The coronary capillary blood volume is approximately 10% of the volume of perfused myocardium (33). The oxygen content of this blood is presumably not lower than that found in the coronary sinus—about 5%/100 ml blood in the resting conscious dog (32). Therefore, the amount of oxygen available to the 50 g of myocardium from this source would be something in excess of 0.25 ml. In addition to this amount, the oxygen combined with myoglobin and that dissolved in the 40 g (about) of tissue water in the muscle is also available for exchange. Thus, myocardial oxygen stores are greatly in excess of the oxygen deficits of 0.05 and 0.1 ml produced by one- and two-cycle occlusions. In addition, during the occlusions some exchange must take place between blood in the downstream conductance and resistance vessels and that in the capillary circulation, further increasing available oxygen. Any small reduction in oxygen content will result in only minor decreases in \( \text{Po}_4 \) since, at 5%/100 ml, the oxygen dissociation curve is relatively flat. For these reasons it seems unlikely that a one-cardiac cycle occlusion in a resting conscious dog would affect myocardial cellular metabolism because of oxygen lack or that even a two-cycle occlusion would do so.

A more likely mechanism to explain our results involves the intrinsic properties of coronary vascular smooth muscle. We did not measure peripheral coronary arterial pressure in these one- and two-cycle occlusion experiments, but in the similar preparation used for the restricted inflow studies occlusions reduced the pressure to low levels immediately. Thus, a myogenic response could account for the changes we measured. Such a mechanism is known to contribute to reactive hyperemia in skeletal muscle (34) but, although Folkow (28) has discussed the possible role of myogenic responses in the regulation of coronary blood flow, so far as we are aware these mechanical effects have never been demonstrated in the coronary circulation. We suggest that our experiments provide inferential evidence for their existence.

Support for this idea comes from our earlier studies which demonstrated that coronary vascular reactivity and reactive hyperemia are both temporarily reduced in the immediate post-reactive hyperemic period and that the recovery times of each coincide very closely (6). Thus, there is independent evidence to show that intrinsic mechanisms in vascular smooth muscle contribute to reactive hyperemia in the heart.

Although further experiments are required to firmly establish a role for myogenic responses in the heart, the results so far suggest that they do contribute to reactive hyperemia and the regulation of coronary blood flow. Myogenic effects may be responsible in part for the disproportionately large repayment of the flow debt consistently found on release of a coronary artery occlusion.

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