Effect of Heart Rate and Intracoronary Isoproterenol, Levarterenol, and Epinephrine on Coronary Flow and Resistance

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Numerous studies have been published on the effect of heart rate and various drugs on coronary flow. It has not been possible to estimate the relative importance of changes in intravascular and extracellular resistance in determining the observed alterations in coronary flow. Recently, Sabiston and Gregg suggested that in a heart in which coronary arteries were perfused at constant pressure the immediate change in flow induced by vagal asystole was due to the removal of the extravascular resistance of the contracting myocardium. They found that coronary flow consistently rose and concluded that extravascular resistance acted to impede coronary flow. In the present experiments, a similar approach was used to determine the effect of changes in heart rate and of intracoronary epinephrine, norepinephrine, and isoproterenol on extravascular and intravascular resistance.

Methods

Twenty-two adult mongrel dogs weighing between 11 and 18 Kg. were anesthetized with intravenous pentobarbital approximately 25 mg./Kg. Respiration was maintained via an endotracheal tube with a Phipps and Bird respirator utilizing room air. The anticoagulant was heparin, 1,000 units/Kg. initially and 500 units/Kg. every 30 minutes thereafter. Asystole was produced either by vagal stimulation or by momentarily disconnecting an external pacemaker driving the ventricles of a heart in which complete atrioventricular block had been produced earlier in the experimental day. In the first type of preparation, the vagi were carefully isolated in the neck and stimulated with a Grass stimulator at voltages from -5 to 30 and a frequency of 30/sec. In the second type of preparation, heart block was produced by the method of Weirich et al. The azygos vein was tied off and the venae cavae were temporarily occluded. The right atrium was then incised and a suture passed around the conduction tissue just below the A-V node and tied. In most cases, complete A-V block immediately ensued. An electrode was placed on the right ventricle in the region of the pulmonary conus and a second electrode was attached subcutaneously. The ventricles were then driven by a Grass stimulator utilizing voltages from 2 to 8. This method of controlling heart rate is superior to merely stimulating the atria or ventricles at a rate slightly above the prevailing rate of the dog because a wider range of heart rates can be investigated. No detrimental effect on the performance of the heart has been found with this preparation.

The left circumflex coronary artery, or in some cases the main left coronary artery, was dissected free. The circumflex was cannulated directly and the main left coronary was cannulated with a specially designed brass cannula which was inserted into the subclavian artery and tied into the coronary ostium by a suture previously placed around the left coronary artery. The cannulated artery was perfused from the carotid artery except during the short period when variables were studied. For the latter, the coronary artery was perfused by gravity from a reservoir of heparinized donor blood kept in a 37 C. water bath until use. This electrically stirred reservoir was maintained at a height above the dog such that the perfusion pressure was approximately 100 mm. Hg. At this perfusion pressure, coronary flow closely approximated that observed when the coronary arteries were supplied from the carotid artery. Blood entering the coronary artery from either source passed first through a continuously recording rotameter. Mean systemic blood pressure was visually monitored with a mercury manometer and recorded by a Statham strain gauge. A reservoir bottle was connected to both femoral arteries; by adjusting its height, systemic blood pressure was maintained between 70 and 80 mm. Hg. In those experiments in which the main left coronary artery was cannulated, a second reservoir bottle was connected to the superior vena cava via an external jugular vein to maintain central venous pressure constant. This was necessary to compensate for the excess blood fed into the left coronary.
artery during gravity perfusion. Recordings of coronary artery flow and systemic pressure were made with a Hathaway oscillograph. Drugs were administered directly into the rubber tubing connected to the coronary cannula by a constant speed infusion pump. No recordings were made until one minute of infusion to allow an equilibrium to be achieved. The drugs were diluted in 0.9 per cent saline and, regardless of drug dosage, the speed of injection was 0.1 ml./min. Injection of 0.9 per cent saline at that rate had no effect on coronary flow in the beating or stopped heart. Only one drug was given to any dog.

The rotameter was adjusted for minimum damping so that less than a second was required for full-scale deflection of the Hathaway galvanometer. Since only the immediate change in flow following elimination of the extravascular compression of the contracting muscle was desired, short periods of asystole sufficed for this experiment.

Results

Effect of Changes in Heart Rate on Left Circumflex Flow in the Stopped and Beating Heart

Three hundred and forty-three observations were made of the effect of heart rates ranging from 90 to 240 per minute on circumflex flow in the blocked and driven heart, and the increase in flow was noted with asystole. A typical series of stoppages is shown in figure 1. At a rate of 90, the control flow was 31 ml./min. and rose to 40 with asystole, an increase of 29 per cent. The small fluctuations in flow seen during asystole were probably due to the contraction of the left atrium as reflected in the flow of the atrial branch of the circumflex artery. These fluctuations were not seen when the atrium was fibrillating. Control circumflex flow was 30 ml. with the heart beating at 120 and rose to 41 ml. with asystole for an increase of 37 per cent. At a rate of 150, the flow rose from 36 to 50 ml. during asystole, a 39 per cent increase, and at a rate of 180, asystole caused flow to rise from 36 to 53 ml., an increase of 47 per cent. Finally, at a rate of 240 per minute, an
increase of 53 per cent was recorded as flow rose from 38 to 58 ml. In this experiment, flow in the beating heart rose from 31 to 38 ml./min.; in the stopped heart, flow rose from 40 to 58 ml./min., and the percentage increase in flow during asystole rose from 29 to 53 per cent as heart rate was increased in small increments from 90 to 240.

Figure 2 and table 1 show the average of 343 separate flow measurements during asystole at different controlled heart rates. At a rate of 90, flow in the circumflex artery averaged 27 ml./min. and rose to 37 during asystole, an increase of 37 per cent. At rate 120, control flow in the circumflex was 26 and with asystole there was a 42 per cent increase in flow to 37 ml./min. Control flow was 29 ml./min. with the heart beating at 150, and the average flow during asystole was 41, an increase of 41 per cent. The control circumflex flow in the beating heart was 32 ml./min. at rate 180, and it rose to 47 during asystole for an average increase in flow of 47 per cent. Finally, at a heart rate of 240, the average control circumflex flow was 36 ml./min. in the beating heart, and at the onset of asystole flow rose to 56, an increase of 56 per cent.

Effect of Intracoronary Drugs on Coronary Flow in the Stopped and Beating Heart

Asystole Produced in Previously Blocked Hearts

Experiments were designed to test the effect of isoproterenol, levarterenol, and epinephrine on coronary flow in the stopped and beating heart.

Isoproterenol. Isoproterenol was infused in doses ranging from 1 to 4 μg./min. Figure 3 and table 1 show the average of the results obtained in three dogs in which heart block had first been produced. Average flow in the beating heart at rate 90 was 21 ml./min. in the control state and 26 during isoproterenol infusion. Asystole caused flow to rise to 30 and 37 ml./min., respectively. This represented an average increase in flow of 43 per cent in the control and 42 per cent during drug infusion. The same trends became more marked as faster heart rates were employed. At a rate of 240, the average control flow was 34 ml./min. and rose to 52 after asystole, an increase of 55 per cent. Infusion of isoproterenol raised flow in the beating heart to 40 and in the stopped heart to 57 ml./min., so that there was a 43 per cent increase in flow with asystole. It can be seen that flows in both the beating and stopped heart were greater after isoproterenol infusion but the percentage increase in flow in asystole was less.

Levarterenol. Figure 4 and table 1 illustrate the results obtained in three dogs with intracoronary infusion of levarterenol in doses from 1 to 4 μg./min. in dogs with heart block. Average control flow in the beating heart at rate 90 was 28 ml./min. and rose to 37 during asystole, while with levarterenol infusion the control flow of 30 rose to 40 during asystole. Percentage increases in flow were 32 and 33 per cent, respectively. Heart rate was again raised in small increments to 240 and similar
Effect of Heart Rate and Drugs on the Coronary Flow in the Beating and Asystolic Heart

*The standard deviations of the coronary blood flows in this table are not meant to be a statistical analysis of the experimental data, but demonstrate the range of flows obtained. The flow may vary greatly in different dogs depending on the circulation of the circumflex artery and the myocardium supplied (not measured in this study).

<table>
<thead>
<tr>
<th>Circumflex artery flow (ml/min)</th>
<th>90</th>
<th>120</th>
<th>150</th>
<th>180</th>
<th>210</th>
<th>240</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beating heart</td>
<td>37 ± 6.5</td>
<td>41 ± 8.2</td>
<td>47 ± 8.7</td>
<td>56 ± 8.9</td>
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<tr>
<td>Asystole</td>
<td>21.0 ± 6.3</td>
<td>25.8 ± 4.7</td>
<td>27.8 ± 4.1</td>
<td>34.0 ± 3.9</td>
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<tr>
<td>Beating heart</td>
<td>37.0 ± 7.5</td>
<td>37.2 ± 5.4</td>
<td>42.3 ± 4.7</td>
<td>52.0 ± 4.8</td>
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<tr>
<td>Asystole</td>
<td>30.0 ± 11.1</td>
<td>31.3 ± 6.3</td>
<td>34.4 ± 6.4</td>
<td>46.0 ± 5.3</td>
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<tr>
<td>Isoproterenol</td>
<td>37.0 ± 11.5</td>
<td>43.8 ± 7.4</td>
<td>48.1 ± 5.5</td>
<td>57.0 ± 7.1</td>
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<tr>
<td>Beating heart</td>
<td>37.0 ± 5.5</td>
<td>31.3 ± 3.4</td>
<td>31.7 ± 3.6</td>
<td>37.0 ± 3.3</td>
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<tr>
<td>Asystole</td>
<td>30.0 ± 2.8</td>
<td>34.7 ± 1.9</td>
<td>40.0 ± 5.2</td>
<td>46.0 ± 1.9</td>
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<tr>
<td>Asystole</td>
<td>40.0 ± 3.6</td>
<td>46.5 ± 2.2</td>
<td>55.6 ± 7.1</td>
<td>63.0 ± 5.9</td>
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<tr>
<td>Beating heart</td>
<td>28.0 ± 6.2</td>
<td>30.7 ± 8.3</td>
<td>34.9 ± 8.1</td>
<td>38.6 ± 7.7</td>
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<tr>
<td>Asystole</td>
<td>41.0 ± 9.2</td>
<td>44.5 ± 14.7</td>
<td>53.3 ± 16.2</td>
<td>59.9 ± 15.3</td>
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<tr>
<td>Epinephrine</td>
<td>32.0 ± 6.1</td>
<td>32.3 ± 5.5</td>
<td>37.2 ± 6.3</td>
<td>39.6 ± 6.3</td>
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</tr>
<tr>
<td>Asystole</td>
<td>37.0 ± 8.9</td>
<td>40.4 ± 8.7</td>
<td>46.4 ± 11.3</td>
<td>54.2 ± 12.4</td>
<td>59.1 ± 11.2</td>
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<tr>
<td>Beating heart</td>
<td>15.2 ± 6.9</td>
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<tr>
<td>Vagal asystole</td>
<td>26.1 ± 8.5</td>
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<tr>
<td>Epinephrine</td>
<td>16.3 ± 5.3</td>
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<td>Vagal asystole</td>
<td>28.1 ± 7.3</td>
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<tr>
<td>Beating heart</td>
<td>26.5 ± 12.1</td>
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<tr>
<td>Vagal asystole</td>
<td>38.3 ± 16.8</td>
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<tr>
<td>Levarterenol</td>
<td>28.6 ± 13.1</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Vagal asystole</td>
<td>39.5 ± 10.9</td>
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</table>

Changes were noted. At the highest rate, average flows of 37 and 60 ml./min. were noted in the control beating and stopped heart, while after levarterenol infusion the flows were 40 and 63. The per cent increases in flow with asystole were 62 per cent in the control and 58 per cent with the drug. As with isoproterenol, flow in both the beating and stopped hearts increased after levarterenol infusion but the percentage increase in flow after asystole decreased.

Epinephrine. Intracorony epinephrine in doses from 2 to 10 µg./min. was the final drug effect of which was determined on coronary flow in asystole (fig. 5 and table 1). In five dogs with blocked hearts driven by the external pacemaker, average control circumflex flow at a rate of 90 was 30 ml./min. and rose to 41 after asystole was induced. When epinephrine was infused, the control flow was 32 ml./min. and rose to 43 after asystole. Thus, the percentage increases in flow after asystole were 37 per cent in the control and 34 per cent during drug infusion. Figure 5 shows that the same trends were noted as heart rate was increased to 240. Epinephrine had the least effect of the three drugs tested, but the direction of the results was usually the same. There was a small increase in flow in the beating heart and the flow increase during asystole was again slightly less during epinephrine infusion.

Asystole Produced by Vagal Stimulation

The effect of levarterenol and epinephrine on circumflex flow in the beating and stopped heart was also determined with asystole produced by vagal stimulation. The results shown in figure 6 and table 1 were similar to those reported above in trend, but the spread of the data was greater than when the blocked and driven type of preparation was used. In any given dog, repeated asystole gave very similar results regardless of the manner in which asystole was produced. Since heart rate often changed when a drug was infused, asystole in the controlled heart rate preparation was
Figure 3
The effect of intracoronary isoproterenol infusion on coronary flow in the stopped and beating blocked-heart preparation at different control heart rates is shown. Flow in cc./min. is on the ordinate and the number of observations at each rate is on the abscissa. Bar (C) shows the flow rise noted in asystole without drug and bar (I) shows the flow rise noted in asystole during isoproterenol infusion. The figure in the blank part of the bar is the percentage increase in flow during asystole.

Figure 4
The effect of intracoronary levarterenol infusion on coronary flow in the stopped and beating blocked-heart preparation at different control rates is shown. Flow in cc./min. is on the ordinate and the number of observations at each rate is on the abscissa. Bar (C) shows the flow rise noted in asystole without drug and bar (I) shows the flow rise noted in asystole during levarterenol infusion. The figure in the blank part of the bar is the percentage increase in flow during asystole.

preferable to vagal asystole for estimating changes in extravascular resistance due to drugs.

In three experiments, main left coronary flow was measured instead of circumflex flow. The flows were considerably larger than those recorded from the circumflex but the effects of heart rate, levarterenol, and isoproterenol were the same as those observed when circumflex flow was measured.

Discussion
It is essential that the method employed to induce asystole in these experiments does not itself alter extravascular or intravascular resistance. Asystole was produced in two ways: by vagal stimulation and by discontinuing the action of an external pacemaker on a heart with complete atrioventricular block. Vagal stimulation has never been conclusively shown to affect coronary flow in an open-chest preparation provided that aortic pressure is kept constant. We stimulated the vagi of dog hearts which had been blocked and were being driven by the external pacemaker and observed no consistent or immediate effect on coronary flow. There was no difference in the flow rise noted in asystole produced by turning off the external pacemaker and the flow rise recorded when, in addition to turning off the pacemaker, the vagi were simultaneously stimulated. Either method of inducing asystole appeared to satisfy the requirements of the present experiment, but the blocked and driven preparation was preferable because heart rate could be controlled.

There are at least two sources of resistance in the coronary bed. First, there is resistance due to the vasomotor state of the coronary vasculature, and secondly, there is resistance due to the impeding effect of myocardial contraction upon flow. When the heart is stopped, the effect of the latter extravascular resistance is largely removed. A rise or fall of this asystolic flow as compared to the control flow would denote an increase or decrease in extravascular resistance. Changes in intravascular resistance can be estimated from a rise or fall in the magnitude of the asystolic flow under different circumstances.

The influence of heart rate on coronary flow has recently been discussed by Wegria et al. and Laurent et al. Both these groups of workers concluded that the ultimate effect of tachycardia was to increase coronary flow. In both cases, tachycardia was induced by stimulating the atria or ventricles at a rate.
faster than the spontaneously beating heart. In our experiments, when complete heart block was first produced and the ventricles driven by external stimulation, it was found that circumflex coronary flow in the beating heart rose from an average of 27 ml./min. at a rate of 90 to 36 ml./min. at a rate of 240. There was no change in flow at heart rates of 90 and 120. Flow increased by small amounts with each successive change in heart rate from 120 to 240. It seems evident that the net effect of increased heart rate was to lower the resistance of the coronary bed.

As the controlled heart rate was raised from 90 to 240, coronary flow increased not only in the beating but also in the asystolic heart. The flow during asystole rose both in absolute value and as a percentage of the control flow at increased heart rates. This denotes a rise in extravascular resistance in the beating heart. It has already been pointed out that increased heart rate caused a fall in net coronary resistance. It is now evident that there was a fall in intravascular resistance with increased heart rate which more than compensated for the rise in extravascular resistance. The present experiments did not explain why intravascular resistance decreased nor whether this was secondary, at least partially, to the increase in extravascular resistance. A possible mechanical explanation for the increased extravascular resistance is the fact that there was a decrease in the relative duration of diastole per minute and, thus, an increase of the time during which myocardial contraction was impeding flow. Changes in extravascular resistance can play an important role in the flow adjustments that take place as heart rate increases.

The actions of the three drugs on coronary flow in the stopped and beating heart were tested and had similar effects in decreasing total coronary resistance, but at comparable dose level isoproterenol had the greatest effect and epinephrine the least. All three drugs, in most cases, caused an increase in flow in both the beating and stopped heart. There must have been a fall in intravascular resistance for the flow in the stopped heart during drug infusion was greater than the asystolic flow without drug infusion. Since the per cent increase in flow in asystole was less after drug infusion, there was also a decrease in extravascular resistance. Using the same three drugs, Denison et al. 8 concluded from phasic coronary flow curves that there
was a more abrupt relaxation of the ventricles which could account for part of the decreased extravascular resistance. We have observed that, as in the spontaneously beating heart, sympathomimetic drug infusion decreased the length of systole in the blocked and driven heart. This is perhaps a partial explanation for the decreased extravascular resistance seen after drug infusion.

Berne\(^9\) has observed that both in fibrillating and beating hearts epinephrine caused a preliminary vasoconstriction followed by vasodilatation which he attributed to the hypoxic state of the myocardium. Only late effects after equilibrium was reached were recorded in our experiments; vasodilatation was also observed at that time. Since cardiac output was not monitored, it cannot be determined whether cardiac work remained constant and the observed vasodilatation was a primary or secondary result of drug infusion.

The increased coronary flow with isoproterenol, levarterenol, and epinephrine was, for the most part, a result of the decreased intravascular resistance. Despite the fact that increased vigor of cardiac contraction was observed when one of the drugs was infused, there was little effect on the extravascular resistance. The changes noted in flow due to decreased extravascular resistance during infusion of these drugs, while consistent and reproducible, were never greater than 20 per cent and usually about 10 per cent of control flow. The possible relationship of this small effect to decreased heart size also observed during drug infusion remains to be explored. It would seem, however, that extravascular resistance is a parameter that can be ignored in any attempt to determine the direct effect of these drugs upon the coronary vasculature.

**Summary**

The effect was determined of changes in heart rate and of intracoronary isoproterenol, levarterenol, and epinephrine on coronary flow in the stopped and beating heart. It was possible by this means to estimate the relative action of these variables on the extravascular and intravascular resistance of the coronary bed in a heart perfused at constant pressure. As heart rate was increased extravascular resistance rose, but intravascular resistance fell to a greater extent indicating a fall in net coronary resistance. Isoproterenol had the greatest and epinephrine the least effect in decreasing the total coronary resistance. The three drugs tested caused only a small fall in extravascular resistance. Since the effect was small, it was concluded that extravascular resistance can be ignored in determining the direct effect of these drugs upon the coronary vasculature.

**References**

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