Directional Coronary Collateral Growth with Chronic Circumflex Occlusion in the Dog

Konrad W. Scheel, Reginald J. Rodriguez, and Leslie A. Ingram

SUMMARY. The object of this study was to determine whether coronary collateral resistances were dependent on the direction of perfusion and to investigate whether a pattern of collateral growth with gradual circumflex occlusion could be discerned. In 12 dogs an Ameroid occluder was placed on the circumflex for 1 month, and in six dogs for 3 months; 12 dogs served as controls. The circumflex, left anterior descending, and right coronary arteries were separately but simultaneously perfused in an isolated heart preparation. The results showed that collateral flows from the right to the left coronaries in control dogs were 3.5-fold larger than when these collateral beds were perfused in the opposite direction. This difference in the 1- and 3-month Ameroid groups was approximately 20-fold. Relative to the control group, the collateral resistances from right to left coronary vessels were an average of 10-fold less in the 1- and 3-month Ameroid groups, but there was no significant difference in resistance in the collaterals perfused from the left to the right. The results strongly suggest that collateral proliferation occurs in response to hypoxia rather than to a pressure gradient, and that collateral development is toward the hypoxic area.

GRADUAL occlusion of a coronary artery in the dog results in marked coronary collateral proliferation. Fulton has shown that collateral growth also occurs in man in response to occlusive vascular diseases, but that the rate of development is slower compared to that in the dog. Although a number of mechanisms for vascular growth have been proposed, such as the velocity of blood flow, hyperoxia, pressure gradients, and radial and tangential stresses on the vessel, the precise mechanism continues to elude investigators.

Previous studies have shown that collateral or retrograde flow to a coronary vessel that had been gradually occluded increased considerably with time. It has also been realized that the source for collateral flow consists of the sum of the contributions from the other major coronary vessels. The purpose of this study was to establish a method that allows a separation of the collateral beds between the major coronary vessels and to determine whether a pattern for vascular proliferation could be discerned. In an isolated heart preparation the three major coronary arteries were perfused separately but simultaneously under conditions of maximum vasodilation. The collateral resistances were determined from measurements of retrograde flows made on two vessels simultaneously.

From the Department of Physiology and Biophysics, University of Tennessee Center for the Health Sciences, and the Department of Electrical Engineering, Christian Brothers College, Memphis, Tennessee.


Address for reprints: Dr. Konrad W. Scheel, University of Tennessee, Center for the Health Sciences, Department of Physiology, 951 Court Avenue, Room 450D, Memphis, Tennessee 38163.

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References

Methods

We used 30 young adult male mongrel dogs weighing between 15 and 18 kg. A normal electrocardiogram (leads I, II, III) and negative tests for microfilaria (heartworm) were required before selecting dogs for a 3-week conditioning program. This consisted of treatment for intestinal parasites and vaccination for distemper and hepatitis. The coronary and collateral flows were determined for 12 control and 18 experimental dogs in an isolated heart preparation. In the latter group an Ameroid occluder was placed on the left circumflex coronary artery of 12 dogs for 30 days and of six dogs for 90 days.

SURGICAL PLACEMENT OF AMEROID CONSTRICTOR

The experimental dogs were anesthetized with sodium pentobarbital (30 mg/kg, iv). We carefully observed sterile procedures and entered the chest through the 5th intercostal space while ventilation was maintained with a Bird Mark 7 respirator. The pericardium was cut from the base to the apex of the heart, and the circumflex coronary artery was isolated just distal to the main left coronary artery. The latter procedure was performed bloodlessly and with a minimum of tissue trauma to avoid the development of widespread adhesions. An Ameroid occluder with an inner diameter of 2.77 mm (Three Point Product Co., Montreal) was placed around the circumflex artery during continuous monitoring of lead II of the electrocardiogram (ECG). The ECG was observed for several minutes after placement of the Ameroid occluder to ensure that improper placement had not caused premature closure of the vessel. The heart was lavaged with saline. The saline was removed by suction before closing the pericardium. The ribs were proximated with two strands of stainless steel wire and the chest was closed in a routine manner. A chest drainage tube was inserted through the 7th intercostal space and connected to a water seal. As the dog began to recover from the anesthetic, the chest tube was removed and 30 mg of pentazocine (Talwin, Winthrop) was administered subcutaneously as an analgesic.

EXPERIMENTAL PROTOCOL FOR STUDIES ON THE ISOLATED HEART

The circumflex, right, and anterior descending coronary vessels were cannulated and perfused simultaneously in an isolated heart preparation, which has been described in detail previously. In the experimental dogs the circumflex artery was cannulated just distal to the occluder. To obtain maximum vasodilation dipyridamole was injected into the blood perfusion reservoir in the amount of 5.0-10.0 mg/700 ml of blood volume.

The isolated heart perfusion system and the coronary and collateral vessels are schematically shown in Figure 1. Three large (4.76-mm inner diameter) Silastic tubes led from the constant pressure perfusion reservoir to T-connectors. The retrograde flow was measured through one leg of this connector (F_A-retro, F_C-retro, F_R-retro) (for identification of all symbols, see Table 1); the other leg was connected to Statham cannulating blood flow transducers (FT) and terminated in cannulas which were inserted into the coronary arteries. Since collateral vessels in the dog exist at a high arterial level, capillary bed of the major coronary vessels R_A, R_C, and R_R. Because the flows to each coronary vessel are not identical and cannulas of different sizes were used, the pressure losses between the reservoir and the coronary vessel could be different. This implies that the pressures (P_A, P_C, and P_R) were not necessarily identical. Thus, the

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<th>Table 1 Symbols</th>
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<td>LAD</td>
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<td>F_A</td>
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direction of blood flows through the collateral vessels depends on the relative magnitudes of the pressures. If, for instance, \( P_c > P_a \) and \( P_c > P_R \), blood flows through the collaterals from the circumflex coronary artery to the anterior descending, and the collateral resistance was designated \( R_{CA} \); similarly, blood flows from the circumflex through the collaterals \( R_{CR} \) to the right coronary artery. When the retrograde flow valves (indicated by \( \times \)) were closed, the "control experiment" was performed.

**THE DOUBLE RETROGRADE FLOW EXPERIMENT**

A schematic representation of an experiment in which the retrograde flows were determined for the anterior descending and right coronary arteries simultaneously is shown in Figure 2. Blood flows through the perfusion system \( F_{AX} \) and \( F_{RX} \) were interrupted by two valves and the retrograde flow valves \( F_{A-retro} \) and \( F_{R-retro} \) were opened. Retrograde flows were collected in either tapered test tubes or beakers for 30 seconds. For a pressure relationship in which \( P_c > P_a \), blood flow would be through the collaterals \( R_{CA} \); and if \( P_c > P_R \), flow would occur through \( R_{CR} \). Although \( P_a \) and \( P_R \) were small, since retrograde flows were measured against atmospheric pressure, some blood would flow through the collaterals \( R_{AR} \) if \( P_a > P_R \). It should be noted that collateral flow through \( R_{CR} \) is also directed to the right coronary vessel \( R_R \). If the resistance of the retrograde flow system is large with respect to the resistance of the right coronary bed most of the blood flowing through the collaterals \( R_{CA} \) would be directed through \( R_R \). Thus, the retrograde flow would underestimate actual collateral flow. On the other hand, if the resistance of the retrograde flow system was much smaller than the resistance of the right coronary bed, retrograde flow would almost equal the collateral flow. Thus, the resistance of the retrograde flow system has to be considered in determining the collateral resistance \( R_{CR} \). Although, as has been mentioned earlier, collateral flow \( R_{AR} \) could be relatively small, it was also taken into account in calculating collateral resistance \( R_{CR} \). The above analysis can similarly be applied for the collateral resistance \( R_{CA} \).

The equations for determining collateral resistances under the above experimental conditions are described in detail in the Appendix.

In the experimental protocol double retrograde flow experiments also were performed for the anterior descending and circumflex and for the circumflex and right coronary arteries. These types of experiments produced blood flows through a given collateral bed in two directions; for example, from the circumflex to anterior descending coronary arteries to allow \( R_{CA} \) to be determined and then from the anterior descending to circumflex coronary arteries to calculate the collateral resistance \( R_{AC} \). From the foregoing discussion it is apparent that the coronary vascular bed with its collateral connections could consist of nine resistances: the resistance of the anterior descending coronary bed, \( R_A \), the resistance of the circumflex bed, \( R_C \), and the resistance of the right coronary bed, \( R_R \), and the collateral resistances \( R_{CA} \), \( R_{AC} \), \( R_{CR} \), \( R_{RC} \), \( R_{AR} \), and \( R_{RA} \). To determine nine unknown resistances, nine independent equations must be obtained to allow a solution. From a set of the three double retrograde flow experiments nine independent equations can be written as shown in the Appendix. In summary, our experimental protocol, by taking advantage of the retrograde flow method developed by other investigators,\(^{14,15}\) allowed us to determine all coronary and collateral resistances without neglecting flow diversions to other vascular beds.

Between each double retrograde flow experiment the heart was allowed to recover; that is, coronary flows returned to control values when antegrade flows were reestablished (control experiment of Fig. 1). A set of three double retrograde flow experiments took an average of 5 minutes to complete. Several sets of experiments were usually done with good reproducibility, and the retrograde flows stabilized within 1 or 2 seconds to a new steady state level after the flow direction was changed. All data were recorded on a Hewlett-Packard model 7758A strip chart recorder and a Hewlett-Packard 3960 magnetic tape recorder. After termination of the experimental procedure the electromagnetic flow transducers were calibrated for blood flow, the hematocrit was obtained, and the heart was weighed. The pressure losses in the perfusion system and the retrograde flow system were determined as described earlier.\(^{6}\) Collateral resistances were calculated, as outlined in the Appendix, and corrected for a hematocrit of 40 vol \%.\(^{6}\)
Results

COLLATERAL RESISTANCES AS A FUNCTION OF PERFUSION DIRECTION

The resistances of the collateral vessels for the control group and 1- and 3-month circumflex occlusion groups are summarized in Table 2. Since the collateral resistances exhibited a logarithmic-normal distribution, the original data were transformed to natural logarithms before Student's t-tests were applied. When the collateral flow direction in control hearts was from the anterior descending to the circumflex coronary artery, the resistances \( R_{AC} \) [18.38 mm Hg/(ml/min)] were not significantly different from the collateral resistances \( R_{CA} \) (21.31) which were determined for a collateral flow direction from the circumflex to the anterior descending coronary artery \((P = 0.10, \text{ paired } t\)-test). However, the collateral resistance values \( R_{CR} \) (162.91) and \( R_{AC} \) (42.09) as well as \( R_{AR} \) (205.71) and \( R_{AR} \) (69.78) were significantly different \((P < 0.001)\), depending on the direction of blood flow through these collateral beds. In the group of dogs subjected to 1 month of Ameroid occlusion, the resistances \( R_{AC} \) (1.36), were significantly less than the resistances \( R_{CA} \) (1.82) determined during perfusion in the opposite direction \((P < 0.01)\). Similarly, the resistances \( R_{RC} \) (6.37) were significantly smaller than \( R_{CR} \) (172.06, \( P < 0.001)\), and resistances \( R_{RC} \) (13.84) were less than \( R_{AR} \) (216.68, \( P = 0.001)\).

The data of the 3-month Ameroid occlusion group did not show a significant difference between the resistances \( R_{AC} \) (1.17) and \( R_{CA} \) (1.92, \( P < 0.20)\). On the other hand, the resistances \( R_{RC} \) (3.88) were significantly less than the resistances determined for \( R_{CR} \) (77.47, \( P = 0.01)\). Similarly, \( R_{RA} \) (10.14) was significantly smaller than \( R_{AR} \) (168.26, \( P = 0.001)\).

In summary, when the collateral vessels were perfused from either one of the left coronary vessels to the right coronary artery, the resistances \( R_{AR} \) and \( R_{CR} \) were significantly larger than the resistances \( R_{RA} \) and \( R_{RC} \) when the perfusion direction was from the right to the left coronary arteries. However, there was no significant difference with directional changes of perfusion between the left coronary vessels \( R_{AC} \) and \( R_{CA} \) in the control and 3-month Ameroid groups.

CHANGES IN COLLATERAL RESISTANCES WITH LENGTH OF AMEROID OCCLUSION

The collateral resistances of the control group and 1- and 3-month Ameroid occlusion groups are plotted on a logarithmic scale vs. time in Figure 3. The upper section of Figure 3 shows a clear separation of data for collateral resistances \( R_{AR} \) and \( R_{CR} \) perfused from the left coronary vessels to the right coronary artery. In the group of dogs studied after 1 and 3 months of circumflex occlusion, \( R_{AR} \) showed no significant difference in collateral resistances compared to control when a nonpaired \( t\)-test was applied to these data \((P' = 0.20 \text{ and } P' = 0.55)\), respectively, as shown in Table 2). The collateral resistances \( R_{CR} \) for the 1-month occlusion group were not significantly different from control \((P' = 0.10)\), but were less for the 3-month Ameroid group \((P' = 0.05 \text{ relative to control})\). In comparison to the above changes occurring during perfusion from the left to the right heart, all collateral resistances during perfusion from the right to the left heart showed highly significant decreases in collateral resistance for the 1- and 3-month groups relative to control values. \( R_{RA} \) was 69.78 for control dogs, 13.84 for the 1-month group \((P' = 0.001 \text{ relative to control})\), and 10.14 for the 3-month

Table 2: Collateral Resistances

<table>
<thead>
<tr>
<th>Group</th>
<th>( R_{AC} )</th>
<th>( R_{CA} )</th>
<th>( R_{CR} )</th>
<th>( R_{RC} )</th>
<th>( R_{RA} )</th>
<th>( R_{AR} )</th>
</tr>
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<tbody>
<tr>
<td>Control (no. of dogs = 12; Hct = 41.6 ± 1.0; heart wt = 167.8 ± 8.0 g)</td>
<td>18.38</td>
<td>21.31</td>
<td>162.91</td>
<td>42.09</td>
<td>205.71</td>
<td>69.78</td>
</tr>
<tr>
<td>Average resistance (( \bar{x} ))</td>
<td>16.04-21.06</td>
<td>18.24-24.89</td>
<td>129.75-204.55</td>
<td>33.56-52.78</td>
<td>166.96-253.45</td>
<td>53.71-90.66</td>
</tr>
<tr>
<td>( P )</td>
<td>0.10</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<td>&lt;0.001</td>
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<tr>
<td>1-month Ameroid (no. of dogs = 12; Hct = 41.3 ± 1.4; heart wt = 166.0 ± 7.4 g)</td>
<td>1.36</td>
<td>1.82</td>
<td>172.06</td>
<td>6.37</td>
<td>216.68</td>
<td>13.84</td>
</tr>
<tr>
<td>Average resistance (( \bar{x} ))</td>
<td>1.23-1.50</td>
<td>1.66-2.00</td>
<td>101.07-292.90</td>
<td>4.92-8.24</td>
<td>141.59-331.60</td>
<td>12.14-15.78</td>
</tr>
<tr>
<td>( P )</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.10</td>
<td>&lt;0.001</td>
<td>0.20</td>
<td>0.001</td>
</tr>
<tr>
<td>3-month Ameroid (no. of dogs = 6; Hct = 36.8 ± 2.3; heart wt = 173.0 ± 4.8 g)</td>
<td>1.17</td>
<td>1.92</td>
<td>77.47</td>
<td>3.88</td>
<td>168.26</td>
<td>10.14</td>
</tr>
<tr>
<td>Average resistance (( \bar{x} ))</td>
<td>0.96-1.43</td>
<td>1.48-2.48</td>
<td>36.77-163.20</td>
<td>2.54-5.92</td>
<td>119.06-237.80</td>
<td>7.88-13.05</td>
</tr>
<tr>
<td>( P )</td>
<td>&lt;0.20</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
<td>&lt;0.001</td>
<td>0.55</td>
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See Table 1 for symbols.

\( \bar{x} \) = average resistance in mm Hg/(ml/min) corrected to a hematocrit of 40 vol %.

\* Average ± 1 SEM reconverted from logarithmic to original units. \( P \) values relative to control were obtained using the nonpaired Student’s \( t\)-test on logarithmic data.
Collateral resistances from the right to the circumflex coronary artery, $R_{RC}$, were 42.09 for control dogs, 6.37 for the 1-month occlusion group ($P' < 0.001$), and 3.88 for the 3-month group, which was significantly different from control ($P' < 0.001$). The lowest collateral resistances were observed between the circumflex and anterior descending coronary arteries, $R_{AC}$ and $R_{CA}$. These resistances were 21.31 and 18.38, respectively, for the control group and were significantly lower in the 1-month group (1.82 and 1.36, $P' < 0.001$). For the 3-month group, $R_{CA}$ was 1.92 and $R_{AC}$ was 1.17. Both resistances were significantly lower compared to control ($P' < 0.001$).

**Discussion**

In this study, we observed that the resistance to blood flow in the coronary collateral beds could be dependent on the direction of perfusion, and that with 1 and 3 months of Ameroid occlusion of the circumflex coronary artery, certain collateral resistances decreased significantly, that is, collateral flows increased. A certain pattern in collateral flows could be discerned such that the collateral beds leading toward the left heart experienced the largest increase in flow. Within the left ventricle, the lowest collateral resistance was from the anterior descending to the circumflex (the impaired vessel) coronary artery.

To our knowledge, a difference in coronary collateral resistances with direction of perfusion has not been observed. However, a possible explanation for this difference in resistance was suggested when we studied vinyl casts of the coronary and its collateral vessels. Consider a parent vessel with a single branch, shown in Figure 4, and with a flow direction from A to B. Blood entering at A would experience a relatively low resistance path to both B and C (solid line). Blood flow leaving B would be determined by the diameter of the parent and branch vessels and its angle to the parent vessel.16-17 When blood enters at B (dotted line) and arrives at the branch vessel, flow would have to be directed at an acute angle to arrive at C.

Such blood flow would experience a large resistance in the direction of the branch, and the path of lowest resistance would be through the parent vessel to A. To further test the possibility of the influence of geometrical configurations on the resistance to blood flow, a tubing system consisting of a main trunk with five branches was constructed. When the main trunk was perfused first in one direction and then in the opposite direction a 10-fold change in flow rate was observed.

From casts we had obtained of the coronary vessels of hearts with prolonged Ameroid constriction, it was evident that collaterals between the anterior descending and circumflex connect in an almost U-shaped fashion across the apex and at higher levels.1,2 This anatomical symmetry

![Figure 4 Model of a parent vessel with a branch indicating the blood flow pathways when the parent vessel is perfused from A to B (solid line), and from B to A (dashed line).](image)
of intercoronary collateralization between the left coronaries may be responsible for the relative identical values of \( R_{AC} \) and \( R_{CA} \) (Table 2 and Fig. 3). The same kind of anatomical symmetry, however, does not exist between collaterals which connect between the right and circumflex, or right and anterior descending coronary arteries. These connections are often tortuous, with small diameters and many branches,\(^{18,19} \) and could account for the differences in resistance to blood flow with directional flow changes.

Ameroid occlusion of the circumflex coronary artery has a profound effect on the growth of intercoronary collateral vessels.\(^{1,2} \) The methods and analysis used in this study have added further definition of the behavior of individual collateral beds and have allowed the recognition of a certain growth pattern of collateral vessels. From Figure 3 it can be seen that marked decreases in collateral resistances occur in those collaterals (\( R_{RA} \) and \( R_{RC} \)) leading toward the left ventricle, that is, the hypoxic area, while resistances of the collateral beds from the left to the right heart (\( R_{AR} \) and \( R_{RC} \)) were initially high and did not undergo the same decrease in resistance. It was also shown that (within the left ventricle) collateral resistances between the circumflex and anterior descending coronary arteries had the lowest values (Fig. 3). At 1 month of Ameroid occlusion the resistance from anterior descending to circumflex, \( R_{AC} \), was significantly lower than \( R_{CA} \). This result seems to indicate that the main hypoxic stimulus is from the circumflex vascular bed, which is the vessel that had been subjected to Ameroid occlusion.

Although most of the results of this study could be explained by a pressure gradient hypothesis,\(^{8} \) inspection of Figure 3 shows that the resistance \( R_{RA} \), which connects between the right and anterior descending coronary arteries, decreases significantly with length of Ameroid occlusion. There is, however, no pressure difference between these vessels to account for the marked increase in collateral growth. In light of these results and prior studies\(^{8,10} \) it seems even more appropriate to think of vascular growth occurring along a hypoxic gradient, but the question whether the stimulus is the lack of oxygen per se, the accumulation of metabolic end products, or the release of some yet unknown hormone by injured tissue remains to be answered.

**Appendix**

To obtain a solution for the nine unknown resistances of Figure 1, nine independent equations must be written. These resistances are the three coronary resistances, \( R_{A} \), \( R_{C} \), and \( R_{R} \), and the six collateral resistances, \( R_{AC} \), \( R_{CA} \), \( R_{RA} \), \( R_{AR} \), \( R_{RC} \), and \( R_{RC} \). The following equations were derived in terms of the measured flows \( F_{AX} \), \( F_{CX} \), and \( F_{RX} \) utilizing "Kirchhoff's current law." Each double retrograde flow experiment yields three equations. Thus, for the double retrograde flow experiment in which the retrograde flows were measured on the anterior descending and circumflex coronary arteries and a pressure relationship in which \( P_{A} > P_{C} > P_{R} \), the following equations were obtained:

\[
F_{AX} = P_{A} \frac{1}{R_{A}} + (P_{A} - P_{R}) \frac{1}{R_{AR}} + (P_{C} - P_{A}) \frac{1}{R_{AC}}, \quad (1)
\]

\[
F_{CX} = P_{C} \frac{1}{R_{C}} + (P_{C} - P_{A}) \frac{1}{R_{CR}} + (P_{C} - P_{R}) \frac{1}{R_{RC}}. \quad (2)
\]

\[
F_{RX} = P_{R} \frac{1}{R_{R}} + (P_{R} - P_{A}) \frac{1}{R_{RA}} + (P_{R} - P_{C}) \frac{1}{R_{RC}}. \quad (3)
\]

The pressures \( P_{A} \), \( P_{C} \), and \( P_{R} \) were the pressures at the tips of the respective coronary cannulas. These were experimentally obtained and depend on the perfusion systems and the hematocrit of blood.\(^{9} \) For the double retrograde experiment in which the retrograde flows were measured on the anterior descending and circumflex coronary arteries and a pressure relationship in which \( P_{A} > P_{C} > P_{R} \), the following equations were obtained:

\[
F_{AX} = P_{A} \frac{1}{R_{A}} + (P_{A} - P_{C}) \frac{1}{R_{AC}} + (P_{A} - P_{R}) \frac{1}{R_{RA}}. \quad (4)
\]

\[
F_{CX} = P_{C} \frac{1}{R_{C}} + (P_{C} - P_{A}) \frac{1}{R_{CR}} + (P_{C} - P_{R}) \frac{1}{R_{RC}}. \quad (5)
\]

\[
F_{RX} = P_{R} \frac{1}{R_{R}} + (P_{R} - P_{A}) \frac{1}{R_{RA}} + (P_{R} - P_{C}) \frac{1}{R_{RC}}. \quad (6)
\]

Similarly, for a double retrograde flow on the circumflex and right coronary arteries, and a pressure relationship in which \( P_{A} > P_{C} > P_{R} \), the final three equations were obtained:

\[
F_{AX} = P_{A} \frac{1}{R_{A}} + (P_{A} - P_{C}) \frac{1}{R_{AC}} + (P_{A} - P_{R}) \frac{1}{R_{RA}}. \quad (7)
\]

\[
F_{CX} = P_{C} \frac{1}{R_{C}} + (P_{C} - P_{A}) \frac{1}{R_{CR}} + (P_{C} - P_{R}) \frac{1}{R_{RC}}. \quad (8)
\]

\[
F_{RX} = P_{R} \frac{1}{R_{R}} + (P_{R} - P_{A}) \frac{1}{R_{RA}} + (P_{R} - P_{C}) \frac{1}{R_{RC}}. \quad (9)
\]

These nine equations were solved for the nine unknown resistances by matrix techniques with a PDP-7 digital computer.

**References**

Effects of Adrenergic Amines on Electrophysiological Properties and Automaticity of Neonatal and Adult Canine Purkinje Fibers

Evidence for α- and β-Adrenergic Actions

MICHAEL R. ROSEN, ALLAN J. HORDOF, JOSEPH P. ILVENTO, AND PETER DANILIO, JR.

With the assistance of Kathy J. Slavin

SUMMARY We determined age-related differences in automaticity and responsiveness of cardiac Purkinje fibers from adult and neonatal dogs to graded concentrations of epinephrine, isoproterenol, and phenylephrine. Purkinje fibers were studied with standard microelectrode techniques during superfusion with Tyrode's solution at 37°C. Control spontaneous rates for adults and neonates did not differ significantly. There was a biphasic response to all agonists such that rate decreased at low and increased at high concentrations. The decrease was greater with phenylephrine and epinephrine than with isoproterenol. The increase in rate was greater with isoproterenol and epinephrine than with phenylephrine. Propranolol shifted the dose-response curves downward and to the right for all agonists; phentolamine, shifted the curves upward and to the left. Epinephrine and isoproterenol dose-response curves for the neonates were upward and to the left of those for adults. Phenylephrine curves were identical for adults and neonates. Thus there are α- and β-adrenergic effects on Purkinje fiber automaticity; the former decrease and the latter increase rate. Furthermore, the effects on automaticity of β-adrenergic amines are greater in the neonates than in the adult.

In the present study we determined the effects of adrenergic amines on automaticity and action potential (AP) characteristics of Purkinje fibers from neonatal and adult dogs. A number of recent studies have indicated that adrenergic amines have α and β agonistic effects on cardiac fibers. Ledda et al.1 showed that phenylephrine, which has a high ratio of α to β agonistic activity, increases AP duration of sheep Purkinje fibers. Giotta et al.2 observed that isoproterenol decreases the duration of the Purkinje fiber AP, an action blocked by propranolol but not by phentolamine. They also found that norepinephrine decreases AP duration in the presence of phentolamine and increases AP duration in the presence of propranolol. These results led the authors to suggest that prolongation of the AP duration is an α-adrenergic effect and that its shortening is a β-adrenergic effect.3

In 1971 Posner and Vassalle4 and Vassalle and Bnabale5 reported that low concentrations of norepinephrine decrease 42K uptake by canine Purkinje fibers but higher concentrations increase 42K uptake. They concluded that the reduction of the K+ uptake at low norepinephrine concentrations is an α-adrenergic function mediated through depression of the Na+-K+ exchange pump. Stafford,6 in studies of rabbit atria, found epinephrine to increase 42K uptake; this action was blocked by dichloroisoproterenol but not by phenoxbenzamine. This study suggested that the epinephrine-induced increase in K+ flux is mediated by the activation of the β-receptor. Blinks6,7 showed that epinephrine, isoproterenol, and norepinephrine induce a concentration-dependent increase in automaticity of feline atria, and Hoffman and Singer8 reported that epinephrine increases the slope of phase 4 depolarization of canine Purkinje fibers and results in enhanced automaticity. Posner et al.9 reported that low concentrations of epinephrine decrease Purkinje fiber automaticity and K+ uptake, and that higher concentrations increase automaticity and K+ uptake. The former effect, which was blocked by phentolamine, was interpreted as an α-adrenergic and the latter as a β-adrenergic effect.

From the Departments of Pharmacology and Pediatrics, Columbia University College of Physicians and Surgeons, New York, New York.

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K W Scheel, R J Rodriguez and L A Ingram

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