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The Transmural Distribution of Coronary Blood Flow During Maximal Vasodilation[1] (39000)

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(Introduced by Carleton H. Baker)

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During systole intramyocardial stresses compress the coronary arteries severely limiting blood flow to the subendocardium (1). Because of the high compression in that tissue it is particularly vulnerable to ischemia in the presence of coronary artery disease (2). However, some anatomical safeguards may be present in the heart that act to ensure that subendocardium receives an adequate blood supply. Estes *et al.* noted that patients with coronary artery disease had a well-developed vascular plexus in the subendocardium which was lacking elsewhere in the heart (3). Though such a plexus has not been described in the canine, the subendocardium has been reported to have a greater vascular volume than subepicardial regions in the dog's heart (4). These findings suggest that there is a greater vascular density in the subendocardium which is compensatory of its systolic compression. To investigate this possibility further the transmural distribution of the coronary flow was examined in arrested hearts whose coronary arteries were dilated to the maximum. This distribution was measured by examining the uptake of arterially introduced ^{42}K or ^{86}Rb, blood flow indicators (5).

Methods. Three series of experiments were conducted. Mongrel dogs of either sex ranging between 10 and 20 kg were used. All dogs were initially anesthetized with 30 mg/kg sodium pentobarbital intravenously and additional anesthesia was administered as required. Using electrocautery to promote hemostasis, the hearts were exposed by a left thoracotomy in the fourth intercostal space. Ventilation with 100% O_2 was maintained with a positive pressure respirator. Five hundred units per kilogram of heparin were administered intravenously to prevent clotting in the perfusion tubing. The main left coronary artery was cannulated with the perfusion system shown in Fig. 1. Arterial blood entered the tubing from a carotid artery. The tubing was arranged so that flow could be controlled with a peristaltic pump if required. A branch of the tubing went to the side arm of a 1-liter bottle which could be pressurized with the aid of a squeeze bulb. A mercury manometer measured pressure in the bottle and a magnetic stirrer kept the blood within in suspension. Flow through the coronary cannula was monitored by a Biotronix sine wave electromagnetic flowmeter. To reduce circulatory reflexes all animals received a bilateral cervical vagotomy.

Group I. In this series left ventricular stresses were minimized by arresting the heart and the transmural distribution of the coronary flow during reactive hyperemia and with normal perfusion pressure was determined. Five dogs were used in this series.

Stimulating electrodes were placed on the distal ends of the cut vagi. Stimulus was a 50-V 30-cps square wave. A snare was placed around the pulmonary artery to inhibit venous return to the arrested left ventricle.

First the reservoir was filled with about 200 ml of blood; then the bottle's outflow was occluded with a clamp and it was pressurized to 100 mm Hg. The coronary arteries were then caused to dilate by occluding the tubing to the carotid artery thus stopping coronary flow. At this time 0.1–0.2 ml of ^{42}KCl in saline were injected into the perfusion line near the coronary canula. After 10–15 sec of stopped flow the clamp on the branch to the

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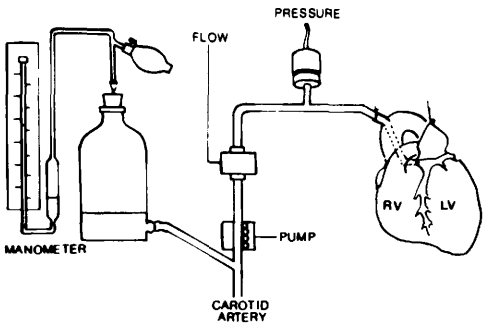

FIG. 1. Diagram of the perfusion system used for these experiments. See methods for details.

reservoir was removed, the vagus nerves stimulated, and the pulmonary snare was drawn tight. Seven to ten seconds of arrest were achieved before the first escape beats occurred. Thus, the isotope was carried into the coronary circulation while the heart was arrested and experiencing a reactive hyperemia.

Perfusion continued from the bottle for 30 sec after which the heart was quickly removed from the dog by cutting the vessels at the base of the heart. Each excised heart was rinsed under tap water. The atria and free wall of the right ventricle were removed and the remaining left ventricle was placed in a freezer. When the tissue had frozen solid, sections were cut from the posterior and anterior apex and the posterior and anterior base, each being approximately 1.5 cm square and having the full thickness of the ventricular wall. These four pieces were in turn sliced into four layers from the epicardium to the endocardium. Thus, four myocardial depths were sampled from four locations on the left ventricle. Each of the 16 samples were weighed to the nearest mg and deposited into a test tube containing 3 ml of nitric acid. When the samples were completely digested to insure a uniform, geometry, they were counted in a well-type scintillation detector.

The count rate for each sample was corrected for decay and background. The corrected count rate was then divided by the sample weight to yield an activity per gram. Since no consistent differences were seen between the regions sampled, all of the data were pooled and analyzed only with respect to myocardial depth. The data were normalized by dividing the activity of each sample by the activity of the entire transmural section from which it came. The average activity of four samples representing each depth was calculated for each heart. Then the means and standard errors of these average activities were determined for each depth with an N equal to the number of hearts studied.

Group II. In this series the hearts were arrested again, but this time the coronary flow rate was maintained at the control rate with the aid of a peristaltic pump and maximal dilation was achieved by pharmacologic means rather than a reactive hypermia. Two dogs were subject to this protocol.

The preparation was exactly the same as for Group I. The procedure was as follows. The pump was set to deliver a flow which was equal to the autoperfused rate. The coronary artery was then perfused with the pump. About 200 cc of blood was allowed to fill the reservoir. The tubing from the carotid artery was then occluded and the branch from the reservoir opened so that the pump perfused the coronary artery with blood from the reservoir. 60 μg of adenosine was injected into the coronary artery to produce a maximal dilation, the snare on the pulmonary artery was drawn tight, the vagus nerves stimulated, and 0.1–0.2 ml ^{86}RbCl in saline was injected into the tubing near the coronary cannula. After 30 sec of perfusion the hearts were removed and analyzed as described in Group I.

Group III. In this series the effect of systole on the dilated coronary bed was examined. In order to maximize intramyocardial stresses, the hearts were paced to the highest rates they would consistently follow. The preparation again was the same as used in Group I except that a pacing electrode was placed on the free wall of the right ventricle. Three volt, 40 msec pulses were applied between an alligator clip on the left atrium and electrode. A rate of 200 beats/min was chosen. Five dogs were examined.

In this procedure the hearts were paced to tachycardia while being autoperfused through the carotid artery branch. The pump was

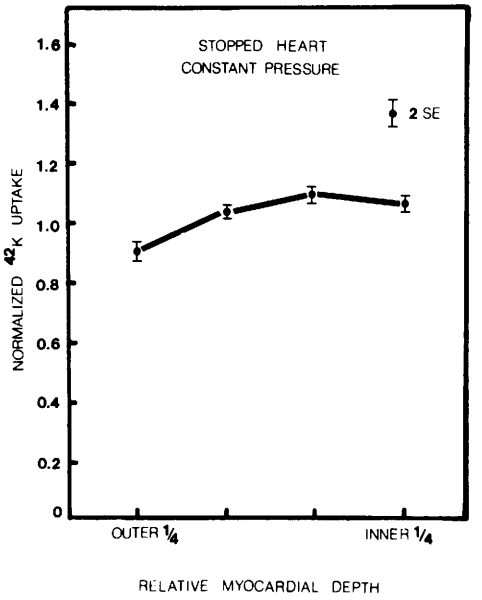

FIG. 2. The distribution of coronary blood flow across the ventricular wall of the stopped heart as indicated by the uptake of ^{42}K. The coronary arteries were maximally dilated by reactive hyperemia and perfusion pressure was held constant. A flow gradient is indicated which favors the subendocardium.

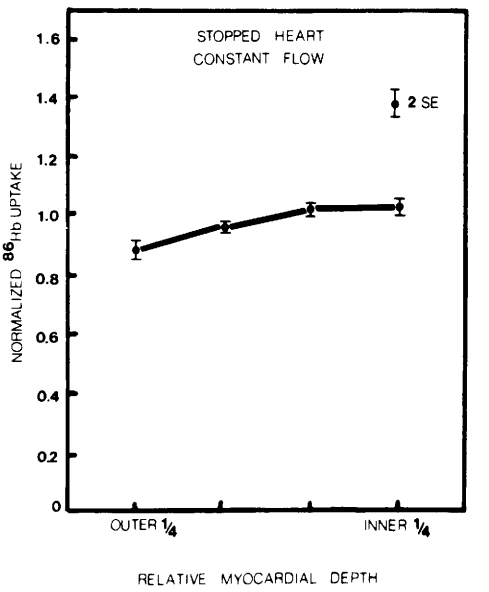

FIG. 3. The distribution of coronary blood flow across the ventricular wall of the stopped heart as indicated by the uptake of ^{86}Rb. Adenosine was used to maximally dilate the coronary arteries while inflow rate was held constant with a pump. A flow gradient identical to that in Fig. 2 is seen.

not used for this series. The reservoir was again filled with about 200 cc of blood and pressurized to 100 mmHg. A clamp was placed on the carotid artery branch interrupting the perfusion and ^{42}KCl as in Group I was injected into the tubing. After 10 sec of occlusion the clamp on the branch from the reservoir was removed and the heart was perfused from the reservoir for 30 sec. The hearts were then removed and analyzed as described in Group I.

Results. Group I. These animals experienced vasodilation induced by 10 seconds of occlusion accompanied by vagal arrest. The distribution of isotope under these conditions appears in Fig. 2. Since the local uptake of ^{86}Rb or ^{42}K is primarily limited by flow these distributions can be interpreted to be in proportion to local blood flow (5). The results indicate that the subendocardium received about 20% more flow than the subepicardium.

Group II. This series was performed to test for possible artifacts in the protocol for Group I. Because the isotope's extraction rate declines with increasing flow rates (6), differences in flow tend to be underestimated by this technique. The resulting error at normal flow rates is small but at higher flow rates it can become appreciable. The high flow rate associated with maximal dilation and constant pressure perfusion was, therefore, avoided by maintaining flow at the control rate with a pump. Also since it is debatable whether 10 sec of total occlusion can induce a maximal dilation, pharmacologic means were employed to achieve this state. Fig. 3 shows the results of these experiments. Again a gradient of flow favoring the subendocardium is seen which is similar to that from Group I. Since this series was of a confirmatory nature, only two dogs were studied. Accordingly the standard errors for Fig. 4 are calculated for an N of 8 representing the total number of samples examined for each depth.

Group III. In this series the effect of systole on the transmural distribution of blood flow in the maximally dilated heart was examined. The effect of systole was maximized by pacing the heart to tachycardia. Since increases in rate are primarily at the expense of the dias-

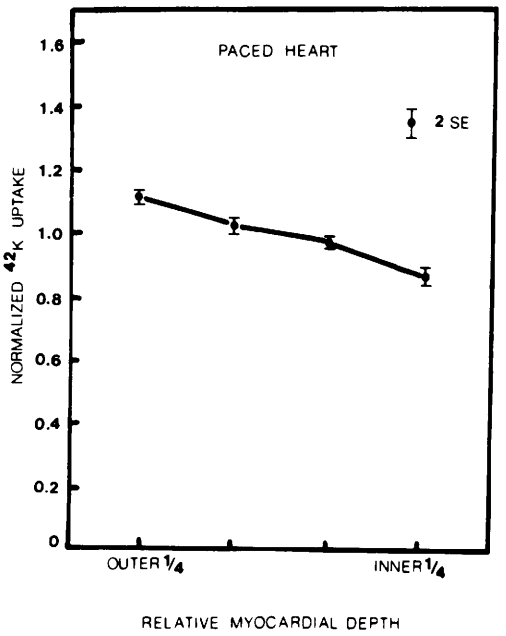

FIG. 4. The distribution of the coronary blood flow across the ventricular wall of hearts paced to tachycardia as indicated by the uptake of ^{42}K. The coronary arteries were maximally dilated by reactive hyperemia and perfusion pressure was held constant. A flow gradient favoring the epicardium is seen in these hearts.

tolic period these paced hearts were spending a greater percentage of their cardiac cycle in systole.

Figure 4 shows that the gradient experienced in Groups I and II during arrest is reversed in the presence of tachycardia. In these hearts the subendocardium experienced about 20% less blood flow than the subepicardium.

Discussion. In the heart the effect of contraction is to selectively inhibit blood flow to the innermost layers of the ventricular wall (1). This is the result of an elevated tissue pressure associated with systole (7). In the normal heart the flow deficit experienced at the subendocardium during systole is compensated by a hyperemia during diastole. This causes the average flow over the entire cardiac cycle to be uniformly distributed across the wall (2, 8, 9). This hyperemia is thought to be effected by a gradient of vascular resistance across the heart wall which opposes the tissue pressure gradient (10). The present experiments indicate that this gradient of vascular resistance persists when the coronary arteries are maximally dilated. Whether the coronary vessels were actually dilated to the maximum in Groups I and II is, of course, central to this conclusion. In each of these experiments varying periods of occlusion were tested prior to the actual measurement. Periods of occlusion in excess of 10 sec did not result in any further decrease in coronary resistance. Coffman and Gregg report that the hyperemia in a branch of the left coronary artery is still influenced by the duration of the occlusion period when it exceeds 90 sec (11). Though occlusion of a coronary artery branch may not produce as severe an ischemic insult as occlusion of the entire vessel since collateral flow is still present in the former, their results would suggest that some further dilation may have been possible. Unfortunately, we could not examine extended periods of occlusion since more than 20 sec of occlusion usually depressed cardiac function to the point that blood pressure fell. Therefore, adenosine, a powerful coronary dilator (12), was substituted for occlusion in Group II. Adenosine in the dose employed produces a dilation whose magnitude is dose independent. Since the uptake of isotope in these animals revealed a flow pattern identical to that in Group I we conclude that 10 sec of total occlusion produces a dilation which is either maximal or one whose residual dilatory reserve is equal at all depths of the myocardium.

The subendocardium has been found to be particularly vulnerable to ischemia when a major coronary artery is partially occluded (2). Moir (13) hypothesizes that autoregulation dilates the coronary vessels to their maximum, removing the gradient of vascular resistance which compensates blood flow to the subendocardium during diastole. Thus, the gradient of flow away from the subendocardium during systole becomes unopposed and preferential ischemia of the subendocardium during systole becomes unopposed and preferential ischemia of the subendocardium is the result. Such a hypothesis implies a near uniform distribution of vascular resistance once tone has been abolished which is not compatible with the present

findings. Furthermore, evidence indicates that the gradient in resistance which we have demonstrated in the maximally dilated state is of a sufficient magnitude to completely compensate the flow gradient occuring in systole. If that were not the case, maximal dilation alone in the normally beating heart should result in a gradient of flow which favors the epicardium. Such a condition has not been found. Cutarelli and Levy perfused the circumflex coronary artery in dogs using ^{86}Rb as a flow indicator following 2–3 min of occlusion. Such a period of arrested flow should have unequivocally dilated the vessels to their maximum (11). Yet the transmural distribution of the indicator was essentially uniform (14). Moir also found flow to be uniformly distributed when the coronary arteries of beating hearts were dilated with dipyridamole (10). The present data (Group III) indicate that only when time spent in diastole is greatly reduced, in this case by tachycardia, will the gradient of resistance present with maximal dilation fail to compensate the systolic gradient of flow. Clearly then, the process whereby partial occlusion of a coronary artery selectively reduces perfusion of the subendocardium is more complex than previously thought.

The factors that promote growth of blood vessels are not well understood, but evidence indicates that circumferential stress in the vessel wall is a factor. Thus, a vessel that is caused to dilate for long periods, increasing its circumferential stress through the Laplace relationship should undergo cell division and growth (15). Such a theory could explain our finding of an increased vascularity in the subendocardium. A compensatory dilation experienced by the subendocardial vessels in the developing heart would eventually result in increased subendocardial vascular development in the adult. Estes reports that patients with longstanding coronary insufficiency have a well-developed subendocardial plexus (3). This may simply be an extension of the physiologic vascular gradient resulting from even further dilation of these vessels with impending subendocardial ischemia.

Summary. Experiments were performed to examine the transmural distribution of the coronary blood flow during maximal vasodilation and when intramyocardial pressures were either minimized (cardiac arrest) or maximized (tachycardia). The results reveal a gradient of vascular resistance across the ventricular wall that favors flow to the subendocardium in the presence of maximal vasodilation. Thus a flow gradient favoring the subendocardium was seen when intramyocardial pressures were minimized by cardiac arrest, but when tissue pressures were maximized through tachycardia this gradient of flow was reversed.

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