Intraventricular Pressure and the Distribution of Coronary Blood Flow

By Renato Cutarelli, M.D., and Matthew N. Levy, M.D.

With the assistance of Harrison Zieske, Jr., and Geraldine Nelson

In both clinical and experimental conditions, the effects of coronary occlusion upon the endocardial and epicardial halves of the myocardium are known to be different. In a review of autopsy cases, it was found that infarcts not associated with demonstrable acute coronary occlusion are localized to the subendocardial portion of the myocardium. On the other hand, in the same series, it was observed that even in acute transmural infarctions, the necrosis is more extensive in the inner two-thirds of the myocardium than in the subepicardial region. Others have also observed that myocardial infarctions are more extensive in the subendocardial zone. In addition, subendocardial infarctions heal less rapidly than those in the center of the myocardium or beneath the endocardium.

Experimentally, the necrosis following ligation of a coronary artery in the dog has been found to appear earlier and to be more extensive in the subendocardial than in the subepicardial region. In another study, the area of infarction in the subendocardial region in experimental coronary occlusion has been better defined than, although of similar size to, that in the subepicardial zone.

One of the mechanisms most frequently proffered to explain the differences between these two layers of the myocardium in coronary occlusion is the effect of intraventricular pressure upon the distribution of blood in the inner and outer layers of myocardium. In order to test this hypothesis, a radioactive isotope of rubidium, Rb86, has been used to determine coronary flow. The uptake of Rb86 by the subendocardial and subepicardial halves of the canine myocardium has been compared at different intraventricular pressure levels.

Methods

Three series of experiments were conducted on a total of 105 mongrel dogs (6.3 to 15.6 kg). All animals were anesthetized with iv sodium pentobarbital (30 mg/kg). Artificial respiration was instituted and the chest opened through the fourth left intercostal space. Heparin (3 mg/kg) was given iv to prevent blood coagulation.

The first series included 20 dogs, divided into four groups, according to the level of mean arterial pressure which was maintained. In each experiment, the left circumflex coronary artery was isolated about one cm before the origin of the ramus marginis obtusus. A carotid artery was cannulated and connected to a blood reservoir. By adjusting the height of the reservoir, it was possible to maintain the mean arterial pressure at 40 mm Hg (seven animals) or 100 mm Hg (seven animals). In seven other animals, the descending thoracic aorta was ligated, in order to raise the pressure to levels well above 100 mm Hg (mean, 158.8). These different pressure levels were produced in a rotating sequence. Eight animals developed ventricular fibrillation during coronary artery cannulation.

Immediately after ligation of the left circumflex coronary artery, the distal end was cannulated. Immediately after the time of the ligation, perfusion with arterial blood containing 5 μc of Rb86Cl (specific activity, 1.85 mci/mg) was begun from an elevated reservoir. In all experiments, the perfusion reservoir was maintained at a constant height equivalent to a hydrostatic pressure of 100 mm Hg. At the end of the perfusion, ventricular fibrillation was induced electrically. The heart was immediately removed, washed under running water, and blotted dry. The region of the myocardium between the ramus marginis obtusus and the posterior descending branch was excised. Three samples were taken from this area; a basal, a central, and an apical specimen. Each sample was then divided into inner and outer halves, and each specimen was placed in a previously tared lusteroid tube and weighed. The Rb86 content of an aliquot of the
infused blood and of the tissue specimens was determined in a well-type scintillation detector, and the isotope content of each sample was expressed as counts/min per g.

The second series included 37 animals. Of those, 12 fibrillated spontaneously after coronary occlusion and were not subjected to further study. The remaining 25 dogs were divided into three groups in a rotating sequence, according to the mean arterial pressure maintained: 40 ± 0.100 ± 0, and 151.8 ± 6.3 (SD) mm Hg. The procedure was identical to that used in the first series, except that the left circumflex vascular bed was not perfused with arterial blood after the vessel itself had been ligated. Instead, the Rb86 (150 µg in 30 ml 0.9% saline) was administered via the superior vena cava by means of a constant rate syringe, approximately two or three minutes after the circumflex artery had been ligated. The infusion lasted precisely two minutes, at the end of which time ventricular fibrillation was induced. Arterial blood samples were drawn at seven points in time during this infusion to permit calculation of the myocardial clearance of Rb86, as described previously.

The third series included the remaining 27 dogs. This time, ventricular fibrillation was initiated prior to the infusion of Rb86. The infusion was made from a reservoir at a constant height equivalent to 100 mm Hg into the distal end of the ligated circumflex coronary artery. In nine animals, the intraventricular pressure during the infusion was the prevailing pressure in the fibrillating heart, namely, 4.7 ± 2.6 (SD) mm Hg. In the other dogs, the intraventricular pressure was raised by connecting an elevated reservoir of isotonic saline to the left ventricular chamber via a large bore needle inserted through the apex. The ascending aorta was ligated and the pulmonary veins were occluded by ligating securely the roots of both lungs. The anterior descending and right coronary arteries also were ligated near their origins. In nine experiments, the intraventricular pressure was adjusted to 16.3 ± 0.9 mm Hg and, in the remaining nine, to 26.4 ± 2.7 mm Hg.

**Results**

The object of the first series of experiments was to determine whether the distribution of blood flow to the subepicardial and subendocardial regions of the heart would be altered by changes in intraventricular pressure when flow was delivered via the normal channels. To accomplish this, the level of blood pressure was varied in the four groups comprising this series. In the first group, the infusion was made while the heart was fibrillating ("F" in fig. 1). In the second, third, and fourth groups, the mean arterial pressure was adjusted to levels of 40 ± 0, 101 ± 3 and 159 ± 4 mm Hg (mean ± 80) respectively. Thus it is clear that intraventricular systolic pressures were varied over a wide range of values related to the levels of the mean arterial pressure. Actual recordings of intraventricular pressures were not obtained in these experiments, however.

The mean Rb86 content was determined for the three subepicardial and the three subendocardial samples taken from the posterior left ventricular myocardium in each experiment. The ratios of the mean content of the subepicardial to that of the subendocardial specimens were then computed. The geometrical means (computed logarithmically) of these ratios (expressed as per cent) were calculated for each group. As figure 1 shows, the means of each group did not vary significantly from 100%, or from each other (P > 0.10 by the analysis of variance). In other words, in this series, the subepicardial-subendocardial ratio of Rb86 contents was not affected to any ap-
preciable extent by changes in intraventricular pressure.

In the second series of experiments, Rb\textsuperscript{86} was injected into the superior vena cava after the left circumflex coronary artery had been ligated. Therefore, the Rb\textsuperscript{86} present in the area ordinarily supplied by this artery must have been delivered via the collateral vessels. In the normal zone, adjacent to the anterior descending coronary artery, the mean Rb\textsuperscript{86} clearances for the entire thickness of the myocardium were 31.2, 60.3, and 76.4 ml/min per 100 g tissue for the 40, 100, and 152 mm Hg pressure groups, respectively. The corresponding mean clearances for the ischemic posterior ventricular myocardium were 9.0, 20.8, and 32.4 ml/min per 100 g, respectively. These clearance values represent approximately the same fraction of the values in the normal zone as were reported in a previous study.\textsuperscript{15} Also, the observation of a progressive increase in collateral circulation (as assessed by the Rb\textsuperscript{86} clearances in the ischemic zone) as a function of mean arterial pressure confirms the findings of Kattus and Gregg,\textsuperscript{16} which were obtained by the retrograde flow technic.

The purpose of the second series of experiments was to determine whether collateral blood flow to the subendocardial and subepicardial layers of the region affected by coronary occlusion would be influenced by changes in intraventricular pressure. The results depicted in figure 2 show that the ratio of subepicardial to subendocardial Rb\textsuperscript{86} contents is definitely altered by an increase in intraventricular pressure. Indeed, in the 152 mm Hg pressure group, the ratio of Rb\textsuperscript{86} content of subepicardial to subendocardial layers is significantly above 100\% (\(P = 0.005\)), and is also significantly different from the mean value for the 40 mm Hg pressure group (\(P = 0.005\)). Also, by the analysis of variance, the groups are significantly different (\(P = 0.025\)).

In the third series of experiments, Rb\textsuperscript{86} in arterial blood was infused directly into the distal end of the ligated circumflex coronary artery, as in the first series. However, unlike the first series, the myocardium was not normally beating, but ventricular fibrillation had been induced prior to the infusion. The geometrical mean of the ratios of epicardial to endocardial Rb\textsuperscript{86} contents was computed for...
the three levels of intraventricular pressure. It is evident from figure 3 that the mean ratio was significantly different ($P = 0.02$) from 100% in the third group. Furthermore, the mean of the third group was also significantly different ($P = 0.05$) from the mean of the first group.

**Discussion**

The rate of uptake of Rb$^{86}$ by an area of myocardium is dependent upon rate of blood flow to the region, and upon the rate of capillary exchange of the isotope. It has previously been reported that the clearance of Rb$^{86}$ is equal in the inner and outer thirds of the normal myocardium, and the clearance of the middle third is only slightly higher. In our study, the myocardium was divided in two approximately equal halves, so that the higher uptake by the middle third is probably equally represented in the subendocardial and subepicardial specimens. Since the rate of capillary exchange of Rb$^{86}$ in the samples from the two layers is probably equal, their Rb$^{86}$ contents will depend largely upon the rate of coronary blood flow delivered to both layers.

In the first series, Rb$^{86}$ was mixed with arterial blood and perfused into the cognate vessel (left circumflex artery) at a pressure of 100 mm Hg. Undoubtedly, this was adequate to maintain a normal, or nearly normal, contraction in the myocardium supplied by that artery. Under these conditions, Rb$^{86}$ uptake by the inner and outer halves of the myocardium was not significantly different, nor was this influenced by the level of intraventricular pressure (fig. 1).

In the second series of experiments, on the other hand, the intraventricular pressure exerted a pronounced effect upon the distribution of Rb$^{86}$ between the inner and outer halves of the myocardium in the region ordinarily supplied by the left circumflex artery (fig. 2). Any deviation from unity in the ratios of Rb$^{86}$ uptake in the two layers of myocardium is probably indicative of at least equivalent, or probably somewhat greater, deviations in the ratios of blood flows to these regions, because of the inverse relationship which exists between extraction and blood flow.$^{10,18}$

Experimentally, there are two major features which distinguish the second series from the first: (1), the absolute rate of blood flow to the posterior left ventricular myocardium was considerably less in the second series, and (2), the Rb$^{86}$ which reached this region was delivered by collateral rather than by the cognate vascular channels. Relative to the first of these features, it has been demonstrated that within seconds after ligation of a major coronary artery, the affected myocardium will cease contracting normally and will actually bulge during systole.$^{19}$ In the second series, therefore, the alteration in distribution of blood flow evoked by higher intraventricular pressures may be attributable either to its effects upon the non-contracting myocardium, or to its influence upon collateral rather than cognate channels.

The third series of experiments was conducted to distinguish between these major alternatives. In these experiments, the effects of variations in intraventricular pressure upon blood flow distribution through the cognate channels was ascertained in the non-beating heart. Figure 3 demonstrates that, at higher intraventricular pressures, the ratio of subepicardial to subendocardial Rb$^{86}$ uptake increases. In these experiments, much lower pressure levels were employed than in the first two series. However, these intraventricular pressures were applied continually, whereas the intraventricular pressures in the first two series were exerted only during the systolic phase of the cardiac cycle. Since the isotope ratios did vary as a function of intraventricular pressure in the third series, and since the isotope was infused through the cognate channels, it would appear that the intraluminal pressure does not exert its influence only upon collateral channels. By exclusion, therefore, it may be deduced that intraventricular pressure alters the distribution of blood flow in the non-beating heart, or in non-beating regions of the contracting myocardium.

In the normally beating heart, the intra-
myocardial pressure at any point is a function of the active tension exerted by the myocardial fibers in the neighborhood of that point, as well as of the intraluminal pressure. It has been reported that intramural pressure in the subepicardial region is less than that in the subendocardial layer. According to Johnson and di Palma, intramural pressure exceeds intraluminal pressure at all depths in the normal myocardium. According to Laszt and Müller, on the other hand, the intramyocardial pressure is less than the peak intraventricular pressure. Even in the more superficial layers of the myocardium, however, it is likely that intramural pressures exceed the hydrostatic pressure in the capillaries. Therefore, it is likely that capillary blood flow will be impeded to approximately similar degree during systole at all intramural levels in the normally beating heart. This would account for the observed ratios approximating unity (fig. 1). In a non-beating, ischemic zone produced by acute coronary artery occlusion, the myocardial fibers would be expected to behave more like passive elastic elements. The gradient of intramural pressures from the endocardial to the epicardial surface would undoubtedly be altered. It may be postulated that this altered gradient is responsible for the observed influence of intraluminal pressure upon the intramural distribution of collateral blood flow in the ischemic myocardium.

Summary

The subepicardial:subendocardial ratio of Rb\textsuperscript{86} contents was measured and used as an index of the distribution of coronary blood flow to the more superficial and deeper layers of the canine myocardium. In the normally beating heart, the level of intraventricular pressure did not exert any detectable influence upon this ratio of Rb\textsuperscript{86} contents. In the fibrillating heart, or in an ischemic (and presumably non-beating) region of the beating heart, on the other hand, this ratio increased as intraventricular pressure was progressively raised. It is concluded, therefore, that the intraventricular pressure exerts a significant influence upon the distribution of blood flow to the deeper and more superficial layers of myocardium only in regions which are not beating normally.

References


Intraventricular Pressure and the Distribution of Coronary Blood Flow
RENATO CUTARELLI, MATTHEW N. LEVY, Harrison Zieske, Jr. and Geroldine Nelson

doi: 10.1161/01.RES.12.3.322

*Circulation Research* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1963 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/12/3/322

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation Research* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Circulation Research* is online at:
http://circres.ahajournals.org/subscriptions/