Coronary Blood Flow and Myocardial Oxidative Metabolism at Rest and during Exercise in Subjects with Severe Aortic Valve Disease

By George G. Rowe, M.D., Skoda Afonso, M.D., Jorge E. Lugo, M.D., Cesar A. Castillo, M.D., William C. Boake, M.D., and Charles W. Crumpton, M.D.

Available data concerning coronary flow in intact human subjects have indicated that there is a strong tendency for the blood flow per unit weight of myocardium to fall in the usual range under a wide variety of circumstances and for the coronary vessels to be capable of adapting themselves to most situations sufficiently well to maintain usual coronary flow as long as myocardial metabolism is not deranged. When myocardial metabolism is deranged, the coronary circulation adapts to these derangements as, for example, in thyrotoxicosis and thiamine deficiency. The question of adaptation of human coronary flow to mechanical interference prompted the present study of coronary blood flow in subjects with aortic valve disease because of the following considerations.

The best current estimates from animal studies indicate that the major portion of coronary flow occurs during diastole, even though flow during systole is considerable. It has been emphasized repeatedly, however, that the time of flow into the coronary arteries, as measured by a flowmeter near their aortic origin, may bear little if any relation to flow through the capillary bed and circulatory exchange within the myocardium. Indeed, blood flow out of the coronary sinus is maximal during systole and hence during passage through the myocardium the phase of flow shifts 180 degrees. The nitrous oxide method for measurement of coronary blood flow depends upon interchange between the blood and the myocardium and, therefore, mean capillary flow. Presumably mean capillary flow is most important to the myocardium and therefore the human with aortic stenosis or insufficiency should be an ideal experimental subject for investigation of the response of the coronary circulation to factors that stress, respectively, the adaptation to systolic and to diastolic impairment of coronary blood flow. Thus coronary flow may be deficient in the presence of aortic stenosis, since, due to outflow tract obstruction, the systolic intramural left ventricular pressure may exceed coronary perfusion pressure. Although there may be question as to the ultimate accuracy of the measurements, there seems little doubt that the intramural pressure is very high and capillary flow probably stops in part of systole even in the normal, so surely the obstruction must be greater in those with aortic stenosis. Furthermore in aortic insufficiency, coronary flow may be inadequate, since the pressure in the central aorta is reduced during diastole when the greatest coronary inflow should normally occur. It is widely appreciated that left ventricular work is increased by aortic valve disease and that this should aggravate any tendency toward ischemia secondary to reduced coronary blood flow. In addition, it has long been suspected clinically that coronary blood flow may be inadequate in subjects with aortic valve disease because of their known susceptibility to angina pectoris.

Material and Methods

Cardiac output and coronary blood flow were

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measured in a series of subjects with severe aortic stenosis and insufficiency. These patients were selected from the general hospital wards because the severity of their aortic valve disease indicated that definitive surgical therapy was urgently required if they were to survive. All subjects were treated carefully medically until cardiac compensation was considered to be achieved. It should be emphasized that criteria for compensation were clinical, since in the presence of aortic valve disease the left ventricular end-diastolic pressure may be elevated as a result of regurgitation of blood through the aortic valve or from the sudden rise in pressure produced by atrial systole. Two cardiac catheters were used in most subjects to facilitate the procedure. These were introduced through the same vein or two adjacent veins in the same small surgical field and guided fluoroscopically into the pulmonary artery and the coronary sinus. A Courand needle was placed percutaneously in the brachial artery for recording pressure and obtaining blood specimens. Cardiac output was measured by the direct Fick principle, whereas coronary blood flow was determined by the nitrous oxide saturation technique utilizing a partition coefficient of one. Statham strain-gauge pressure transducers were used for recording pressures on a Waters photographic recorder. The mean pressure was obtained by electrical damping with slow period galvanometers, whereas left ventricular systolic mean was determined by planimetry. Expired air was collected in a Tissot spirometer and analyzed for oxygen and carbon dioxide by the method of Scholander. Blood gas analyses for oxygen and carbon dioxide were done by the method of Van Slyke and Neill, whereas nitrous oxide analyses were done by the method of Orcutt and Waters. All blood gas analyses for oxygen and carbon dioxide were done in duplicate, and oxygen determinations were required to check within 0.2 ml./100 ml. Cardiac output was determined by the Fick principle both at rest and during exercise. Calculations of cardiac work were done by the usual formulas.9 “Useful left ventricular work” was calculated by the aortic mean pressure in the Starling formula, whereas “actual” left ventricular work was calculated in those with aortic stenosis using the left ventricular systolic mean pressure. “Actual” left ventricular work in subjects with aortic insufficiency could not be calculated because no quantitative estimate of the volume of aortic regurgitation was made.

In some subjects exercise was studied first and rest second, and in other subjects the order was reversed in order to randomize the data. The exercise consisted of pedaling a bicycle ergometer attached to the foot of the fluoroscopic table. No effort was made to obtain a standard degree of exercise, since the exercise tolerance of the subjects depended on the severity of their disease, and in some subjects exercise produced anginal pain or syncope. Furthermore, they were required to attain a degree of exercise that they could continue throughout 3 to 5 minutes for stabilization, 3 minutes for determination of cardiac output, and 10 minutes for measurement of coronary blood flow, as well as during the short inevitable delays between portions of the study.

After the determination of cardiac output and coronary blood flow at rest and during exercise, left heart catheterization was carried out transseptally for measurement of left atrial and left ventricular pressures, and by retrograde catheterization of the central aorta and left ventricle through the right brachial artery for measurement of the gradient across the aortic valve. Since the resting measurements were not made simultaneously with the left-sided pressures and the cardiac output, the data must be interpreted with the reservation that the only assurance the left-sided pressures are related to the cardiac output and coronary flow data is that both were obtained in the same individual at rest during the same catheterization procedure. Competence of the aortic and mitral valves was estimated in most instances by injection of indocyanine green distal to the valve and sampling from a catheter placed proximal to the valve. The amount of dye that appeared in the chamber proximal to the valve as compared to that in the simultaneously recorded peripheral arterial curve was equated roughly with the quantity of valvular insufficiency (fig. 1). The severity of aortic stenosis was estimated from the pressure gradient and blood flow at rest. Further observations of valve function were made during cineangiography with injection of contrast substance into the left ventricle or aorta. Depending upon the final assessment of the cardiac valve function, derived from the pressure tracings, dye curves, cineangiograms, and clinical picture, subjects were subdivided into those with predominant or pure aortic stenosis, and predominant or pure aortic insufficiency. At times this decision was difficult, however inspection of the results of the study reveal that it was not important, since the results are basically the same in each “group.” Table 1 indicates the ultimate distribution of the subjects into “groups,” as well as the final summary of the pooled data for the two “groups.”

**Results**

The body oxygen consumption of these subjects increased modestly but significantly
CORONARY BLOOD FLOW IN AORTIC VALVE DISEASE

During exercise, and although arteriovenous oxygen difference increased, the cardiac index rose significantly. Both right and "useful" left ventricular work were significantly increased. "Actual" resting left ventricular work, as calculated for the subjects with aortic stenosis (utilizing left ventricular systolic mean pressure in the Starling formula) was markedly greater than the "useful" work accomplished (utilizing aortic mean pressure in the Starling formula). Similar figures were not available during exercise, since the left ventricular systolic mean was not measured during exercise.

The resting coronary blood flow per unit weight of myocardium was in the same range in each group. Although the coronary sinus oxygen content did not change during exercise, the arterial oxygen content rose. (Arterial oxygen content was determined simultaneously with the coronary sinus oxygen content but not included in the table for sake of simplicity.) There was a significant increase in the arterial-coronary sinus oxygen difference but the oxygen extraction A-V/A remained constant at 68.7 percent and 69.1 percent, respectively. Simultaneously coronary blood flow increased significantly, as did left ventricular oxygen consumption. Including both rest and exercise values good correlations were demonstrated between the oxygen consumption of the heart and the body as a whole (r = +0.70, p < 0.001), as well as between cardiac index and coronary blood flow (r = +0.54, p < 0.01). The calculated coronary vascular resistance (MABP / CBF) decreased during exercise. In two of these subjects (cases 2 and 3), syncope occurred during catheterization. In both instances, the exercise study was done first and the syncope episode occurred after completion of the resting study. These episodes were characterized by decreased central venous pressure and systemic arterial hypotension, and were corrected by elevating the lower extremities, increasing the rate of administration of intravenous fluids through the cardiac catheter, inhalation of 100 percent oxygen by mask, and, in one case (case 2), administration of 30 mg. of neosynephrine. The left-sided procedures were done after recovery from syncope had taken place and the patient felt normal again.

Discussion

The present results show that the coronary blood flow is in the usual range per unit weight of myocardium in the subjects with angina pectoris and aortic valve disease and that it increases during exercise. This is in line with preceding observations, indicating that coronary blood flow per unit weight of muscle is in the same range in resting subjects with angina pectoris as it is in normal subjects and that their coronary blood flow increases in response to exercise as it does in normal individuals. Possibly the results in subjects with angina pectoris indicate that the myocardium will not survive unless its blood flow is adequate and, when inadequate, it undergoes fibrosis. In one subject (case 1) coronary artery disease was demonstrated by cineangiocardiography in addition to aortic

Figure 1

In the center panel of the diagram is indicated the positions of catheters placed transseptally in the left ventricle and retrograde into the central aorta just above the aortic valve. On the right panel are two simultaneous indicator-dilution curves obtained from femoral arterial and left ventricular blood, after injecting indicator into the central aorta. The large quantity of dye aspirated from the left ventricle is related to the amount of aortic insufficiency. On the left panel are simultaneous pressure curves obtained from the left ventricle and central aorta in a subject with aortic stenosis. They reveal the pressure gradient across the aortic valve and are related to the degree of aortic stenosis.

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<table>
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<tr>
<th>Group</th>
<th>Exercise</th>
<th>AVP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>Hematocrit (%)</th>
<th>Left Atrial Pressure (mm Hg)</th>
<th>Mean arterial pressure (mm Hg)</th>
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Note: AVP = Arterial Vascular Pressure, LVEDP = Left Ventricular End Diastolic Pressure, Hematocrit = Red Blood Cell Volume, Mean arterial pressure = Mean Arterial Blood Pressure, Stroke volume = Blood Volume per Stroke.
Table 1 (Continued)

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<th>Cardiac flow (ml/100 G. min.)</th>
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<th>Fem. art. pH</th>
<th>Cor. sinus pH</th>
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<th>RV work index</th>
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12.3                    | 0.80                           | 14.6    | 43          | 7.42         | 7.37          | 3.5                                 | 1258                              | 231           | 4.7                       | 87               | 10.5                | 1.22              |
13.1                    | 0.81                           | 14.7    | 44          | 7.39         | 7.34          | 4.4                                 | 1166                              | 274           | 6.8                       | 130              | 17.0                | 0.91              |

11.6                    | 0.79                           | 14.5    | 46          | 7.43         | 7.40          | 3.1                                 | 1292                              | 242           | 4.0                       | 95               | 11.0                | 1.01              |
13.1                    | 0.77                           | 15.6    | 47          | 7.42         | 7.38          | 4.5                                 | 935                               | 378           | 6.2                       | 105              | 13.8                | 0.97              |
14.3                    | 0.78                           | 15.3    | 45          | 7.43         | 7.40          | 4.2                                 | 925                               | 377           | 4.6                       | 101              | 14.4                | 0.80              |
14.1                    | 0.77                           | 15.8    | 46          | 7.44         | 7.39          | 3.6                                 | 1289                              | 585           | 4.7                       | 109              | 15.4                | 0.89              |
13.8                    | 0.77                           | 14.4    | 41          | 7.43         | 7.32          | 4.1                                 | 824                               | 184           | 4.2                       | 130              | 17.9                | 0.58              |
13.7                    | 0.79                           | 14.7    | 42          | 7.41         | 7.37          | 4.3                                 | 1023                              | 307           | 5.8                       | 247              | 33.8                | 0.40              |
12.5                    | 0.78                           | 14.1    | 41          | 7.53         | 7.36          | 4.2                                 | 1215                              | 149           | 6.0                       | 106              | 12.8                | 1.00              |
12.8                    | 0.88                           | 14.5    | 43          | 7.36         | 7.35          | 3.5                                 | 1121                              | 193           | 9.5                       | 151              | 18.9                | 0.85              |

13.0                    | 0.78                           | 14.6    | 43          | 7.46         | 7.37          | 3.9                                 | 1064                              | 238           | 4.7                       | 108              | 14.0                | 0.85              |
13.4                    | 0.80                           | 15.2    | 45          | 7.41         | 7.37          | 4.5                                 | 1092                              | 306           | 6.6                       | 153              | 20.5                | 0.78              |

12.5 ± 1.2              | 0.79 ± 0.06                    | 14.5 ± 0.7 | 43 ± 3      | 7.42 ± 0.4   | 7.38 ± 0.5   | 3.7 ± 0.7                           | 1181 ± 228                        | 239 ± 61     | 4.7 ± 1.0                 | 95 ± 26           | 11.8 ± 3.1          | 1.08 ± 0.3         |
13.2 ± 1.1              | 0.80 ± 0.04                    | 14.8 ± 0.6 | 44 ± 2      | 7.40 ± 0.4   | 7.35 ± 0.5   | 4.4 ± 0.6                           | 1123 ± 187                        | 283 ± 119    | 6.7 ± 1.3                 | 138 ± 41          | 18.2 ± 5.7          | 0.86 ± 0.2         |
+5.6                   | +1.3                           | +2.1      | +2.3        | -0.3         | -0.4         | +18.9                               | -4.9                              | +18.4        | +42.6                    | +60              | +45.3               | +54.2             |
0.01                   | 0.4                            | 0.2       | 0.1         | 0.3          | 0.2          | 0.01                                | 0.5                               | 0.2          | 0.001                    | 0.001            | 0.01                | 0.001              |
stenosis but still coronary flow increased during exercise.

Since the left ventricular weight of these subjects is known to be increased and the coronary flow per unit of weight normal, it is apparent that their total coronary blood flow is also increased. It is interesting to speculate that the degree of hypertrophy of the cardiac muscle and of cardiac vascular supply are apparently directly related, although the possibility of persistent vasodilatation as the mechanism of increased coronary flow is not excluded by this study. If the distance from the capillaries to the center of the muscle fibers is significantly abnormal in these subjects it is not reflected in the results given by the nitrous oxide method; a method that depends on diffusion. Conceivably, although unimportant during rest, or the degree of exercise achieved here, the relationships could become significant during greater exertion. Clearly, we cannot draw conclusions concerning the specific mechanism of anginal pain from these studies, since the subjects did not have angina during the measurement of coronary blood flow.

The coronary flow is clearly not decreased either at rest or during exercise in the present subjects with aortic insufficiency, even though the diastolic pressure in some of them was as low as 40 mm. Hg, when directly recorded and zero when estimated by the auscultatory method. A previous study in dogs showed that when a large arteriovenous fistula was opened, coronary blood flow increased in response to the increase in cardiac rate and work even though the fistula was of sufficient size that the diastolic pressure in the central aorta was markedly reduced. Thus, coronary vessels are able to adapt themselves to very low diastolic pressures both in animals and in man to provide adequate perfusion of the myocardium. It would be interesting to know how the relative quantities of systolic and diastolic flow are altered by aortic insufficiency but the data cannot be obtained by the nitrous oxide method. It has been concluded previously that the major change permitting increased coronary flow has usually been due to active coronary vasodilatation and the present data strongly support this contention since heart rate rose and the length of diastole decreased with exercise, whereas coronary flow increased.

The fact that coronary blood flow in the subjects with aortic stenosis is within the usual range at rest and during the present modest degree of exercise is of particular interest, since four of them had angina pectoris and two were subject to syncope. Because of the marked gradient across the aortic valve during systole it seems probable that capillary flow in their myocardium must occur predominantly during diastole. Although maximal stress to the coronary circulation may well have occurred in those with combined stenosis and insufficiency because of both systolic and diastolic restriction, these subjects fall into the same pattern as the others and coronary flow is in the same range.

Conclusions

Systemic and coronary hemodynamic observations have been made in a group of subjects with severe aortic stenosis and insufficiency and mixed stenosis and insufficiency.

Resting coronary blood flow per unit weight of muscle was in the same range as is found in normal subjects.

During exercise, the cardiac index, cardiac work, and coronary blood flow increased significantly.

Those who were subject to angina pectoris increased their coronary flow in response to exercise, as did those who were not.

The mechanism of anginal pain in aortic valve disease was not discovered by this study although the coronary blood flow per unit of heart weight at rest and during exercise indicates that the explanation is probably not simple.

References


Structure and Movement of the Heart
Richard Lower—1631-1690

Richard Lower (1631-90) was one of the early members of the Royal Society. His careful studies of the musculature of the heart and the form of its contraction exhibited his extraordinary powers of observation, matching in skill if not in originality his observations on the oxygenation of blood in the lungs. Here Lower has probably received less credit than he has deserved. This may well have been in part because of his irascible personality and barbed pen, and the numerous enemies that he acquired. When he died, among the poetic tributes was the following:

"Upon Dr. Lower's Death, Being a Man of a Morose Disposition:
Had not good nature o'er ye ill prevail'd
Death in attempting Dr. Lower had fail'd
Who might have lived with us many a year
Prepared (in his own pickle) vinegar.
But when ye Alkali had killed ye soure
His blood being sweetened, off went Dr. Lower."

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