Effect of Acute Experimental Aortic Stenosis on Coronary Circulation

By Marvin R. Blumenthal, M.D., Hsueh-Hwa Wang, M.B., and S. C. Wang, M.D., Ph.D.

The effect of aortic stenosis on the coronary circulation warrants further investigation because the few previous studies led to conflicting conclusions based on small series of experiments. Moreover, aortic stenosis presents a unique situation for a study of the determinants of coronary blood flow. On the one hand, the location of the stenosis, between the left ventricle and the aortic origin of the coronary arteries, creates a systolic pressure gradient unfavorable for coronary flow. This flow-reducing factor is augmented by the increase in extravascular compression resulting from the prolonged systolic ejection phase in aortic stenosis. Indeed, a decrease in coronary blood flow was noted by Green when he produced aortic stenosis by inflating a balloon in the aortic orifice.

On the other hand, it has generally been observed that coronary blood flow increases whenever the load on the left ventricle is increased. It would seem logical that a similar increase in load would result from constriction of the outflow tract, whether it be proximal or distal to the coronary ostia. It has been repeatedly demonstrated that aortic constriction distal to the coronary ostia results in an increase in coronary blood flow. Moreover, Gregg and Shipley noted an increase in coronary blood flow in a modified preparation of aortic constriction that was analogous to aortic stenosis. In their preparation, the ascending aorta was constricted, and the left coronary artery was perfused from a carotid artery.

In the present study, aortic stenosis was produced just proximal to the aortic valve, and the effects on the coronary circulation and cardiac dynamics were measured. The experimental method permitted study of the effects of a comparable degree of aortic constriction distal to the coronary ostia in the same animal.

Methods

Dogs weighing between 20 and 27 Kg. were premedicated with morphine sulfate, 1 mg./Kg. intramuscularly, and were anesthetized 30 minutes later with chloralose, 100 mg./Kg. intravenously. The common carotid arteries and external jugular veins were exposed through a cervical incision, and a cannula was inserted in the trachea. Both femoral arteries and one femoral vein were exposed, and a slow intravenous infusion of physiological saline was started. The left side of the chest was opened, and respiration was maintained with a Palmer Ideal Pump. Room air was supplemented with a steady flow of oxygen, 4 L./min., at the air inlet. The brachiocephalic and the left subclavian arteries were dissected. The descending thoracic aorta was freed for a length of 5 cm. by ligating two or three pairs of intercostal arteries. The pericardium was incised and the heart suspended in a pericardial cradle. Anticoagulation was effected with intravenous heparin, 10 mg./Kg., and was maintained for the duration of the experiment with a supplementary injection of 5 mg./Kg. one hour later.

Left ventricular output, excluding the coronary blood flow, was measured by a Shipley-Wilson rotameter according to the method reported and modified by Wégrzyn et al. (schematically illustrated in figure 1A). When the descending thoracic aorta was ligated, the blood ejected by the left ventricle flowed through the brachiocephalic and left subclavian arteries into the rotameter, whence it was returned to the head circulation via both carotid arteries cannulated distally and to the rest of the body via both femoral arteries cannulated proximally and distally. The areas supplied by the aorta caudal to the ligature were...
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Figure 1

A. Sketch depicting method of determining left ventricular output and direction of blood flow; placement of instrument for producing aortic stenosis; location of clamp for producing aortic constriction; location of arterial blood pressure sampling point (P). Left ventricle (LV). B. Plan of instrument for producing aortic stenosis. Proximal end is lower left; distal end is upper right. Proximal and distal ends are connected with triple concentric brass tubing. Measurements are in inches; see text for further description.

Thus perfused in a retrograde fashion through the proximal femoral arterial cannulae.

Coronary sinus outflow was measured with a second rotameter. A modified Morawitz cannula was inserted via the external jugular vein into the coronary sinus. The blood flowed through the cannula into the rotameter and was returned to the right atrium via the right external jugular vein. Coronary sinus outflow was used as an index of left coronary artery flow. This measurement is justified since the coronary sinus outflow in the dog is derived from the left coronary artery and represents a constant portion of the left coronary flow in each dog.

Arterial blood pressure was recorded by a Sanborn strain gauge transducer Model 267A connected to the inflow tubing of the left ventricular output rotameter. Mean arterial blood pressure was calculated by adding one-third of the pulse pressure to the diastolic pressure.

Left intraventricular systolic pressure was measured with a Statham pressure Transducer Model P23AC through a needle inserted into the left ventricle.

The above four measurements were recorded simultaneously and continuously on a Sanborn multichannel recorder Model 150 or on a Grass polygraph. Heart rate was counted directly from the pressure traces.

Runs of aortic stenosis were produced by utilizing the specially designed instrument illustrated in figure 1B. The proximal end of the instrument was an umbrella of waterproof material that could be opened and closed by adjusting the large knobs at the distal end. The umbrella had a large apical orifice which could be progressively narrowed by an obturator. The position of the obturator could be controlled by adjusting the small knob at the distal end of the instrument. The closed umbrella with open apical orifice was introduced through the proximal end of the ligated descending aorta and passed retrograde through the aortic arch and aortic valve. The umbrella was opened within the left ventricle and secured against the muscular ring proximal to the aortic valve (fig. 1A). With the apical orifice of the umbrella open, the instrument offered no obstruction to the flow of blood and remained in place throughout the experiment. Its position was checked by postmortem examination in every dog. Aortic insufficiency was not observed, since the aortic valve closed normally during diastole around the narrow tubing connecting the proximal and distal ends of the instrument. To produce a run of aortic stenosis, the obturator was inserted, thus narrowing the orifice at the apex of the umbrella. To end the run, the obturator was withdrawn, thereby again permitting unobstructed blood flow. Each run of aortic stenosis was followed by a matched run of aortic constriction, as judged by a comparable elevation of the left intraventricular systolic pressure. Aortic constriction was produced by adjusting a screw clamp on the inflow tubing of the left ventricular output rotameter. This clamp was placed proximally to the point where arterial blood pressure was measured (fig. 1A).

Arterial and coronary sinus blood were simultaneously sampled prior to and toward the end of each run of aortic stenosis.
Aortic Stenosis and Coronary Circulation

Table 1
Average Values and Range of Results in Aortic Stenosis and Aortic Constriction Compared to Their Respective Controls

<table>
<thead>
<tr>
<th></th>
<th>Left intra-ventricular systolic pressure (mm. Hg)</th>
<th>Arterial blood pressure (mm. Hg)</th>
<th>Left ventricular output (ml./min.)</th>
<th>Coronary sinus outflow (ml./min.)</th>
<th>Coronary oxygen A-V difference (vol. %)</th>
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</thead>
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<tr>
<td></td>
<td>Systolic pressure</td>
<td>Diastolic pressure</td>
<td>Mean pressure</td>
<td>Pulse pressure</td>
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<td>Aortic stenosis Control</td>
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<tr>
<td>Range</td>
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<td>84</td>
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<td>Control</td>
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<td>86</td>
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</tbody>
</table>

*See text for additional description of results.

of each run in some matched pairs. Oxygen content, expressed in volumes per cent, was determined on all samples by the spectrophotometric method. From these data coronary oxygen arteriovenous difference was calculated.

Results

In 12 dogs, 45 runs of aortic stenosis were matched with runs of aortic constriction. The matching was considered satisfactory when a comparable elevation of left intraventricular systolic pressure was maintained for an equal length of time at the same heart rate. For the entire series of runs, the duration ranged from one and a half to three minutes and the heart rate from 114 to 190 beats per minute. The heart rate remained constant in each pair of matched runs and its controls. This constancy was a necessary factor in controlling the matching of runs, because changes in heart rate alone have been shown to influence coronary blood flow. Table 1 is a summary of the results, and figure 2 is a graphic representation of these data.

The left intraventricular systolic pressure increased in all runs of aortic stenosis and aortic constriction. The rise in left intraventricular systolic pressure was the most obvious compensatory effect. Consequently, this parameter was used to match the run of constriction to the preceding run of stenosis. The average increase in aortic stenosis was 20 mm. Hg, with a range of 10 to 40 mm. Hg. The average increase in aortic constriction was 18 mm. Hg with a range of 10 to 35 mm. Hg.

The systolic arterial blood pressure fell in all runs except in one of aortic stenosis, where it remained the same. The average systolic arterial blood pressure fell less in aortic stenosis than in aortic constriction. The diastolic arterial blood pressure in aortic stenosis was unchanged in 20 runs, increased in nine, and decreased in 16; the change was not more than 5 mm. Hg in all but one run, and there was no significant change in the average. The diastolic arterial blood pressure in aortic constriction was unchanged in 16 runs, increased in 18, and decreased in 11; the change was not more than 5 mm. Hg except for eight runs, and there was again no significant change in the average. The pulse pressure decreased in all runs; the average decrease in aortic stenosis was
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Figure 2

Graph representing the average changes from control in aortic stenosis (solid line) compared to aortic constriction (broken line). Note the parallel changes in left intraventricular systolic pressure, mean arterial blood pressure, and left ventricular output; coronary sinus outflow increases slightly less in aortic stenosis; coronary oxygen A-V difference increases in aortic stenosis and decreases in aortic constriction.

The left ventricular output in aortic stenosis showed no change in 19 runs and decreased less than 5 per cent in 14; in only two runs was the decrease more than 10 per cent, and the average change for the series was —3 per cent. The left ventricular output in aortic constriction showed no change in 20 runs and decreased less than 5 per cent in 16; the decrease was never more than 10 per cent, and the average change for the entire series was —2 per cent.

The coronary sinus outflow increased in all runs of aortic stenosis and aortic constriction. The average increase in aortic stenosis was 9 per cent or 7 ml./min., with a range of 2 to 14 ml./min. The average increase in aortic constriction was 12 per cent or 9 ml./min., with a range of 3 to 17 ml./min. The difference between the increase in aortic stenosis and the increase in aortic constriction was not statistically significant (P = 0.68).

Figure 3 is the tracing of a typical pair of matched runs to illustrate the above results. The left intraventricular systolic pressure rose comparably in both aortic stenosis and aortic constriction; the pulse pressure decreased less in aortic stenosis, but there was no significant change in mean arterial blood pressure. The left ventricular output initially dipped slightly in both but quickly attained the control levels. The coronary sinus outflow in aortic stenosis dipped slightly at the beginning of a run, slowly increased over a period of 30 seconds to above control, and remained above control throughout the rest of the run. On the termination of the run, there was a further increase in the coronary sinus outflow for a short period of time—a reactive hyperemia—before it returned to control. By contrast, the coronary sinus outflow in aortic constriction increased abruptly at the beginning of a run, remained elevated throughout, and fell abruptly to control level.

*This discrepancy was due to the placement of the clamp for aortic constriction distal to the aortic arch (see fig. 1A). As a result, the aortic arch, between the aortic valve and the clamp, was a more effective, elastic damping chamber during aortic constriction than during aortic stenosis. Since this damping chamber was proximal to the point where arterial blood pressure was measured, the pulse pressure was decreased more during aortic constriction.

Circulation Research, Volume XI, October 1958
without any reactive hyperemia at the end of the run.

Coronary oxygen A-V difference was measured in 10 pairs of matched runs of aortic stenosis and aortic constriction in eight dogs. The coronary oxygen A-V difference increased in eight runs of aortic stenosis but decreased or remained the same in eight runs of aortic constriction. The average change in aortic stenosis was an increase of 0.5 vol. per cent, and the average change in aortic constriction was a decrease of 0.5 vol. per cent. The increase during aortic stenosis and the decrease during aortic constriction are significantly different from their respective controls ($P < 0.01$). Table 2 lists the results for these 10 pairs of matched runs.

It should be noted that greater degrees of aortic stenosis were not tolerated so well as greater degrees of aortic constriction. When a greater degree of aortic stenosis was attempted, it resulted in ventricular alternation or in an irregular ventricular rate because of frequent premature ventricular contractions. With either occurrence, a steady recording was not obtained in any of the parameters, and heart rate was changed. These runs were impossible to match with aortic constriction and were therefore discarded.

**Discussion**

The response of the cardiovascular system to aortic stenosis was comparable to aortic constriction (fig. 2). The induction of either condition caused a sudden obstruction to flow which resulted in an initial dip in left ventricular output. The immediate effect must have been an increase in residual volume and, consequently, end-diastolic volume of the left ventricle. The resultant lengthening of the muscle fibers led to a more forceful contraction. This factor was augmented by an increased duration of contraction. The combined effect of a more forceful and prolonged contraction was an elevation of left intraventricular systolic pressure sufficient to overcome the obstruction to flow and to return the output to or toward control. The increase in left intraventricular systolic pressure was also largely responsible for the maintenance of mean arterial blood pressure.

The coronary sinus outflow increased in every run of aortic stenosis as well as in every run of aortic constriction. In general, an increase in coronary blood flow can be effected through one or any combination of three factors: increased coronary perfusion pressure, decreased extravascular compression; and decreased coronary vasomotor tone.

In aortic constriction, the coronary per-
<table>
<thead>
<tr>
<th>Dog number</th>
<th>Duration of run (min.)</th>
<th>Heart rate (beats/min.)</th>
<th>Left intraventricular systolic pressure (mm. Hg)</th>
<th>Arterial blood pressure (mm. Hg)</th>
<th>Left ventricular output (ml/min.)</th>
<th>Coronary sinus outflow (ml/min.)</th>
<th>Coronary oxygen A-V difference (vol. %)</th>
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fusion pressure rises with the increased intraventricular systolic pressure, since the coronary ostia are proximal to the constriction. Extravascular compression increases because of the increased left intraventricular systolic pressure and the prolonged systole. The status of vasomotor tone is undetermined. Since the net result was an increase in coronary blood flow, the increased coronary perfusion pressure must have overcome the flow-reducing effect of increased extravascular compression. Indeed, the characteristics of the coronary sinus outflow tracing, as illustrated in figure 3, are consistent with this explanation. The coronary sinus outflow rose abruptly with induction of aortic constriction, paralleling the rise in left intraventricular systolic pressure. On release of the constriction, the coronary sinus outflow fell abruptly to control, again paralleling the left intraventricular systolic pressure, and there was no evidence of reactive hyperemia of the coronary bed.

Although coronary perfusion pressure is an important determinant, the coronary blood flow can increase in the face of no rise, or even a fall, in perfusion pressure, as was reported in A-V fistulae, tachycardia, and mitral insufficiency. In these conditions, therefore, the increase in coronary blood flow must be due to decreased extravascular compression and/or decreased vasomotor tone. It is not possible to separate the relative effect of each of these determinants, since only the net result is known. By contrast, such a separation can be made in aortic stenosis. In aortic stenosis, the coronary ostia are distal to the stenosis, and therefore, the coronary perfusion pressure does not rise with the increase in left intraventricular systolic pressure. The extravascular compression definitely increases as a result of the increase in left intraventricular systolic pressure and the prolongation of systole. The coronary blood flow increases despite the flow-reducing effect of increased extravascular compression and without the benefit of increased coronary perfusion pressure. Consequently, decreased vasomotor tone alone must be responsible for the increase in coronary blood flow.

The decrease in coronary vasomotor tone, or coronary vasodilatation, may be caused by one or any combination of three separate, recognized mechanisms: myocardial anoxia, accumulation of vasodilating metabolites, and action of neurohumoral agents (catecholamines). Myocardial anoxia may be responsible for the coronary vasodilatation, since coronary oxygen A-V difference tended to increase in aortic stenosis. However, it is difficult to explain the increase in coronary blood flow on the basis of myocardial anoxia per se in the two experiments where coronary oxygen A-V difference actually decreased. Metabolites and catecholamines were not measured in this study. Vasodilating metabolites may have accumulated as a result of the increased metabolism of the left ventricle. Catecholamine release may have been accelerated through a reflex increase in sympathetic discharge. The type of coronary sinus outflow tracing observed in aortic stenosis (fig. 3) would be consistent with any or all of the aforementioned mechanisms. The coronary sinus outflow rose gradually from an initial dip to a level above control, and after release of the aortic stenosis, there was a short period of reactive hyperemia. An interesting corollary of this latter observation is that reactive hyperemia after an experimental situation indicates that coronary vasodilating mechanisms had been active during the experiment.

Coronary oxygen A-V difference tended to increase in aortic stenosis and to decrease in aortic constriction. This divergence (fig. 2) is additional evidence that the mechanism whereby the heart is supplied with the necessary substrates in aortic stenosis differs from that in aortic constriction. Moreover, the increase in coronary oxygen A-V difference in aortic stenosis indicates that the myocardium can extract additional substrates from the coronary blood when an increase in coronary blood flow is difficult to attain. This source is limited, however, since coronary sinus blood is highly unsaturated under normal conditions.
The data reported in this paper appear to be in agreement with the observations of Gregg and Shipley and at variance with those of Green. Possibly the degree of stenosis in Green’s experiments was more extreme, and the fall in coronary blood flow was associated with a fall in cardiac output or heart rate which were not measured. It is also possible that the coronary bed in Green’s preparation was already maximally dilated, and without this mechanism, the flow-reducing effect of increased extravascular compression could not be overcome.

In the experiments reported herein, it was noted that a greater degree of aortic stenosis was not tolerated as well as a greater degree of aortic constriction. In other words, the cardiac reserve was less when the heart was subjected to aortic stenosis than when it was subjected to a comparable degree of aortic constriction. Cardiac reserve may be divided into coronary and myocardial components. Coronary reserve is the ability of the coronary arteries to supply additional substrates by an increase in coronary blood flow and coronary A-V difference. Myocardial reserve is the additional ability of the heart muscle to perform against challenges of rate, stretch, and resistance, providing sufficient substrate is available. In aortic stenosis, the cardiac reserve was limited by the coronary reserve, since coronary vasodilatation was the only means of increasing the coronary blood flow. In aortic constriction, the coronary reserve was not so limited because coronary blood flow could increase through increased coronary perfusion pressure as well as through coronary vasodilatation. In fact, vasodilating mechanisms might not have been required, since reactive hyperemia did not occur and coronary oxygen A-V difference tended to decrease. If aortic constriction had been increased to the point where cardiac output and arterial blood pressure were not maintained, myocardial reserve rather than coronary reserve might have proved the limiting factor.

The clinical translation of the data presented in this paper is quite literal. In the patient with aortic stenosis, the coronary blood flow must increase whenever the heart responds to an increased load, whether it be exercise, a large meal, or an emotional upset. It is only when the coronary reserve is relatively depleted that the patient may experience the pain of coronary insufficiency.

Summary

Acute experimental aortic stenosis was produced by a special instrument in dogs anesthetized with morphine and chloralose. The effect of aortic stenosis was compared to aortic constriction distal to the coronary ostia in 45 matched runs in 12 dogs. In 10 pairs of matched runs in eight dogs, coronary oxygen A-V difference was measured. The runs were matched as to duration, heart rate, and rise in left intraventricular systolic pressure. With the increase in left intraventricular systolic pressure, the mean arterial blood pressure did not change significantly, and the left ventricular output either remained the same or decreased only slightly. The coronary sinus outflow increased in all runs of aortic stenosis as well as in aortic constriction. The coronary oxygen A-V difference tended to increase in aortic stenosis and to decrease in aortic constriction. The rise in coronary blood flow in aortic stenosis was due to vasodilatation alone, since the perfusion pressure remained the same and there was an increase in extravascular compression; in aortic constriction, the increased coronary blood flow was best explained by increased coronary perfusion pressure.

Acknowledgment

The authors wish to express their gratitude to Mr. David Barge, for the manufacture and maintenance of the instrument used to produce aortic stenosis, and to Miss A. Katherine Rupkey, for her valuable technical assistance.

References

4. Gregg, D. E., and Shiple, R. E.: Augmentation of left coronary inflow with elevation of left ventricular pressure and observations on the mechanism for increased coronary inflow with increased cardiac load. Am. J. Physiol. 142: 44, 1944.

Book Reviews


This book contains extracts from the authors' more comprehensive work on blood group serology. It has been prepared for the nonspecialist in pathology or the technician who is responsible for the routine serology in a hospital laboratory. The individual steps in blood grouping are explained in some detail, supplemented with a list of reagents and equipment. The interpretation of results is discussed briefly but clearly.

Two International Symposia on Blood:
1. Blood Platelets, Edited by Shirley A. Johnson, Raymond W. Monto, John W. Rebuck, and Robert C. Horn, Jr. Boston, Little, Brown & Co., 1961, 732 pages, illustrated. $18.50. The symposium was sponsored by the Henry Ford Hospital and held at Detroit, Michigan, March 17 to 19, 1960. The 56 participants in the formal program have covered the following aspects: platelets in blood vessel integrity, platelet clumping, hemostasis, role in thrombosis, platelet fraction, metabolism, clot retraction, altered function, preservation, and immunological aspects of platelets. The remarks of the 78 discussants have been recorded. The index is very helpful in locating information, but an index of authors cited would be a welcome addition.

2. Anticoagulants and Fibrinolysins, Edited by R. L. MacMillan and J. F. Mustard. Philadelphia, Lea & Febiger, 1961, 449 pages, illustrated. $10.00. The symposium was held in Toronto, Canada, February 2 to 4, 1961, under the auspices of the Ontario Heart Foundation and the University of Toronto. Thrombogenesis and the clinical application of anticoagulants and fibrinolysins are discussed by 47 participants. The summary of the entire proceedings by Dr. J. F. Mustard deserves special attention, and many readers are advised to read it prior to embarking on a systematic reading of the papers presented.
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*Circ Res.* 1962;11:727-735
doi: 10.1161/01.RES.11.4.727

*Circulation Research* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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