Effects of Aortic Insufficiency on Circulatory Dynamics of the Dog

With Special Reference to Coronary Blood Flow and Cardiac Oxygen Consumption

By James W. West, Ph.D., Herbert Wendel, M.D., and Elwood L. Foltz, M.D.

In dogs with chronic aortic insufficiency accompanied by cardiac hypertrophy, the coronary blood flow, cardiac oxygen consumption, coronary arteriovenous oxygen difference, coronary oxygen utilization, systolic pressure and cardiac rate are increased significantly above the normals, while coronary venous oxygen saturation, coronary resistance and diastolic pressure are significantly decreased.

In a previous study we dealt with changes in cardiac hemodynamics of dogs during the development of cardiac hypertrophy associated with renal hypertension. This report presents results of corresponding effects of cardiac hypertrophy due to experimentally induced aortic insufficiency. As noted elsewhere, our main purpose was to produce stable, chronic, low-output congestive failure for the purpose of studying rapid digitalization, but this was not fully attained. Nevertheless, we were able to accomplish our lesser objective, study of the changes in coronary blood flow and cardiac oxygen consumption after chronic aortic insufficiency. These findings appear noteworthy since cardiac hypertrophy developed as in studies in renal hypertension, but hypertension was present only in the latter.

Methods

Aortic insufficiency was induced in mongrel dogs weighing 18 to 30 Kg. by the technic of Bazett and sands. This consists essentially of passing a bullet-shaped metallic stylet (maximum diameter 3.5 mm.) via a common carotid artery and ascending aorta to the aortic valve cusps, with the aid of fluoroscopy, until one of the valves is engaged and punctured. One or more aortic valve cusps was perforated in this manner. Three or more days later the animals were studied under anesthesia by intramuscular injections of morphine (3 mg./Kg.) followed by intravenous injections of a combination of equal parts of pentobarbital-sodium veterinary solution (60 mg./ml.) and Dial-urethane solution (100 and 400 mg./ml. respectively), the dosage being 0.25 ml. of the mixture/Kg. An augmenting dose of morphine (1.5 to 2 mg./Kg.) was given 2 to 2½ hours following the initial dose of morphine, as described by Foltz et al. The coronary sinus and the main pulmonary artery were catheterized to obtain coronary venous blood and mixed venous blood for estimating coronary blood flow by the nitrous oxide technic of Kety and Schmidt, and cardiac output (direct Fick method), respectively. The two cardiac catheters and a catheter (via needle puncture) in a femoral artery were connected to individual manifolds for simultaneous anaerobic collection of blood in specially prepared (oil, heparin) syringes. The analysis of the blood samples for oxygen and carbon dioxide was done by the manometric method of Van Slyke and Neil.

For application of a nitrous-oxide gas mixture (15 per cent N₂O, 21 per cent O₂, 64 per cent N₂) and the collection of the expired air (for periods of 5 min.) by a Tissot spirometer, the trachea was intubated by a suitably large plastic cannula with balloon cuff to insure controlled respiratory exchange through a flutter valve of low resistance. Expired air samples were collected from the Tissot spirometer by a Ciba Pharmaceutical Products, Inc., Summit, N. J.
spirometer into a tonometer for analysis of oxygen and carbon dioxide by the technic of Scholander.6

Systemic arterial pressure (from a needle in a femoral artery) and mean pulmonary arterial pressure were measured by a Lilly capacitance manometer and a water manometer, respectively. Respiratory rate was recorded by a Statham strain gage attached to a pneumograph. Electrocardiograms were made through conventional limb and chest leads. Each experimental procedure consisted of a 5 min. period for the estimation of cardiac output, which was immediately followed by a 10 min. period for the estimation of coronary blood flow. An interval of 25 min. between duplicate runs was allowed for the removal of the nitrous oxide gas.

Calculations. By employing the derived data, the following various cardiodynamic and metabolic functions were calculated as previously1-4: mean coronary blood flow in ml./100 Gm. heart/min. by the method of Kety and Schmidt;5 cardiac oxygen consumption in ml./100 Gm. heart/min. (coronary flow \times coronary arteriovenous oxygen difference); cardiac output in milliliters per minute by the direct Fick method; cardiac work (Kg. M./min.) from mean arterial blood pressure and cardiac output; coronary resistance, expressed as mean arterial blood pressure \div coronary flow; and coronary oxygen utilization (coronary arteriovenous oxygen difference \div arterial oxygen content in vol. per cent).

The amount of hypertrophy in 7 of the animals was determined at the end of the series of observations by weighing the entire heart and then excising10 the left ventricle and weighing it separately.

RESULTS

The results of this study are based on 13 dogs in which the following aortic valve lesions were produced: the left aortic cusp in 2 dogs; the right aortic cusp in 1 dog; the posterior aortic cusp in 2 dogs; the left and posterior aortic cusps in 7 dogs; and the left and right aortic cusps in 1 dog.

Effects of Aortic Insufficiency. To illustrate the immediate effects as well as the compensatory changes which occur from aortic insufficiency on arterial blood pressure and heart rate, measurements were made before and immediately after the lesions were produced and were repeated several days later (figs. 1 and 2). Immediately after aortic insufficiency was produced, the systolic pressure and heart rate increased, while diastolic pressure decreased and mean arterial pressure decreased or remained essentially the same depending on the degree of insufficiency and the extent of the immediate compensation. After 3 or more days had elapsed, systolic pressure and heart rate were still elevated, while diastolic pressure remained low and mean arterial pressure returned to the control level.

Table 1 shows the mean values of the present series of 13 aortic insufficiency dogs which were studied 3 to 31 days postoperative (with the exception of 1 dog studied 121 days after operation), together with an earlier series of 11 comparable normal dogs.4 To test the significance of these results, the t test as described by Mainland11 was utilized. In table 1 the significant changes associated with aortic insufficiency are increases in coronary blood flow, cardiac oxygen consumption, coronary arteriovenous oxygen difference, coronary oxygen utilization, systolic pressure, cardiac rate and left ventricular weight, and decreases in diastolic pressure, coronary resistance and coronary sinus venous oxygen saturation. In addition to these findings between normal and aortic insufficiency dogs, the coronary blood flow, cardiac oxygen consumption and diastolic pressure appear to be higher in the group with 1 valve lesion than in those with 2 valve lesions; while heart rate is higher in the latter group.

Stability of the Aortic Insufficiency preparations. Our results have demonstrated that the circulation of the renal hypertensive animal is labile; it therefore seemed of interest to determine whether a similar liability also existed in this type of animal preparation. The results of duplicate determinations completed within 25 min. in 12 different aortic insufficiency dogs are shown
in table 2. There was slightly greater variation in some functions (coronary blood flow and cardiac oxygen consumption) than in others as evidenced by the standard deviations of the individual differences in these animals in comparison with an earlier study in normals. Therefore this preparation, like the hypertensive, appears to be slightly more labile than the normal.

Repeated Observations in Individual Animals. Six of the 13 animals with aortic insufficiency were selected for repeated flow studies to determine changes in their disease pattern. Two animals (each with 2 valve lesions) died prior to the second study as a result of an extension of the disease process (fulminating pulmonary edema). The second or third repeated study made 1 to 4 weeks apart in the remaining 4 animals did not disclose any consistent changes from the original flow experiments.

Electrocardiogram Findings. All of these animals exhibited normal sinus rhythm. However, when one compares the electrocardiogram before and after aortic insufficiency, one finds in many of these dogs a shift in the axis of the P wave with essentially no change in the amplitude and duration. This is probably secondary to the positional shift of the heart as shown by the change in the QRS axis pictured in lead 1 in figure 3 and therefore does not necessarily indicate atrial pathology. In addition, to the P wave shift, there is considerable change in the QRS-T complex. In all leads, especially CR3 and CR4, there is a higher voltage of the QRS complex and the T waves become biphasic or inverted (fig. 3). These changes, increase in QRS voltage and the biphasic or inverted T wave, would seem to indicate left ventricular hypertrophy and "strain." Similar findings as well as others were also observed by Bazett and Sands and by Hamilton and associates.

Pathologic Findings. Seven of these animals were sacrificed immediately following the experimental study to determine the weight of the left ventricle and pathologic changes in various organs; the remaining animals were saved for a subsequent study (combined lesions). The duration of the aortic insufficiency in these 7 animals varied...
**TABLE 1.—Mean Values of First Runs on 11 Normal Dogs and 13 Dogs with Aortic Insufficiency**

<table>
<thead>
<tr>
<th></th>
<th>Normal dogs</th>
<th>1 and 2 Valve lesions (13 dogs)*</th>
<th>1 Valve lesions (5 dogs)</th>
<th>2 Valve lesions (8 dogs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary blood flow (ml/100 Gm./min.)†</td>
<td>85</td>
<td>111</td>
<td>131</td>
<td>99</td>
</tr>
<tr>
<td>Cardiac O₂ consumption (ml/100 Gm./min.)†</td>
<td>9.3</td>
<td>14.2</td>
<td>16.9</td>
<td>13.1</td>
</tr>
<tr>
<td>Cardiac work (Kg. M./min.)</td>
<td>3.86</td>
<td>3.41‡</td>
<td>3.74‡</td>
<td>3.13‡</td>
</tr>
<tr>
<td>Cardiac output (ml/min.)</td>
<td>2850</td>
<td>2300‡</td>
<td>2450‡</td>
<td>2260‡</td>
</tr>
<tr>
<td>Systolic pressure (mm. Hg)</td>
<td>146</td>
<td>182</td>
<td>187</td>
<td>181</td>
</tr>
<tr>
<td>MABP (mm. Hg)</td>
<td>101</td>
<td>108</td>
<td>109</td>
<td>103</td>
</tr>
<tr>
<td>Diastolic pressure (mm. Hg)†</td>
<td>84</td>
<td>73</td>
<td>78</td>
<td>67</td>
</tr>
<tr>
<td>Cardiac rate (B/min.)†</td>
<td>74</td>
<td>102</td>
<td>95</td>
<td>110</td>
</tr>
<tr>
<td>Coronary resistance (P - flow)†</td>
<td>1.32</td>
<td>1.04</td>
<td>0.88</td>
<td>1.08</td>
</tr>
<tr>
<td>Coronary sinus venous O₂ saturation (%)†</td>
<td>29.6</td>
<td>22.6</td>
<td>23.6</td>
<td>20.4</td>
</tr>
<tr>
<td>Coronary A0₂ - V0₂ (vol. %)†</td>
<td>11.4</td>
<td>13.1</td>
<td>12.9</td>
<td>13.4</td>
</tr>
<tr>
<td>Arterial Hb. (Gm./100 ml)</td>
<td>13.2</td>
<td>13.3</td>
<td>13.6</td>
<td>13.2</td>
</tr>
<tr>
<td>Coronary O₂ utilization (%)†</td>
<td>69.0</td>
<td>76.1</td>
<td>75.8</td>
<td>78.9</td>
</tr>
<tr>
<td>Left ventricular weight (Gm./Kg.)†</td>
<td>4.4</td>
<td>5.8</td>
<td>6.0§</td>
<td>6.7§</td>
</tr>
</tbody>
</table>

* These 13 dogs are the sum of the 5 dogs with 1 aortic valve lesion and 8 dogs with 2 aortic valve lesions.

† Statistically significant (p<0.02) difference between normal and aortic insufficiency dogs.

‡ Regurgitant volume not reflected in measurements.

§ Based on 5 of the 5 dogs.

Based on 4 of the 8 dogs.

between 4 and 30 days, except 1 which was 121 days postoperative. The average duration of aortic insufficiency in these animals was 30 days. A general dissection of the abdominal viscera was made with special attention to the heart and circulatory tree. At autopsy, blocks of tissues were taken from the heart, aorta, lung, liver, spleen and kidney for histologic examination.

Upon gross examination the heart exhibited hypertrophy of the left ventricle. Enlargement of individual muscle fibers was observed histologically in all cases. Examination of the perforated aortic valve showed it to be usually thick and scarred near the base of the cusp and in many cases its appearance was more like cartilage than connective tissue. In some cases a thrombotic mass suggestive of bacterial endocarditis was seen on the valve, accompanied by areas of necrosis in the heart muscle.

The chief findings in the lungs were usually those of localized edema, passive congestion and occasional bronchopneumonia. The liver often showed passive congestion of moderate degree. In those cases which demonstrated thrombi (vegetation) on the aortic valves and areas of necrosis in the heart muscle, there were also emboli in some of the small branches of the splenic and renal arteries which led to infarcts in these organs.

**DISCUSSION**

Studies reported in the literature on the effects of acute (uncompensated and compensated) as well as chronic (cardiac hypertrophy) aortic insufficiency on coronary blood flow are in disagreement. The reasons for this difference are not immediately apparent in the acute studies as they appear to be in the chronic studies. Nevertheless, in the former case one of the important factors which may account for some of the discrepancy appears to be the extent of uncompensation during the insufficiency; while in the chronic studies the disagreement is probably...
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superficial, resulting from a paucity of data.

Smith, Miller and Graber13 made the earliest measurements of coronary sinus outflow during acutely induced aortic insufficiency and found it reduced, which they attributed to the fall in diastolic pressure. In their experiments mean arterial blood pressure was lower after aortic insufficiency than before. Later experiments by Green14 showed that uncompensated (low mean arterial blood pressure) aortic insufficiency was accompanied by a decrease in coronary blood flow which occurred chiefly during diastole because of the low aortic diastolic pressure which was partially compensated by a concomitant increase in the coronary flow during systole and because of a relative lowering of the systolic peripheral coronary resistance. He postulated further, on the basis of experiments in which he restored mean arterial blood pressure by partially compressing the aorta, that compensation through peripheral vascular constriction, sufficient to restore a normal mean arterial blood pressure, would increase coronary flow to or even above normal. Contrary to the above findings, Wegria and associates15 have recently reported that in acute aortic insufficiency sufficient to (markedly) lower the mean and diastolic aortic pressures, an increase in coronary sinus blood flow and myocardial oxygen consumption regularly occurred.

In contrast to these experiments on acute uncompensated aortic insufficiency, the advent of the technics of coronary sinus catheterization8 and the application of the nitrous-oxide method for measuring coronary blood flow in the intact man16 and dog7 made possible the study of chronic aortic insufficiency on coronary blood flow and cardiac oxygen consumption. Bing and associates16 made the first coronary flow measurements in man (1 patient) during chronic aortic insufficiency. Later Lombardo and associates17 reported observations made in 2 similar patients. The results agreed in indicating that coronary blood flow and cardiac oxygen consumption are increased over normal. However, Regan and associates18 have recently reported similar studies on 9 patients with severe aortic insufficiency with and without angina or heart failure. They found that 2 patients with aortic insufficiency and angina had a reduced coronary flow and cardiac oxygen consumption, while 4 patients in heart failure with aortic insufficiency showed increases in myocardial oxygen consumption and coronary flow. Three patients with aortic insufficiency uncomplicated by angina or heart failure did not differ from the values obtained in a group of 8 normal subjects. However, the values in the latter group of aortic insufficiency patients are higher than those reported for normal subjects by other investigators19,20 and therefore suggest that a larger series of experiments are needed both in the normal subjects and in the patients with aortic insufficiency uncomplicated by angina or heart failure.

<table>
<thead>
<tr>
<th>Table 2.—Mean Values of 2 Observations on the Same 13 Dogs with Aortic Insufficiency, 25 Min. Interval Between Runs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Run</td>
</tr>
<tr>
<td>Coronary blood flow (ml./100 Gm./min.)</td>
</tr>
<tr>
<td>Cardiac O2 consumption (ml./100 Gm./min.)</td>
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<tr>
<td>Cardiac work (Kg. M./min.)*</td>
</tr>
<tr>
<td>Cardiac output (ml./min.)*</td>
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<td>Systolic pressure (mm. Hg)</td>
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<td>Coronary sinus venous O2 saturation (%)</td>
</tr>
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<td>Coronary A02 — Vo2 (vol. %)</td>
</tr>
<tr>
<td>Arterial Hb. (Gm./100 ml.)</td>
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<tr>
<td>Coronary O2 utilization (%)</td>
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</table>

*Regurgitant volume not reflected in measurements.
In general the results in man and ours in dogs agree in indicating that coronary blood flow and cardiac oxygen consumption are increased in chronic compensated aortic insufficiency. In our dogs the increase was found to apply to both a unit weight and the total weight of myocardial tissue. This differs from the renal hypertensive dog in which the increase in coronary blood flow and cardiac oxygen consumption does not apply to a unit weight of tissue but only to the total left ventricular weight. Since the amount of hypertrophy in aortic insufficiency was slightly greater than that present in the early hypertensive group, it would appear that increased coronary resistance is present only in the renal hypertensive, as a part of the generalized increased vascular resistance. In the animal with aortic insufficiency coronary resistance is even significantly lower than normal, although the amount of cardiac hypertrophy is at least as great as in the early hypertensives.

On the basis of the cardiac hypertrophy and the increased coronary blood flow and cardiac oxygen consumption present in the animal aortic insufficiency, it is reasonable to conclude that these changes are associated with an increased cardiac work comparable with that which occurs in the hypertensives. In the latter group the increased work results from an increase in blood pressure while in the aortic insufficiency animal blood pressure is normal but cardiac output must be increased as the result of the addition of a regurgitation volume to the normal venous inflow in the heart and the increased heart rate which also occurs. Our estimations of cardiac output and work show no elevation, but since the direct Fick method does not measure the regurgitant flow, the total cardiac output and therefore the total work of the heart could not be determined. Nevertheless, the development of cardiac hypertrophy in these experiments must result from an increased cardiac output as it has in other similar situations. Bazett and associates, by employing 2 methods to measure cardiac output (acetylene and pulse pressure with pulse wave velocity) have shown that cardiac output is increased in patients with chronic aortic insufficiency. Furthermore, Rose and associates measured cardiac output by the direct Fick method in patients with chronic aortic insufficiency before and after inserting a Hufnagel valve (a prosthesis) in the aorta to prevent regurgitation of blood traversing it; they found that cardiac output was increased after the artificial valve was installed. Finally, Kornor and Shillingford and Lange and Hecht have recently estimated total cardiac output (regurgitant flow included) in aortic insufficiency from an analysis of the shapes of indicator-dilution curves and concluded that the total cardiac output was increased. The increased cardiac output which also must occur in our animals coincided with an in-
creased cardiac rate. However, according to various investigators, this is not a constant finding. Stewart,26 and Wiggers27-28 and Wegria15 have reported little change in pulse rate while Hasenfeldt and Romberg29 noted a moderate increase and Marey30 and Bazett and Sands3 demonstrated marked increases in heart rate in aortic insufficiency. The presence of a tachycardia of itself has been shown to be associated with an increase in coronary blood flow and cardiac oxygen consumption.21, 22 It therefore seems reasonable to conclude that the increase in heart rate and an increase in cardiac work are responsible for the increase in coronary blood flow and cardiac oxygen consumption which occurs in these experiments.

SUMMARY
In dogs with chronic aortic insufficiency accompanied by cardiac hypertrophy and a compensated mean arterial blood pressure, the coronary blood flow, cardiac oxygen consumption, coronary arteriovenous oxygen difference, coronary oxygen utilization, systolic pressure and cardiac rate are increased significantly above normal dogs; while coronary venous oxygen saturation, coronary resistance and diastolic pressure are decreased significantly.

The stability of these preparations in duplicate determination was found to be less than that of the normal dog preparation.

ACKNOWLEDGMENT
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SUMMARIO IN INTERLINGUA
In canes con chronic insufficientia aortic accompaniate de hypertrophia cardiac e un compensate tension medie del sanguine arterial, le fluxo coronari de sanguine, le consumption cardiac de oxygeo, le differentia arterio-venose del oxygeo in le sanguine coronari, le utilisation coronari de oxygeo, le tension systolic, e le frequentia cardiac es augmentate significativamente in comparation con le valores de ille parametros in canes normal. Le saturation oxygene del sanguine coronari-venose, le resistentia coronari, e le tension diastolic, del altere latere, es redutcite significativamente.

REFERENCES


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