Mechanisms of Angina in Aortic Stenosis

By Ernest L. Fallen, M.D., William C. Elliott, M.D., and Richard Gorlin, M.D.

SUMMARY
The pathophysiology of cardiac pain in pure aortic stenosis has primarily been ascribed to an augmented left ventricular demand outstripping energy supply. This report provides evidence that not only is the energy demand increased but the supply in terms of coronary vascular reserve may be impaired, particularly in response to stress. Hemodynamic and coronary circulatory changes were studied in 18 patients with aortic stenosis during standard isoproterenol infusion. It was not possible to differentiate any patient with or without angina pectoris or patients with or without coronary artery disease on a basis of change in any measure of left ventricular dynamics. On the other hand, differences did occur in the mechanisms of energy delivery during isoproterenol stress: (1) In group A (aortic stenosis without angina or coronary artery disease), coronary flow increased normally, myocardial oxygen extraction decreased, and myocardial lactate production occurred in only one of seven patients. This suggested that energy supply was, generally, adequate to demand. (2) In group B (critical aortic stenosis with angina but no coronary disease), coronary flow rose insignificantly, myocardial oxygen extraction actually increased in three of five patients, and abnormal glycolysis occurred in all patients. This suggested that little or no reserve for increased coronary flow existed and that compensatory mechanisms had to be summoned. (3) In group C (aortic stenosis with angina and coronary artery disease), coronary flow rose normally, myocardial oxygen extraction decreased normally, but abnormal lactate metabolism occurred in most patients. This suggested adequate overall coronary reserve but evidence of regional ischemia.

Additional Indexing Words: Coronary flow Oxygen extraction coefficient Lactate metabolism

Left ventricular hypertrophy Isoproterenol Coronary artery disease

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HE REPORTED INCIDENCE of angina pectoris in aortic stenosis varies from 35 to 50%.1-4 If these figures are corrected to include only those patients with pure aortic stenosis without morphological evidence of coronary disease, then the incidence is approximately 20%.1,8 So far no method is available for distinguishing whether the cardiac pain is due to the valvular lesion per se or to coexistent coronary artery disease. Although it has been maintained by some that the characteristics of angina in aortic stenosis are usually atypical,2 this concept has been seriously challenged4,5 and is quite unreliable from a practical clinical standpoint.

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ANGINA IN AORTIC STENOSIS

Cardiac pain is believed to occur whenever the myocardial blood supply is insufficient to meet the energy demands of the heart. The clinical observation that angina is common to more than one distinct pathological entity provides a unique opportunity to explore some of the mechanisms through which angina may be elicited. Such an exploration has received only sporadic attention in the past and has culminated in two general schools of thought. The inciting mechanism of the angina in aortic stenosis has been ascribed by some investigators to those variables of augmented ventricular function which either compromise coronary blood flow directly or increase the energy demands of the heart beyond its ability to deliver an adequate coronary flow. Conversely, other investigators have emphasized the need for a more deliberate search into the problems of coronary vascular autoregulation and perfusion in the hypertrophied left ventricle.

The purpose of this presentation was to demonstrate whether a stress to cardiac energy metabolism could distinguish any differences in hemodynamics or coronary circulatory response or both in patients with aortic stenosis and angina depending on the coexistence of coronary artery disease.

Methods

Eighteen fasting subjects were studied by left heart and coronary sinus catheterization. All patients were classified into three groups (table 1). Group A consisted of seven patients with aortic stenosis and no history of angina pectoris. Group B consisted of five patients with aortic stenosis and angina of at least 6 months' duration, and group C comprised six patients with aortic stenosis, angina of at least 6 months' duration, and angiographic evidence of coronary artery disease. All but two patients in group A had selective coronary angiography. Patients were said to have coronary artery disease when intraluminal encroachment of any major vessel or its branches or both were readily visualized and exceeded 50% of vessel diameter.

Premedication consisted of 50 mg of meperidine and 50 mg of pentobarbital (Nembutal) given intramuscularly prior to each study. The following measurements were made during a resting control state and were repeated during intravenous infusion of isoproterenol at rates of 3 to 5 \( \mu g/min \): simultaneous arterial and coronary sinus oxygen content and capacity (manometric) and lactic acid concentration; coronary blood flow using \(^{85}Kr\) or \(^{131}I\) odoantipyrine; arterial and left ventricular pressures using Statham P23D strain-gauge manometers; and cardiac output measured in duplicate with the indicator-dilution technique using indocyanine green. The systolic ejection period (SEP), mean systolic ejection rate, and pressure-time per minute (PTM) were derived as described previously. Postmortem heart weights and careful bread-loaf sectioning of the coronary vessels were available in three cases in group B and in one in group A.

Statistical analysis for the group comparisons were based on the standard error of the mean differences. Probability values were derived from standard tables for the distribution of \( t \).

Results

Response to Isoproterenol

Group A (Aortic Stenosis Without Angina)

Only three of seven patients in this group had a critical valve area of 0.5 cm² or less and the mean systolic resting gradient across the aortic valve for the group was 42 mm Hg (table 1). The average cardiac index at rest was low at 2.6 L/min/m² and increased significantly with isoproterenol (table 2). This

Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of patients</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Angina</th>
<th>Coronary artery disease</th>
<th>Valve area (cm²)</th>
<th>Gradient (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>7</td>
<td>6</td>
<td>1</td>
<td>50</td>
<td>38-55</td>
<td>0</td>
<td>1.1 ± 0.5</td>
</tr>
<tr>
<td>B</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>56</td>
<td>46-64</td>
<td>+</td>
<td>0.5 ± 0.1</td>
</tr>
<tr>
<td>C</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>58</td>
<td>44-70</td>
<td>+</td>
<td>0.7 ± 0.2</td>
</tr>
</tbody>
</table>

*Values expressed ± so. Gradient refers to mean systolic pressure gradient across the aortic valve.
†Two of the seven patients in this group did not undergo selective coronary arteriography; the remainder had no evidence of coronary artery disease.

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increase was met primarily by an elevation in heart rate whereas stroke index increased moderately from 33 to 37 ml/beat/m². The time spent during systole each minute (SEP) was abnormally prolonged at 28 sec. The SEP increased moderately to 33 sec with isoproterenol. The average systolic ejection rate was low at rest but increased by 34% with the drug although individual variation was such that no significant difference occurred. The average resting PTM was elevated at 4,300 mm Hg-sec and increased by 22% with isoproterenol. The augmented energy requirements were met by a significant elevation in the coronary blood flow of 47% (fig. 1) and a decrease in both the coefficient of oxygen extraction and the coronary vascular resistance (figs. 2 and 3). Only one of seven patients in this group showed evidence of abnormal myocardial glycolysis with negative differences in arteriovenous lactate across the coronary bed (fig. 3). It should be noted that this patient was one of the two who did not undergo selective coronary arteriography (table 1). The average resting end-diastolic pressure (EDP) was elevated at

*The average systolic ejection period per beat was corrected for rate by dividing by the square root of the cycle length.4

Table 2
Effect of Isoproterenol on Hemodynamics in Aortic Stenosis

<table>
<thead>
<tr>
<th>Index</th>
<th>State*</th>
<th>Group A n = 7</th>
<th>Group B n = 5</th>
<th>Group C n = 6</th>
<th>Δ %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure time/min (mm Hg-sec/min × 10²)</td>
<td>R 43±10</td>
<td>43± 8</td>
<td>40± 9</td>
<td>+3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>I 52±11</td>
<td>51± 5</td>
<td>42±19</td>
<td>+3</td>
<td></td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>R 2.6±.5</td>
<td>2.3±.3</td>
<td>2.7±.7</td>
<td>+22</td>
<td></td>
</tr>
<tr>
<td></td>
<td>I 3.5±.8</td>
<td>3.2±.8</td>
<td>3.3± 1</td>
<td>+22</td>
<td></td>
</tr>
<tr>
<td>Stroke index (ml/beat/m²)</td>
<td>R 33± 8</td>
<td>31± 6</td>
<td>36±11</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>I 37±13</td>
<td>32± 4</td>
<td>36±14</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Heart rate (beat/min)</td>
<td>R 84±16</td>
<td>75±11</td>
<td>83±16</td>
<td>+30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>I 119±32</td>
<td>111±16</td>
<td>108±15</td>
<td>+30</td>
<td></td>
</tr>
<tr>
<td>Systolic ejection period (sec/min)</td>
<td>R 28± 3</td>
<td>27± 3</td>
<td>28± 2</td>
<td>-7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>I 33± 3</td>
<td>33± 4</td>
<td>26± 3</td>
<td>-7</td>
<td></td>
</tr>
<tr>
<td>Systolic ejection rate (ml/sec/m²)</td>
<td>R 102±23</td>
<td>86±19</td>
<td>121±39</td>
<td>+25</td>
<td></td>
</tr>
<tr>
<td></td>
<td>I 137±44</td>
<td>111±37</td>
<td>151±71</td>
<td>+25</td>
<td></td>
</tr>
<tr>
<td>End-diastolic pressure (mm Hg)</td>
<td>R 16±11</td>
<td>13± 6</td>
<td>13± 8</td>
<td>-12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>I 14±11</td>
<td>18± 9</td>
<td>11± 8</td>
<td>-12</td>
<td></td>
</tr>
<tr>
<td>Arterial diastolic pressure (mm Hg)</td>
<td>R 62±18</td>
<td>55± 8</td>
<td>64±15</td>
<td>-13</td>
<td></td>
</tr>
<tr>
<td></td>
<td>I 58±15</td>
<td>54±14</td>
<td>52±17</td>
<td>-13</td>
<td></td>
</tr>
<tr>
<td>Left ventricular systolic mean</td>
<td>R 184±26</td>
<td>166±39</td>
<td>185±51</td>
<td>-2</td>
<td></td>
</tr>
<tr>
<td>pressure (mm Hg)</td>
<td>I 214±21</td>
<td>192±15</td>
<td>181±65</td>
<td>-2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
* R and I refer to rest and isoproterenol states, respectively.
†% Change from average resting values. There was no significant difference between the standard error of the mean differences among all three groups for each hemodynamic measurement.
16 mm Hg and decreased slightly during catecholamine infusion (table 2).

All but one patient in this group had a valve area of 0.5 cm² or less. The average systolic gradient was 77 mm Hg, the highest of the three groups. Again, the catecholamine-induced increase in the average resting cardiac index (from 2.3 to 3.2 L/min/m²) was met primarily by a rise in heart rate while the average stroke index was still considerably lower than the predicted response to isoproterenol. The mean systolic ejection rate in this group was very low at 86 ml/sec/m² but increased by 31% in response to isoproterenol. The SEP, similarly, increased from a prolonged resting value to 33 sec. The average value for the end-diastolic pressure again increased further from an already elevated resting level. The PTM was elevated and the average value increased by 19% during the

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**Figure 1**
Effect of isoproterenol on coronary flow in aortic stenosis. Diff. S.E.M. = t values based on standard error of mean differences between the groups.

**Figure 2**
Effect of isoproterenol on oxygen extraction in aortic stenosis.

**Figure 3**
Effect of isoproterenol on lactate metabolism and coronary vascular resistance (C.V.R.) in aortic stenosis. Dotted line refers to observed response in a series of normal patients. C.V.R. values represent the mean and standard deviations of each group at rest and during isoproterenol.
stress. Although the energy demands in terms of the increase in PTM were similar at rest and during isoproterenol infusion in groups A and B, a striking contrast occurred in the hearts’ ability to increase coronary flow in order to meet these demands. Thus, whereas group A had a significant increase of 47% in coronary flow with the catecholamine, group B showed a relatively fixed flow with an insignificant average increase of only 22% (fig. 1). The average resting flow of 104 ml/100 g/min in this group did not differ significantly from the other groups (98 for group A and 91 for group C). Furthermore, the mean coefficient of oxygen extraction actually increased in three of five patients while the coronary vascular resistance (CVR) fell (figs. 2 and 3). All five patients in this group showed evidence of abnormal lactate metabolism with myocardial lactate production during isoproterenol infusion in four patients and less than 10% extraction in one patient (fig. 3).

**Group C (Aortic Stenosis with Angina and Associated Coronary Disease)**

Only one patient in this group had a valve area less than 0.5 cm² and the resting mean systolic aortic gradient averaged 31 mm Hg (table 1). The cardiac index was subnormal (2.7 L/min/m²) and increased by 22% with infusion of isoproterenol (table 2). Again, the average stroke index was fixed at 36 ml/beat/m² whereas the chronotropic effect of the drug accounted for the increase in effective output. The SEP was prolonged at 28 sec/min and decreased insignificantly with isoproterenol. The average systolic ejection rate, likewise, changed insignificantly with administration of the catecholamine. This is probably due to a more pronounced effect of isoproterenol in decreasing afterload in this group. As in group A, there was a significant increase in coronary flow from an average value of 91 to 140 ml/100 g/min, an increment of 52% (fig. 1). Both the coefficient of oxygen extraction and the CVR decreased with isoproterenol. Half of the patients in this group had evidence of myocardial lactate production (fig. 3). The resting end-diastolic pressure was slightly elevated at 16 mm Hg and decreased to the same extent as group C.

**Comparison of the Groups**

Comparison of the three groups shows no significant difference in the resting values of all parameters measured. Furthermore, table 2 shows that isoproterenol fails to differentiate the groups on the basis of hemodynamics alone. Directional trends may be apparent, as in the end-diastolic pressure, but the variation is too large to detect a significant difference. On the other hand, clear-cut differences are evident between the groups when changes in coronary dynamics are analyzed. Thus, whereas the patients in groups A and C showed the same directional changes in coronary flow and myocardial oxygen extraction, the response of three of the five patients in Group B to isoproterenol consisted of a virtually fixed coronary flow and an increase in oxygen extraction. When the mean differences are compared among the groups, there is a significant difference between (1) the coronary flow responses to isoproterenol in group B and group C (P = 0.025) and (2) between the changes in oxygen extraction in group B and the rest. Isoproterenol could not distinguish between the groups on the basis of changes in the coronary vascular resistance (fig. 3).

Except for one patient in group A and two in group C, all patients showed either or both electrocardiographic and radiological evidence of left ventricular hypertrophy.

**Postmortem Findings in Four Patients with Aortic Stenosis**

On the assumption that homogeneous coronary flow rates obtain in different regions of a concentrically hypertrophied myocardium, it has been possible to calculate the percentage contribution of the cardiac output to the total coronary blood flow. This has been estimated for three patients in group B and one in group A in whom necropsy findings confirmed the absence of significant coronary lesions. As shown in table 3, 13 to 28% of the cardiac output in patients in group B perfused the myocardium each minute at rest.
Table 3

Contribution of Cardiac Output to Myocardial Blood Flow*

<table>
<thead>
<tr>
<th>Patient's group</th>
<th>Heart weight (g)</th>
<th>Cardiac output (L/min/m²)</th>
<th>Coronary flow</th>
<th>% Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal†</td>
<td>300</td>
<td>5.0</td>
<td>80</td>
<td>4</td>
</tr>
<tr>
<td>B</td>
<td>460</td>
<td>2.0</td>
<td>120</td>
<td>28</td>
</tr>
<tr>
<td>B</td>
<td>650</td>
<td>4.0</td>
<td>120</td>
<td>20</td>
</tr>
<tr>
<td>B</td>
<td>580</td>
<td>3.7</td>
<td>82</td>
<td>13</td>
</tr>
<tr>
<td>A</td>
<td>660</td>
<td>4.1</td>
<td>72</td>
<td>11</td>
</tr>
</tbody>
</table>

*The calculated % contribution of total cardiac output serving the myocardium each minute is derived as the ratio of total myocardial flow to cardiac output in ml/min multiplied by 100.
†Normal refers to average values computed for a man weighing 70 kg as a means for comparison.

Although the one patient in group A had the largest heart (660 g), the calculated percentage of total cardiac output serving his myocardium was low (11%) compared to that of the other patients. All values, however, were elevated when compared to the normal of 4%.

Discussion

The normal response of the coronary circulation to isoproterenol consists primarily of an increase in coronary blood flow in excess of oxygen demand. Hence, the coronary venous oxygen content increases, the coefficient of oxygen extraction falls, and consistent with the drug’s β-adrenergic effect on peripheral arteries, coronary vascular resistance decreases. All these responses were observed in groups A and C. A different response, however, was noted among the patients in group B who had severe aortic stenosis and angina pectoris but no demonstrable coronary arterial lesions. These patients demonstrated a relatively fixed coronary flow in response to the catecholamine (figs. 1 and 2). This occurred despite the fact that the resting flow in this group, although slightly greater, did not differ significantly from that of the other patients. Correspondingly, abnormal mechanisms were summoned to compensate for what appeared to be inadequate coronary flow response to augmented oxygen demands in group B. These included (1) an actual increase in the coefficient of oxygen extraction in three of five patients during the isoproterenol infusion; (2) initiation of anaerobic myocardial glycolysis as evidenced by abnormal lactate metabolism, in that four of five patients produced lactate signifying inadequacy of normal oxidative metabolism. The only patient in group A who produced lactate from the myocardium had a critical valve area of 0.5 cm² while 50% of the group with coronary artery disease showed similar production.

It is noteworthy that in a recent study, two out of four patients with aortic stenosis and angina increased their flow by less than 25%. A valid comparison with the present series is difficult to make since not only was a different stress used (supine leg exercise) but no information was available regarding the presence or absence of coronary artery lesions. This study also alluded to the possibility that near maximum coronary vasodilation at rest may become limiting in patients with aortic stenosis and, thereby, play a role in the etiology of angina with stress. The present study would generally support this thesis in that there may be an encroachment on total coronary reserve capacity. That the system was not maximally dilated, however, was shown by the observation that vascular resistance in group B decreased proportionally more than coronary flow increased. On the other hand, it is conceivable that near maximum coronary flow is already occurring in patients who have severe aortic stenosis with massive hypertrophy, particularly in terms of the heart’s ability to autoregulate its flow, by whatever means, in response to increased demands.
The mechanism for the production of pain at the cellular level may be the same for all groups, and this problem remains unresolved by this type of study. But there appear to be distinctly different pathophysiological processes which may precipitate the myocardial ischemia which presumably causes pain. Although both groups B and C produce lactate, nevertheless, in the group with coronary artery disease, total as opposed to regional coronary reserves is far from exhausted. The angina in this group may very well be related to the arterial obstructive lesions which reduce the flow to local areas of myocardium. Heterogeneity of myocardial blood flow has been assumed to result from significant coronary artery stenosis. This has been demonstrated for the first time by studies showing clearance rates of $^{85}$Kr, injected intramyocardially along the distal course of a stenosed coronary vessel during heart surgery. Both normal and subnormal clearances exist side by side. In group B, however, coronary reserve capacity of the entire left ventricle, not just a region, appears to be threatened. Abnormal mechanisms for energy supply are brought into play including increased oxygen extraction from arterial blood and anaerobic glycolysis. As further testimony, three patients in this group who were studied at necropsy had heart weights from 460 to 650 g and estimated total resting myocardial flow from 475 to 750 ml/min (table 3). Myocardial blood flow thus represented from 13 to 28% of total cardiac output. The "drain" from the remaining circulation can best be appreciated in light of the fact that the normal coronary fraction of total cardiac output is only 4 to 5%.

Some investigators have suggested that myocardial ischemia and, therefore, potentially, the pain mechanism in aortic stenosis is dependent on the hemodynamic mechanisms by which the heart ejects a given volume of blood through a narrow fixed orifice. Such factors may include systolic impedance to coronary flow, prolongation of the systolic ejection period to maintain stroke output at the expense of a decreased diastolic period of nutrient flow, an increase in wall tension outstripping oxygen availability, or a diminished diastolic perfusion pressure in association with coexistent aortic insufficiency. However, all three groups in the present series manifested similar hemodynamic responses to a restricted outflow (table 2): that is, an abnormally elevated PTM, a prolonged SEP, an increased end-diastolic pressure, and a decreased systolic ejection rate (SER) were seen in all groups at rest. Furthermore, these parameters responded variably to isoproterenol, and no discernible pattern could be recognized. Likewise, no significant depression of the diastolic perfusion pressure in the aorta was documented and resting values were comparable.

The selection of flow methods which measure mean capillary diffusion challenge the thesis that the distance from capillary to muscle fiber is a major determinant in limiting nutrient flow to the hypertrophied cell. It has been postulated that different rates of clearance, for any given isotope, can occur by virtue of compartmentation and thus yield different flow values, particularly when flow changes are induced experimentally. In the present study this is obviated since all groups share a common disease process implying that compartmentation would not necessarily be a differential feature. Furthermore, the concept of a quantitative disparity between the number of muscle fibers in hypertrophy and the number of capillaries has been seriously questioned by Linzarc. He maintained that any insufficiency of flow to the hypertrophied myocardium is due to a limitation in the caliber of the large coronary vessels, notably the ostium, rather than a change in diffusion distance. Indeed it has been demonstrated that the diameter of the coronary ostium increases linearly with heart weight but reaches a maximum at heart weights of 500 g. It is hard to invoke such a simple anatomic restriction, particularly in view of the many homeostatic mechanisms governing the regulation of phasic coronary flow. Hence, this theory would not explain the significant...
increase in flow in the patients without angina, in whom there was evidence of hypertrophy by x-ray, ECG, and cineventriculography. In addition, differences in heart weights appeared to have no bearing on the observation that all groups had similar resting coronary flows per unit mass. Rather than an anatomic limitation, a more feasible explanation would be a functional encroachment on the total coronary vascular reserve. Thus the patients in group B when given isoproterenol were able to deliver a modest increase in blood flow to the periphery whereas flow to the myocardium appeared to be almost maximal despite a significant drop in the coronary vascular resistance.

It should be recognized that these observations were made on patients grouped according to a prior history of angina rather than according to the induction of pain during the catheterization procedure. Consequently, any interpretation of a mechanism for inducing pain on the basis of the observed hemodynamic changes is tenuous. Nevertheless, the striking discrepancy in the coronary dynamics among the groups leads us to believe that a classification of patients with aortic stenosis and angina on the basis of the presence or absence of coronary artery lesions is justified. Furthermore, such a perspective of aortic stenosis may have some practical clinical virtue. It is important to know, both diagnostically and prognostically, whether the chest pain in an individual with aortic stenosis is due primarily to his valvular lesion or to associated coronary artery disease. Surgical correction of the aortic lesion can reverse the abnormal coronary dynamics completely or only partially depending on the association of coronary disease. Furthermore, coronary heart disease if extensive enough can make the risk of surgery formidable.

Acknowledgment

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References


Thrombosis 1686
Malpighi

Remarkable morbid states commonly arise in animals, through the caprices of Nature or the vagaries of disease. These states I have always considered as shedding much light on the investigation of Nature's ways of acting; they indicate the capacities and tendencies of the material which stands revealed in the construction of the animal body. And so monsters, and other anomalies dissipate our ignorance more easily and reliably than the chefs d'oeuvre of Nature.

Among these morbid states, brought about quite commonly by disease in the cadaver, not the least noteworthy is the Polyp. For it is found in the most deadly diseases, occupying the body's inmost citadel; and research into it can illuminate problems previously baffling.

The cause of Polyps ought not to be restricted to the conditions already mentioned. For Polyps are found to occur when certain poisons are drunk, and in the mortal fevers due particularly to contamination of the air, and in the plague and other illnesses due to harmful contagion. In these cases it is likely that vapours, or abnormal juices, from perverted ferment in the organs, find entry to the blood, tamper with its structure, and rearrange its particles. They can remove the bonds by which the tiny fragments of white fibres are held in place and linked to the rest. Or else, as if they had hooks, they bind the suspended fibers together into a fine network which precipitates.

On the topic of Polyps, my pen has outrun my original intention; for it is long established that stored blood is always a fertile producer, yet wearies the human mind by the inadequacy of human knowledge.—Marcello Malpighi: De Polypo Cordis Dissertatio with English translation by J. M. Forrester. (Extract from Opera Omnia by Marcello Malpighi, 1686.) Uppsala, Almqvist & Wiksells, 1956, pp. 3 and 12.
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