Intramural Hemorrhage in Coronary Atherosclerosis

By Thomas M. Blake, M.D., and Philip K. Springer, B.S.

The mechanism of the development of acute occlusion of the coronary arteries is subject to considerable discussion. Intramural hemorrhage has been suggested as a cause of acute occlusion by the hematogenous enlargement of atheroma without associated thrombosis. By a systematic study of coronary arteries with a special technic of injection and clearing of the vessels the frequency of this mechanism was determined.

Atherosclerosis is present to some extent in almost every adult in the United States, and occlusive lesions of coronary arteries are found frequently at autopsy in young people who die of noncardiac causes and in whom there had been no clinical evidence of heart disease. Atherosclerosis itself, then, is usually asymptomatic and is important chiefly as a basis for superimposed lesions that result in acute occlusion of arteries, especially coronary arteries. The mechanisms whereby an asymptomatic atheroma suddenly becomes the seat of such a catastrophic complication are not known. A review of the literature indicates that hemorrhage within the substance of an atheroma may well be at least one significant factor. When looked for, such hemorrhages can usually be found in association with acute occlusions and Paterson, who is largely responsible for this observation, has suggested that they may serve to initiate thrombosis. Wartman and Paterson have also described occlusion of coronary arteries by hematogenous enlargement of atheroma without associated thrombosis.

The study reported here was undertaken to determine the incidence of intramural hemorrhage in the coronary arteries of the population at large by means of a technic that allows the stereoscopic study of large segments of arteries and facilitates the recognition of hemorrhages.

Material and Method

Hearts were obtained from every second autopsy done by each prosector in the Department of Pathology of the University Hospital. Only those from children under 5 years of age were excluded. The hearts were placed in normal saline solution at the time of autopsy and refrigerated at 1 to 2 C. for not more than 48 hours—usually 12 to 24 hours. At the time of study they were warmed to 37 C. and the coronary arteries washed with saline by a method described by Durlacher and co-workers and used by Hamilton and Mowbray. When the outflow from the coronary sinus was clear, the perfusion fluid was changed to a 1:8 suspension of Higgins' engrossing ink in water as suggested by Winternitz and associates and the injection was continued until the myocardium was black. The intact heart was then fixed in 10 per cent formalin. Later the subepicardial portions of the coronary arteries were dissected and their adventitia was removed. The remaining parts of the vessels were cut into short segments, cleared by a modified Spalteholz method, and mounted in clear plastic. Tissue for routine microscopic study was taken from the coronary arteries before mounting, and the hearts were studied grossly and microscopically by the usual technics after the arteries had been removed.

The cleared, injected, unstained arteries were studied stereomicroscopically and hemorrhage was recognized by color or identifiable erythrocytes. No attempt was made to evaluate the observations quantitatively; only the presence or absence of intramural coronary arterial hemorrhage was recorded for each heart.

Results

Table 1 shows that no intramural hemorrhage was found in the coronary arteries of any patient less than 45 years old. In men over this age the incidence was 70 per cent; in women, 28 per cent. The mean age of the 27 men in this group was 65 years and that of the 18 women 58. There were 14 men and

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TABLE 1.—Incidence of Intramural Hemorrhage in Coronary Arteries of Human Subjects
Male Ages Ranged from 12 to 85, Female Ages from 13 to 87

<table>
<thead>
<tr>
<th>Age</th>
<th>White</th>
<th></th>
<th>Negro</th>
<th></th>
<th>Total</th>
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<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>45 and over</td>
<td>16 11 69</td>
<td>29</td>
<td>11 8</td>
<td>73</td>
<td>11 3</td>
<td>27</td>
</tr>
<tr>
<td>Under 45</td>
<td>4 0 0</td>
<td>0</td>
<td>3 0</td>
<td>0</td>
<td>5 0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>20 11 55</td>
<td>18</td>
<td>14 8</td>
<td>57</td>
<td>16 3</td>
<td>19</td>
</tr>
<tr>
<td>Summary</td>
<td>31 whites with</td>
<td></td>
<td>30 Negroes with</td>
<td></td>
<td>61 patients in all</td>
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<tr>
<td></td>
<td>13 hemorrhages = 42%</td>
<td></td>
<td>11 hemorrhages = 37%</td>
<td></td>
<td>with 24 hemorrhages = 39%</td>
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TABLE 2.—Incidence of Intramural Hemorrhage as Related to Amount of Atherosclerosis

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<tbody>
<tr>
<td>None</td>
<td>6 0</td>
<td>0</td>
<td>4 0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Little</td>
<td>7 3</td>
<td>29</td>
<td>11 0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>18</td>
<td>2</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Moderate-to-marked</td>
<td>21 16</td>
<td>81</td>
<td>12 5</td>
<td>33</td>
<td>33</td>
<td>22</td>
<td>67</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Total</td>
<td>34 19</td>
<td>56</td>
<td>27 5</td>
<td>19</td>
<td>61</td>
<td>24</td>
<td>39</td>
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**Fig. 1** Top. Normal coronary artery. The intima is outlined by ink particles which give it a "tree-bark" appearance. Note the smooth, translucent wall which is seen tangentially and is of uniform thickness. Its outer edge is indicated by inked lines. × 7.

**Fig. 2** Bottom. Intramural hemorrhage and vasa vasorum. Note irregularity of thickened arterial wall. Some of the opacity in the center of the specimen is evidently calcium (C). × 7.
5 women in the series who were 65 or older, and the incidence of intramural hemorrhage in these small groups was 80 and 60 per cent, respectively. There was no significant difference between the findings in Negroes and those in white subjects.

The degree of atherosclerotic involvement of the arteries in each case was noted arbitrarily as none, little, or moderate-to-marked on the basis of gross observation. Table 2 indicates that hemorrhage was clearly more common with more extensive disease.

There were 20 patients in the series who were defined as hypertensive on the basis of a recorded blood pressure of 150 or more systolic or 90 or more diastolic at some time during hospitalization. Ten of these (50 per cent) had intramural hemorrhage. Seven of the 12 men in this group (58 per cent) and 3 of the 8 women (38 per cent) showed intramural hemorrhage. Only 1 of the hypertensive subjects was less than 45 years old and no hemorrhage was found in his arteries. If he is not counted, the incidence of intramural hemorrhage in the hypertensive group, all 45 or over, was 53 per cent. In the 25 patients 45 or older with normal blood pressure the incidence was 56 per cent. Thus there was no correlation between intramural hemorrhage and blood pressure.

Recent myocardial infaracts were found in 6 hearts, 5 men and 1 woman, and intramural hemorrhage was present in only 4 of these—all men. Both of the patients with myocar-
dial infarction without hemorrhage were hypertensive Negros, a 42-year-old man and a 47-year-old woman, and infarction had not been suspected clinically in either case. Each had congestive heart failure and died in uremia. Only 4 patients were receiving anticoagulant therapy at the time of death. Three of these were being treated for myocardial infarction and 1 for angina, and in none was the prothrombin concentration significantly depressed.

Vasa vasorum were demonstrated in many atheromata. These arose from the lumen of the artery in some instances and came from the outer parts of the wall in others. Many atheromata contained no injected vasa vasorum and often none was seen in the vicinity of frank hemorrhage.

**DISCUSSION**

Atherosclerosis is nearly ubiquitous in man—at least in Americans and Europeans—and not infrequently even produces complete occlusion of coronary arteries without clinical evidence of heart disease. It is the acute occlusive lesions of arteries that sometimes develop in association with atheroma that constitute the real threat posed by atherosclerosis, and these must be considered complications of the disease rather than an inevitable consequence of it. While it is obvious that ultimate hope lies in the prevention of atherogenesis or resolution of lesions already present, it seems worthwhile until this goal is reached to determine if possible the factors responsible for these complications. Intramural hemorrhage has been suggested as a factor and the data reported here emphasize the frequency with which hemorrhage is found as a part of atherosclerosis. It should be pointed out that the method described demonstrated only fresh hemorrhages. If some method of recognizing old ones like that described by Paterson and associates\(^1\) had been used, it is likely that many more would have been found.

It is interesting that the frequency of these lesions was no greater in the presence of hypertension than with normal blood pressure. One very pertinent question, the effect of anticoagulant drugs on the incidence of intramural hemorrhage, remains completely unanswered, since no patient in our series had significantly depressed prothrombin activity at the time of death.

Our observations with regard to vascularization of the lesions are not conclusive but are in accord with those of Paterson and Winternitz and demonstrate that atheromata, like other tumors, have a blood supply. Whether the hemorrhages that occur in their depths are passive as a result of simple necrosis due to "outstripping" of the blood supply, infarction of the atheroma as the result of occlusion of the nutritive vasa, or active rupture of the vasa vasorum, remains speculative. The stereoscopic method used, however, makes it clear that most of the hemorrhages are deep in the wall of the vessel without any communication with the lumen.

The possibility that these hemorrhages are of clinical significance in the production of occlusive complications of atherosclerosis remains an interesting hypothesis. Their existence, however, is a fact and suggests that coronary arteries should be regarded as complicated organs dependent on their blood supply, like the heart itself. It is possible that study of this microscopic blood supply and its disorders may yield information of importance in the control of heart disease.

**Conclusions**

Intramural hemorrhage is a common complication of atherosclerosis and was found in 70 per cent of men and 28 per cent of women over 45, but in no patient under that age. The possibility that these hemorrhages may be a factor in the precipitation of acute occlusive lesions of coronary arteries is discussed.

**Acknowledgment**

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SUMMARIO IN INTERLINGUA

Hemorrhagia intramural es un complication commun de atherosclerosis. Illo esseva incognita in 70 pro cento del masculos e 28 pro cento del femininas de etates de plus que 45 annos sed in nulle patiente de un etate plus juene. Es discute ita possibilitate que iste hemorrhagia es un factor in le precipitation de acute lesions occlusive in le arteries coronari.

REFERENCES


Aortic regurgitation and rheumatoid arthritis have been observed concurrently in 22 male patients between 18 and 64 years of age all but 2 of whom had spondylitis. Fifty-nine per cent of the patients had uveitis. The cardiac lesions tended to be strikingly similar to those of syphilitic heart disease with aortic regurgitation. However, the destructive lesions of the aortic wall remain circumscribed and do not extend beyond the ascending portion of the artery. The cardio-aortitis is thought to represent a systemic manifestation of rheumatoid disease because of the temporal relation between onset of cardiac signs and activity of the arthritis, the absence of evidence implicating syphilis or rheumatic fever, and the basic resemblance of the microscopic changes in the aorta and heart to those of other rheumatoid lesions.

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