Aging Processes in the Arterial and Venous Systems of the Lower Extremities

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Wear and tear degenerative patterns of the arterial system of the lower extremities have been studied in an age series. The intensity of these alterations has been correlated with the distribution of the atheromatus plaques and thrombosis as well as with the effective tension at various levels as calculated by Burton’s formula. Evidence is presented for the concept that the lipids in atheromatos plaques arise as a product of these degenerative reactions within the vessel wall, rather than by diffusion from the circulation through the endothelial barrier.

IN PREVIOUS reports we have defined aging processes in blood vessels as those alterations resulting from the effects of wear and tear factors which have been operating over a relatively long period of time.\(^1\)\(^-\)\(^6\) Specifically, these investigations have dealt with the comparative rates of degeneration, new formation and subsequent calcification of the elastic elements of arteries in various anatomic sites. In general, intimal plaques were observed to occur most frequently in those arteries in which these alterations were most marked along the internal elastic zone, and it was further pointed out that physical factors play an important role in the point of localization and rate of development of these plaques. Thus, the lower portion of the aorta and the coronary arteries show a relatively rapid development of aging processes and a high rate of occurrence of intimal plaques, while the hepatic and pulmonary arteries show atheromata rarely and only a slow and mild progression of elastic tissue calcification. Differences in the rate of development of these changes in elastic elements between Negro and white groups have been studied in comparable segments of coronary, renal, splenic and pulmonary arteries, as well as various portions of the aorta.

Following upon the pioneer descriptive studies of the European founders of pathology, the standard textbooks in this field continue to distinguish three forms of degenerative vascular alterations: atherosclerosis, which is stated to occur primarily in elastic arteries; Mönckeberg sclerosis, which is believed to be principally a disease of muscular arteries; and hyaline intimal proliferation, which is supposed to occur primarily in small arteries and arterioles.\(^7\)\(^-\)\(^9\) It has become apparent from our previous studies that no such anatomic distinction can be made. While in young individuals there is a gradual diminution in the concentration of elastic elements in the medial coat of arteries with increasing order of branching from the aorta, these elastic elements are as capable of reduplication, degeneration and calcification in any of these sites as in the aorta or its first order branches. Furthermore, lipids, from which the term “atherosclerosis” is derived, may be found in elastic arteries, muscular arteries, including those of the lower extremities,\(^10\) and small arteries and arterioles.\(^11\)

That physical forces are important in the determination of the intensity of changes in the elastic elements became apparent when it was noted that “rock” and bone formation occur in such branches as the renal and splenic arteries. Similar changes have also been described in the coronary arteries of infants, probably as a result of some disturbance in calcium metabolism.\(^12\)\(^-\)\(^14\) The present investigations were undertaken in order to study the role of physical forces in the determination of the intensity of changes in the elastic elements. It seemed

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that the vascular tree of the lower extremity would lend itself well to such a study, since the elastic elements in young individuals are sharply defined, a variety of sizes of vessels can be studied and readily measured, and the magnitude of the physical forces exerted upon them can be calculated. The present study, like our previous studies, attempts to relate the frequency and site of plaque formation and thrombosis to the distribution of elastic elements and the intensity of their aging changes. Observations were made on veins as well as arteries.

**Material and Method**

The major arteries and veins were dissected out of 45 lower extremities; most of these were in extremities amputated at the midthigh region and in each of these a full complement of vessels, as designated below, was obtained. The entire length of the vessels was studied grossly for sites of thrombotic occlusion. Thirty-six of the 45 limbs were amputated because of gangrene resulting from vascular occlusion on an arteriosclerotic basis; the youngest patient whose limb was studied was a diabetic, aged 47. Accordingly, the age of the latter case served as a division point between the group showing marked vascular sclerosis and a smaller group of nine younger individuals whose extremities were amputated because of tumor or trauma. The latter group was utilized in order to study the earlier aging changes.

A full complement of arteries for histologic study consisted of a segment of the popliteal artery at a level of about 1 cm. above the popliteal fold, a segment of anterior and posterior tibial arteries obtained 1 cm. distal to the point of bifurcation from the popliteal artery, a second segment of each tibial artery about 1 cm. above the malleolus line, a segment of dorsalis pedis artery about 3 cm. below the malleolus line, and a segment of digital artery (including skin) about 1 cm. distal to the interdigital web. Specimens of gastrocnemius muscle were taken for a study of its nutrient arteries.

In the case of the popliteal and both tibial arteries transverse and longitudinal sections were studied. In most instances additional sections were taken through plaques or thrombi, when such could be found, between the amputation site and the malleolar line. All specimens were fixed in formaldehyde solution diluted 1:10 with dehydrated alcohol and processed as described in previous reports.* A section was stained with hematoxylin and eosin; an adjacent section was stained for elastic tissue by the Weigert-Verhoeff method; a third section was microincinerated and studied by dark field illumination for mineral distribution.

In the course of these studies it became apparent that measurement of the internal diameter of vessels would appreciably aid in interpreting the results. Accordingly, such measurements were obtained from the lower extremities of six cadavers, all over 50 years of age.* In no instance was there evidence of occlusive vascular disease as evidenced by thrombosis of any of the vessels included in this series. From these data the internal hydrostatic pressures at various levels were calculated from the Laplace formula \( T = P \times R \) as developed by Burton, where \( T \) represents the tension, \( P \) the blood pressure, \( R \) the radius of the artery. The height of the pressures thus determined was compared with the intensity of alterations in the elastic elements as well as the frequency of plaque formation and thrombosis.

**Results**

**Aging Changes in the Arteries of the Lower Extremities**

From our previous studies of other arteries, it is apparent that in the newborn the internal elastic lamella of all arteries lies against the endothelial lining. An examination of the lower extremity vessels in several stillborn infants resulted in the same finding. The external elastic lamella consists of several rows of thin, elongated elastic fibers. Microincinerated sections of all of these arteries showed only a nuclear distribution of calcium.

**Popliteal Artery.** By the age of 20, changes from the above basic pattern are already apparent. A thin layer of collagen of irregular thickness separates the endothelium from the inner elastic zone. The latter consists of several parallel wavy fibers, from which finer filaments extend into the media as well as into the intimal layer of collagen; this is accompanied by deposits of calcium along these elastic elements (fig. 1). With increasing age the subendothelial layer of collagen becomes progressively thicker and contains a greater number of elastic filaments; the latter appear to break down into shorter filaments and fine granules which take the elastic stain. Elastic tissue extensions of similar character are also found in the media in progressively increasing amounts, and calcification in the media also becomes progressively more intense. As this process con-

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The aging changes in this vessel are qualitatively similar to those described above, but progress at a much slower rate. Duplications of the internal elastic lamella are much less pronounced at about the age of 20 and there are fewer elastic filaments in the media. Subendothelial collagen deposition is also not as marked, but even in these, elastic filaments may be seen. Actual rock formation was encountered in only one subject, an individual 90 years of age (fig. 6).

Digital and Muscular Arteries. Subendothelial collagen deposition occurs quite late in vessels of the caliber encountered in muscle septa and in the digital vessels. Duplications of the internal elastic lamella are seen very rarely, but fenestrations of the elastic membrane are frequent (fig. 7). The media only rarely shows fine elastic filaments. A thin line of calcium usually outlines the internal elastic membrane in incinerated preparations, but the media calcium remains nuclear in distribution in aged individuals.

Aging Changes in the Veins of the Lower Extremities

Observations were limited to the popliteal and tibial veins and, in general, the findings correspond to those described by Lev and Sapir. Endophlebohypertrophy, consisting of a proliferation of collagenous connective tissue and the appearance of fibrils of elastic staining material in the intima, appears even in specimens from young subjects; these veins also show collections of elastic fibrils between muscle fibrils in the media. An early deposition of calcium along these elastic elements is observed in incinerated specimens. In older individuals there is disruption of the internal elastic lamella and of many elastic fibrils in the intima and media. Resulting from this there are fragments, filaments and granules of elastic staining material in both layers, accompanied by progressively increasing calcification of these elements. Phlebosclerotic plaques are numerous in veins of older individuals, and contain disrupted elastic elements and deposits of calcium (fig. 8). As we have noted in arteries, and as also observed by Lev and Sapir, elastic fibers are abruptly interrupted at the margins of areas of calcification. However, the use of incinerated sections has permitted the additional observation that calcification first occurs along elastic elements, although the latter may subsequently
Fig. 1. Popliteal artery; 21 year old male. Figure 1a illustrates the early duplication of the internal elastic lamella with fine granular elastic staining material between the two wavy fibers as well as between the upper fiber and the endothelial lining. Granular elastic material can be seen along the left half of the microphotograph deep in the media. Figure 1b shows calcification of the duplicated elastic lamella and of the media; some of the latter is not limited to elastic elements. (X 66)

Fig. 2. Popliteal artery; 63 year old male. Both 2a and 2b show bone formation replacing the media. In 2a a thin elastic band courses along the inner surface of the bone, and elastic fibrils and granules are present in the intima. (Compare with fig. 3 which probably represents an earlier stage of this process.) Calcium ash corresponding to the elastic elements and the bone are present in 2b. (X 66)

Fig. 3. Anterior tibial artery; 90 year old male. Figure 3a shows a recanalized thrombus with an elastic lamella about the newly formed lumen. This lamella shows duplications and some granulation. Elastic fibrils are also scattered through the fibrous tissue between the lumen and the original inner elastic zone. The black area at the bottom of the microphotograph is a mass of calcific material typical of Möenkeberg sclerosis, but its contiguity and continuity with elastic elements as well as its affinity for elastic stains indicates elastic extension into the media. Figure 3b shows deposition of white mineral ash along the newly formed elastic elements as well as heavy calcific deposits in the media, the latter resulting in some tearing of the section. (X 66)
Fig. 4. Popliteal artery; 75 year old male. The media of this artery is in the lower left hand corner. It is composed of densely packed elastic elements similar to those seen in figure 3. The identity of the internal elastic lamella can be made out as a continuation of the inner margin of the media towards the right. This area was so heavily calcified in the incinerated specimen that fragmentation resulted in a complete loss of anatomic relationships. The intima is markedly thickened and composed of fibroblasts in a basophilic matrix. Cholesterol slits are present in the lower right hand corner of the intima. A newly formed thin elastic lamella lies immediately beneath the endothelial lining. (× 66)

Fig. 5. Anterior tibial artery; 70 year old male. A large atheromatous plaque has resulted in replacement by fibrous tissue of intima as well as media, including elastic structures. Numerous cholesterol slits are present in the upper part of the photomicrograph. (× 66)

Fig. 6. Dorsalis pedis artery; 90 year old male. Figure 6a shows marked thinning of the wall and several foci of calcification in continuity with elastic elements. Figure 6b shows dense white mineral ash particularly heavy in the zone corresponding to the black portion in 6a. Note lack of elastic material in a relatively thin intima. (× 66)

Fig. 7. Digital artery; 69 year old male. The artery has a relatively “youthful” appearance despite the age of the patient. There is negligible intimal thickening and only slight fragmentation of elastic elements. (× 66)

Fig. 8. Posterior tibial vein; 69 year old male. Note numerous elastic fragments, filaments and granules through all layers of the wall, as well as a plaque-like elevation of the intima. Incinerations of such specimens show extensive calcification. (× 66)
disappear either in a calcific mass or by replacement by collagenous connective tissue.

Furthermore, we have been able to corroborate the observation of Lev and Saphir\textsuperscript{18} that at the point of contact of artery and vein no plaque is formed, but rather they are found to the sides of indentations produced by such contact. Where artery and vein are contiguous however, there is a disruption of elastic elements of the external lamellar zone and calcification of the media.

The Relation of Hydrodynamic Stresses to Aging Changes in Blood Vessels

Several interesting associations can be made from the data shown in Table 1. Those arteries

<table>
<thead>
<tr>
<th>Artery</th>
<th>Number of Cases</th>
<th>Per cent with Plaques</th>
<th>Per cent with Thrombi</th>
<th>Average Calculation</th>
<th>Internal Diameter</th>
<th>Hydrostatic Tension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Popliteal</td>
<td>36</td>
<td>78</td>
<td>30</td>
<td>3.4 + 0.49</td>
<td>26,480</td>
<td></td>
</tr>
<tr>
<td>Tibials (combined)</td>
<td>35</td>
<td>73</td>
<td>70</td>
<td>2.7 + 0.22</td>
<td>11,440</td>
<td></td>
</tr>
<tr>
<td>Dorsalis Pedis</td>
<td>29</td>
<td>31</td>
<td>32</td>
<td>1.7 + 0.14</td>
<td>6,370</td>
<td></td>
</tr>
<tr>
<td>Digital</td>
<td>28</td>
<td>0</td>
<td>0</td>
<td>0.6 + 0.04</td>
<td>1,820</td>
<td></td>
</tr>
<tr>
<td>Muscular</td>
<td>27</td>
<td>0</td>
<td>0</td>
<td>0.4 + 0.02</td>
<td>800</td>
<td></td>
</tr>
</tbody>
</table>

* Figures obtained by measurements on extremities of 16 cadavers.
† Calculated from formula of Laplace, as applied by Burton\textsuperscript{17}: P (Tension) = P (Blood Pressure) x R (Radius of artery).

which show the most intense calcification in incinerated sections also show the highest incidence of plaque formation. The most severe calcification was found in the popliteal artery, in which there was also the greatest frequency of plaque formation; in both instances this was followed by the tibial arteries and then the dorsalis pedis artery. The digital arteries and the nutrient arteries of muscle showed less than 1 plus calcification even in aged individuals and no plaques were observed in these vessels. This same order obtains when the hydrostatic tension, as calculated by the formula of Burton,\textsuperscript{17} is compared with the incidence of plaque formation and with the intensity of calcification. On the other hand, thrombi were most frequently found in one or the other tibial arteries despite the higher incidence of plaques, greater intensity of calcification and higher hydrostatic tension in the popliteal artery.

Discussion

In his original study Mönckeberg\textsuperscript{33} described the changes in the wall of the arteries of the extremities as calcification which could occur independently of "atheromatous disease." This view is still held by many present-day investigators. However, it has become increasingly clear as our investigations have progressed that calcification predominantly occurs in or along elastic fibers, and that the changes of this type along the internal elastic lamella constitute the earliest phase of plaque formation and form an integral part of the atheroma. The appearance of lipids is a late phenomenon, whether in the coronary artery, abdominal aorta, or the popliteal or tibial arteries of the lower extremities.

Further evidence that these elastic tissue changes and the formation of atheromatous plaques are not independent phenomena lies in the fact that there is a close correlation in the degree of severity of these processes in a given artery. Calcification of elastic elements in the coronary artery of the Negro progresses more slowly than in white individuals, and the incidence of coronary artery atheromatosis and thrombosis in the Negro is considerably lower.\textsuperscript{5} The elastic tissue changes progress extremely slowly in the pulmonary artery of both races, and it is well known that atheroma formation is a relatively rare phenomenon in the pulmonary arterial system.\textsuperscript{6} Atheromas do appear in the arteries of this system when pulmonary hypertension, which leads to accelerated elastic tissue alteration and calcification, develops. Similarly, the frequency of atheroma formation can be closely correlated with the severity of elastic tissue calcification in the various segments of the aorta, and in the splenic, hepatic and renal arteries.\textsuperscript{3, 4}

The changes described in the present investigations are qualitatively similar to those previously described in other major arteries and differ only quantitatively. The increased severity can be accounted for in large part by the greater hydrostatic tension obtaining in
the popliteal and tibial arteries than in those occupying a more cephalad location in the upright human.

The reactions produced by hydrodynamic stresses may be most easily studied in vessels normally operating at relatively low pressures, such as veins and the pulmonary arterial tree. As Lev and Saphir16 have pointed out, the first reaction produced by stresses in veins is endo- phlebohypertrophy; intimal hypertrophy is also the earliest reaction in the pulmonary arterial tree, where it normally occurs in the third or fourth decade as compared with the second decade in arteries operating under higher tensions. In both veins and arteries the continuous application of hydrodynamic stresses operating progressively with age results in a disruption of elastic elements and calcification. In vessels functioning at low pressures and relatively low hydrostatic tensions these elastic tissue changes progress slowly and lipid deposits either do not occur, or are observed only in very aged individuals, while in arteries operating at higher pressures and hydrostatic tensions these changes occur with greater rapidity, and plaque formation, including the deposition of lipids, is observed with greater frequency.

Hormonal factors may also play a part in these changes. Wells18 has pointed out that epinephrine is the most important of these. Repeated injections of epinephrine into animals results in the appearance of a marked atheromatous degeneration of the aorta with calcification. This was first observed by Josué and later by Erb, Fischer, Gouget, Loeb and Githens and others.19 These changes resemble most closely those seen in the arteries of the extremities. They may not be due to the heightened blood pressure, since simultaneous injections of substances that depress the blood pressure do not prevent the atheroma from developing, while the injection of certain other substances that elevate blood pressure does not cause atheroma. On the other hand, the slow injection of epinephrine, regulated so that there is an increase in the blood content without significant rise in blood pressure, fails to produce arteriosclerosis.20 Thus, while the histologic changes produced in arteries by epinephrine are well known, the mechanism inducing these changes remains unsolved.

These investigations of vessel wall changes induced by epinephrine indicate that calcification appears predominantly in the elastic tissue, but that there is also calcification of the degenerating smooth muscle of the media. We have observed and reported this calcification pattern in the splenic and renal arteries. It was also found present to some degree in the popliteal and tibial arteries in the present investigations; however, because of its unimportance in the formation of intimal plaques, consideration was not given to this finding in describing our results.

It has become apparent in recent years that the opinion that atherosclerosis is a lesion solely of the elastic arteries is an erroneous one. Several investigators have observed a high incidence of atheromatous plaques in amputated lower extremities, and our results are in agreement. This being the case, one may wonder why thrombosis with ensuing gangrene is not as frequent in arteries of the lower extremities as in the cerebral and coronary arteries. That the incidence of gangrene in the lower extremity is much less than the incidence of cardiac or cerebral infarction could rest, in part, on the ability of the former to develop more effective collateral circulations. However, it is strikingly illustrated by our observations that the caliber of those vessels of the lower extremities which operate under high hydrostatic tension and show frequent atheromatous plaques is larger than that of the coronary or cerebral arteries. It would be expected that atheromatous plaques would be increasingly more conducive to thrombus formation as the vessel in which they resided became progressively smaller. Our observations indicate that whereas the magnitude of atheromatosis in the arteries of the lower extremity diminishes progressively as the caliber of the vessels diminishes, it is in the tibial arteries that the highest incidence of thrombus formation appears. Thus it seems that the relation of vessel caliber and degree of atheromatous change is an important factor in thrombosis. Thrombosis is uncommon in the femoral artery where atheromatosis is marked but vessel caliber relatively large, and in the digital artery where vessel caliber is relatively small but atheromatosis is minimal. The statement of Edwards20 that "thrombosis of the
tibial arteries does not usually lead to gangrene unless the popliteal artery is already occluded by atheromata” is not supported by our observations.

Summary

These investigations consist of a study of the arterial tree of 45 lower extremities, 36 of which were amputated for arteriosclerotic gangrene. The severity of the elastic tissue-calcium changes is correlated with the incidence and severity of atheromatous plaque formation at various levels, and with the hydrostatic tensions operative at those levels.

It is concluded that the medial changes, particularly those along the inner elastic zone, do not differ qualitatively from similar changes observed in elastic arteries and that they bear an intimate relationship to the formation of atheromatous plaques. The concept of independent intimal and medial changes in muscular arteries does not appear to be a valid one, and the term “Mönckeberg sclerosis” is, therefore, misleading.

SUMARIO ESPAÑOL

El deterioro y desgaste degenerativo del sistema arterial de las extremidades bajas ha sido estudiado en una serie de edades. La intensidad de estas alteraciones ha sido correlacionada a la distribución de placas ateromatosas y de trombosis al igual que a la tensión efectiva a varios niveles según calculada por la fórmula de Burton. Evidencia se presenta a favor del concepto de que los lípidos en las placas ateromatosas se originan como un producto de estas reacciones degenerativas dentro de la pared vascular, más bien que por difusión de la circulación a través de la barrera endotelial.

References

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