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Pathology of the splenic artery

by H. Sinzinger and W. Firbas

Atherosclerosis Research Group-ASF-at the Department of Medical Physiology and 1st Department of Anatomy, University of Vienna, Währinger Strasse 13, A-1090 Vienna (Austria)

Key words. Spleen; artery, splenic, pathology of.

The human splenic artery has been attracting the interest of pathologists for a long time, because of the frequent occurrence of an increase in length and tortuosity. Although a number of macroscopical descriptions exist[4], the information concerning morphology, ultrastructure and pathophysiology available so far is limited. In reviewing data obtained from the examination of about 1500 splenic arteries derived from various species during the last 10 years, using a variety of techniques, we will try to summarize the available knowledge about the extrasplenic part of the splenic artery.

Length and diameter

As early as 1935, Thiersch[32] described a splenic artery (SA) with an absolute length which was 3.5 times the direct distance between its origin and the spleen. Springorum[27] was the first to introduce an 'index' $\left(I = \frac{100 \times L}{D}\right)$ for the relation between the length of the artery (L) and the direct distance (D). He saw an autopsy case with an I of 363. Later on values of 390[30] and 505[1] were reported. Carmel[2] observed that in ⅕ of cases the SA follows an extremely tortuous course. In 1973 Tischendorf[31] reported an I-value of 659, the highest yet found.

The direct distance between origin and spleen in man is about 10.5 cm (table). The true length of the SA is about twice that, being significantly greater in males than in females ($p < 0.05$). The total index for males was found to be 192, for females 162. Dividing the direct distance between origin and spleen into quarters and examining the length of the SA, one can observe a continuous decrease from proximal to distal (table). The absolute I-values are always higher in males than in females, but the difference is significant only for the proximal quarter ($p < 0.05$) of the course of the SA. If the material taken from autopsies is grouped according to age (greater or less than 50 years), a longer artery can be seen in the older age group. In studying a larger

quantity of material from 700 autopsy cases, we found a highly significant correlation ($r = 0.76$; $p < 0.005$) between age and I of SA. Similar findings have been obtained[33] using SA-angiograms (fig. 1). Studying a number of fetuses[7] we always found that the SA had a straight course, which suggests that there is a large increase in length later in life. Looking at other species[17] we saw that this tremendous increase in length seems to be characteristic only of the human splenic artery (figs 2 and 3), and to some extent of primates, whereas in the other animals examined an I more or less below 150 was always seen. When individual primate species are considered, I is found to have a wide range between 100 and 200 (fig. 4). The decrease in length from proximal to distal seen in the human SA has not been established in any of these animal species. The inner circumference at the five cutting points demonstrates a continuous decrease from proximal to distal (table): this is, again, significantly higher in males than in females. This circumference exhibits no correlation with the body weight or with blood lipid values[18], but does correlate with the extent of atherosclerosis and with age (as originally hypothetized by Carmel[2]).

Weight

SA weight in males is about twice that in females (table). Estimating the four parts of the SA, a continuous decrease from the origin of the SA to the spleen can be observed, which is more pronounced in males than in females.

A limitation of length gain in the retropancreatic part of the SA, as found by Michels[13], was something we were not able to confirm. The reported increase in inner circumference leads to the fact that although in fetal life the SA is the smallest-sized branch of the Tripus Halleri, in about the 4th decade it becomes the largest one[2], an observation reported by various other authors, among them Meyer and Henschel[11] and Texon[28]. Surprisingly, no correlation with the body size can be detected. Cases where the spleen showed a pathological change in size due to various hematological disorders were excluded from the material studied.

(Pre-?) atherosclerotic lesions

Findings in fetal life

The occurrence of early fat infiltration[10] has been demonstrated to be an important pre-atherosclerotic lesion

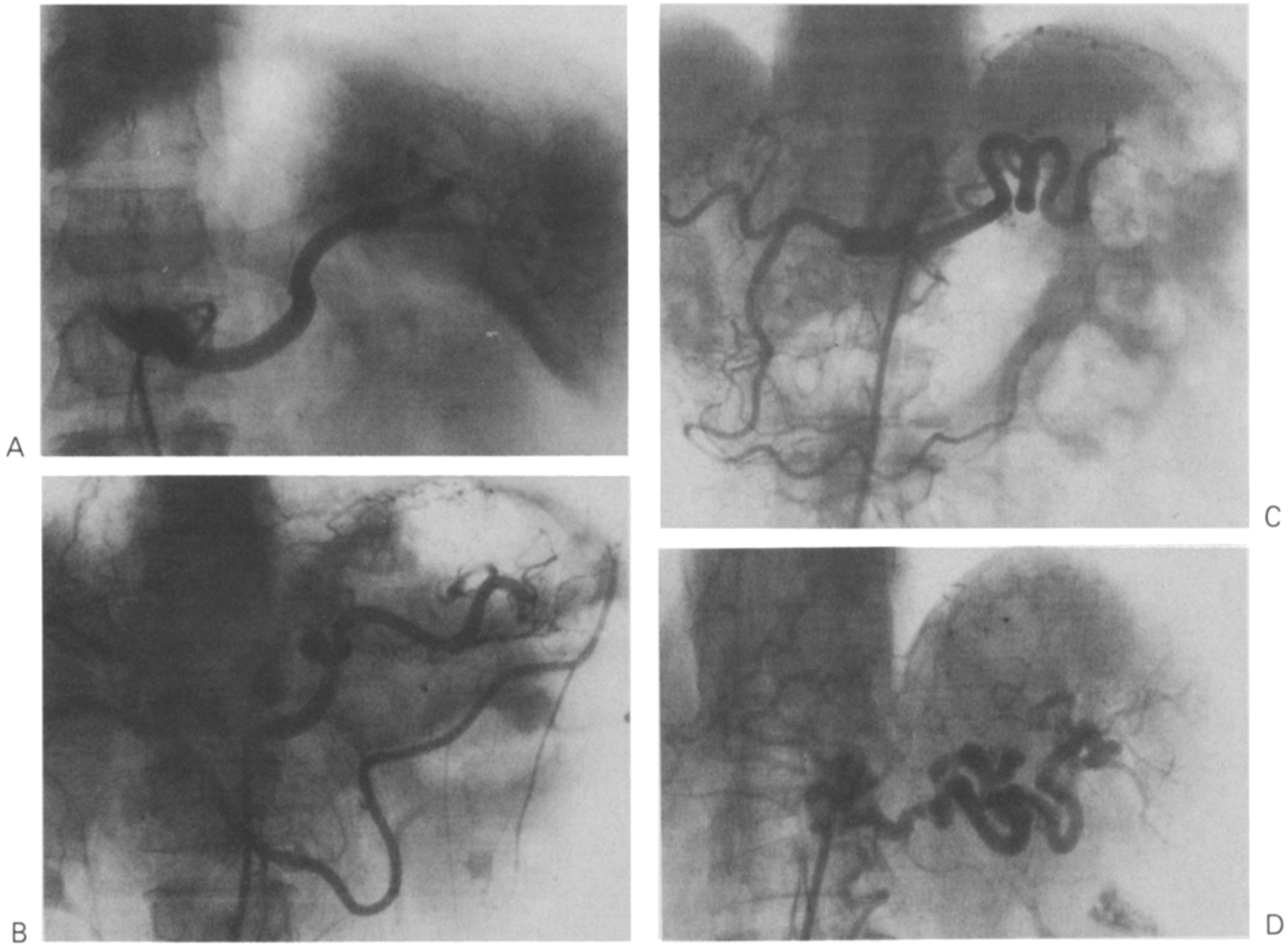

Figure 1. Four angiograms demonstrating various courses of human splenic artery with a continuous increase in length from A to D (ranked according to the patients studied).

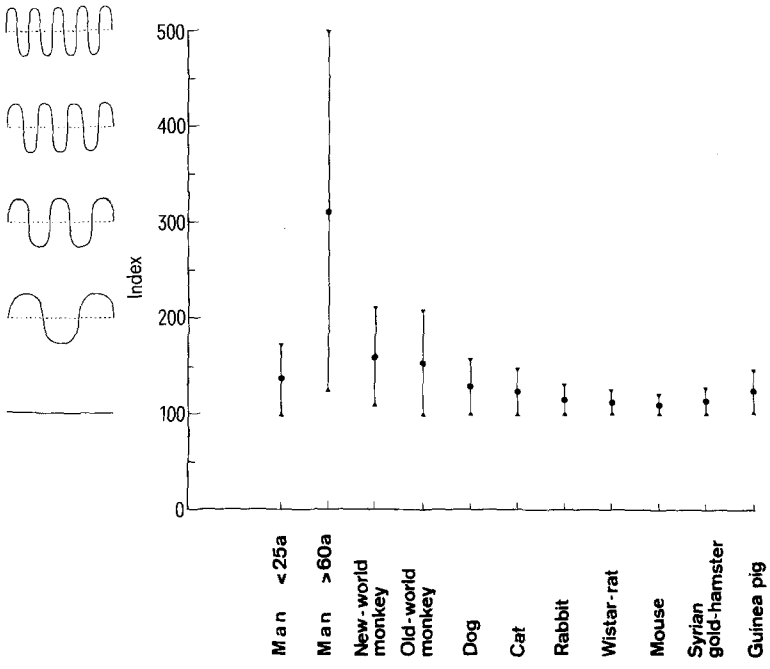

Figure 2. Length of splenic artery in various mammals.

and to occur very early in life[19]. The earliest confirmation was with the human aorta in fetuses[20]. Using a combined staining method developed earlier[3] we investigated the surface involvement (%) in 24 areas from proximal to distal in 41 fetuses. Fatty dots, fatty streaks and calcareous infiltrations[12] have been quantified. The fatty dot lesion, which becomes visible only with Sudan staining, involves distally about 40% of the total SA surface with a continuous decrease (fig. 5) towards the spleen. A similar behavior can be followed up by quantification of calcareous infiltrations, too. It is of great importance that the fatty streak, which is defined from the pathological point of view as an – in part reversible – atherosclerotic lesion, occurs regularly in fetal SA, involving about 5% of the total surface. Altogether, the findings show that the extent of fetal arterial lesions in the SA is considerable; this has not been reported so far (fig. 5).

A quantification of the sudanophilic lesions around the splenic arterial ostium[21] demonstrates a continuous and significant increase with age. The most pronounced changes are localized in the distal (caudal) part of the circumference.

Atherosclerotic lesions in adults

The atherosclerotic lesions as seen by the naked eye are, in general, more pronounced in the proximal than in the distal part of the SA. The fact that the lesions are localized predominantly at the inner curve of the tor-

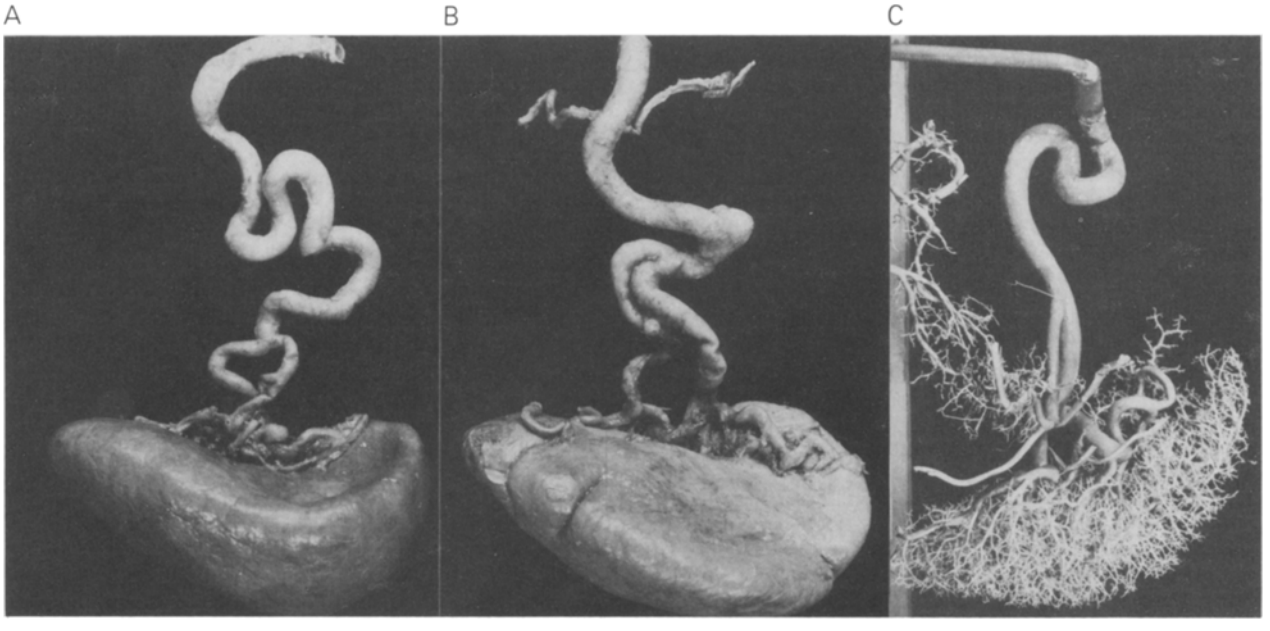

Figure 3. Two human splenic arteries from phenol fixed cadavers (A, B) the lower one with atherosclerotic lesion on a curve. The 3rd picture (C) shows a resin injected splenic artery.

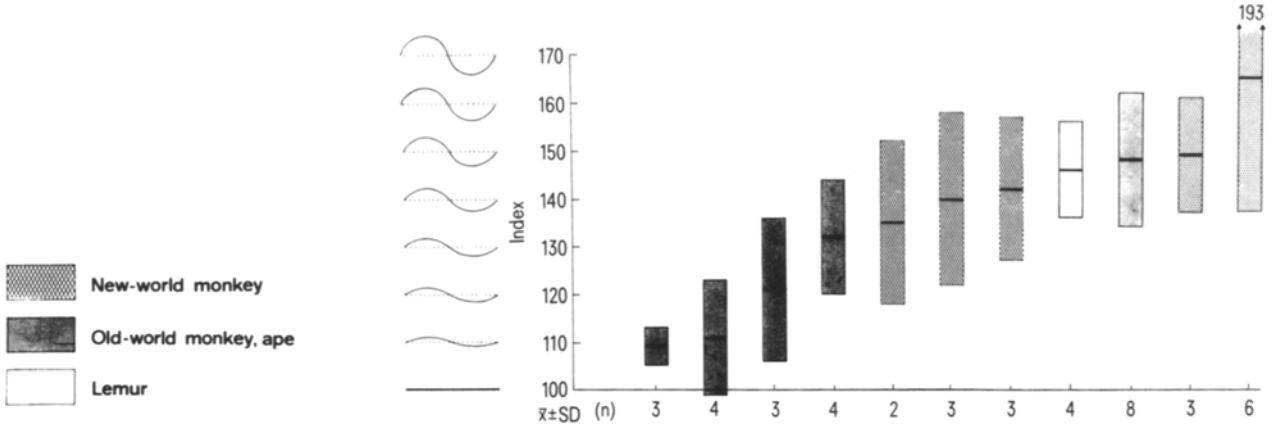

Figure 4. Length of splenic artery in various primates older than 5 years.

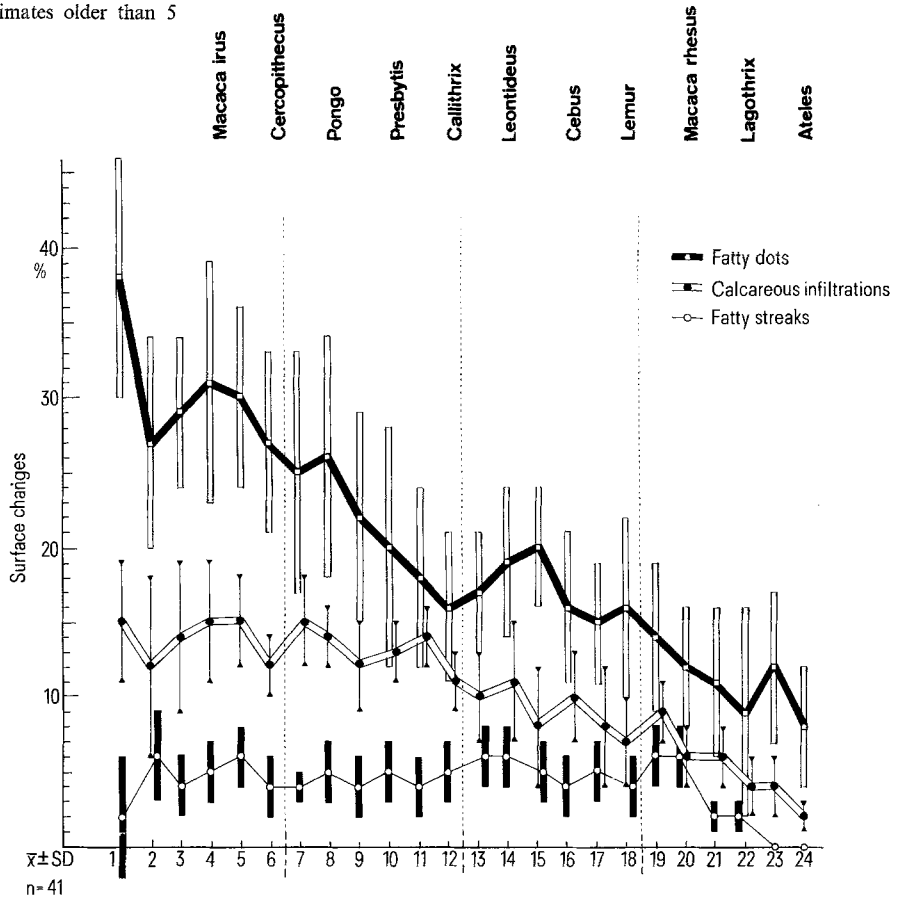

Figure 5. Alterations in fetal splenic artery; the artery is divided into four parts (1–6, 7–12, 13–18 and 19–24). The involvement of the surface in each of the 24 segments has been quantified by means of a compensation polarplanimeter.

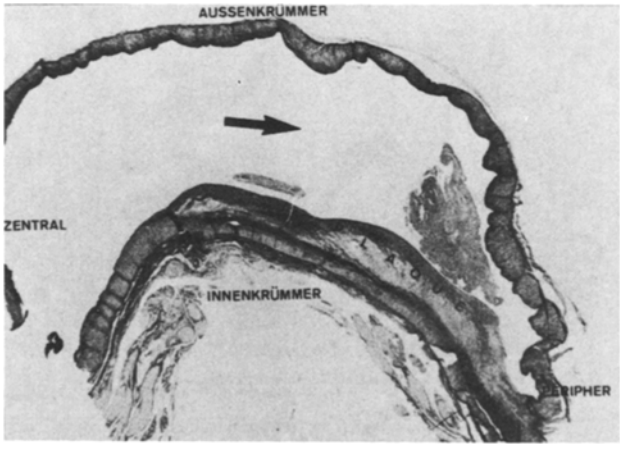

Figure 6. Lower magnification of a human splenic artery (HE staining), showing the plaque formation at the inner curvature with an increase from proximal to distal (according to a figure already published by H. Sinzinger et al., Acta morph. neerl.-scand. *12* (1974) 123–144).

tuosities (fig. 6) fits the hemodynamic concept of atherosclerosis[28]. Complicated lesions (fig. 7), as well as fibrous plaques, decrease in extent the closer they are located to the spleen, whereas the surface involvement by fatty streaks exhibits an increase from about 20–30%. These findings can be interpreted as showing that the more pronounced atherosclerotic lesions are found in the proximal parts; in the distal ones, however, their extent is much less and the earlier lesion types are the predominating ones.

Intima-media-index

The intima-media-index (IMI) has been shown to be, independently of the age-related increase in intima and media diameter, a rather good value for quantifying proliferative atherosclerotic alterations[8]. Between the 3rd and 4th decade (fig. 8) this IMI demonstrates the highest percent age increase, pointing to the highest activity of atherosclerotic disease in this age group. Together with the macroscopical findings the data show rather well that the macroscopical changes observed are related to the histological changes that occur in early childhood.

Internal elastic membrane

For a long time researchers were of the opinion that alterations of the internal elastic membrane (IEM) are of special importance for the development of atherosclerosis. Because these changes appear very early, it has subsequently been questioned whether the IEM alterations cause or are induced by atherosclerosis. The special importance of changes in IEM is derived from the fact that media smooth muscle cells are seen quite frequently in various arteries penetrating the IEM and thus invading the subendothelial space, leading to an intimal thickening afterwards. Quantification of changes in different arteries[22] revealed an age-dependent increase in IEM changes.

The following eight criteria have been quantified using 5-µm elastica-stained sections of SA: loss of regular un-

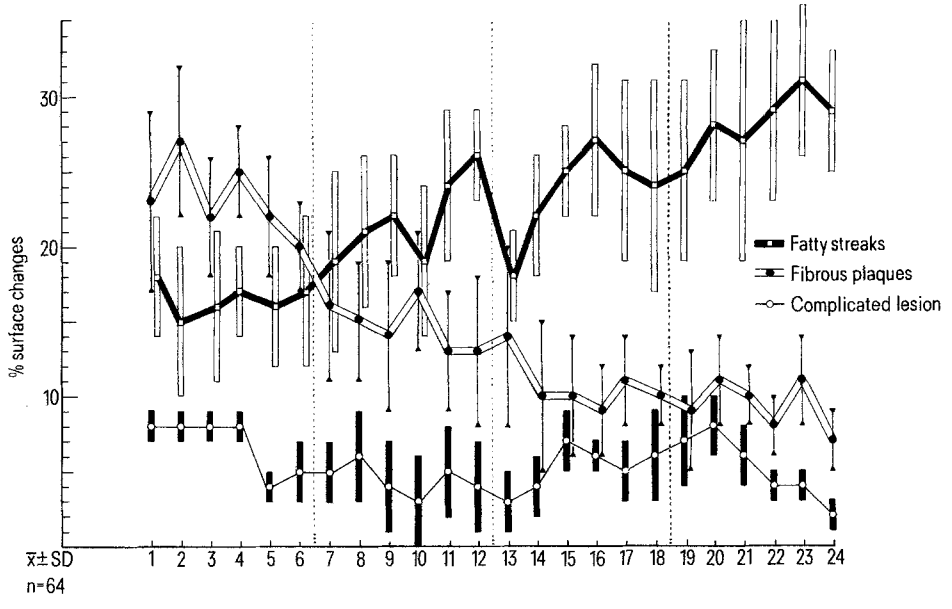

Figure 7. Atherosclerotic lesions in human splenic artery; symbols and quantification as given in figure 5.

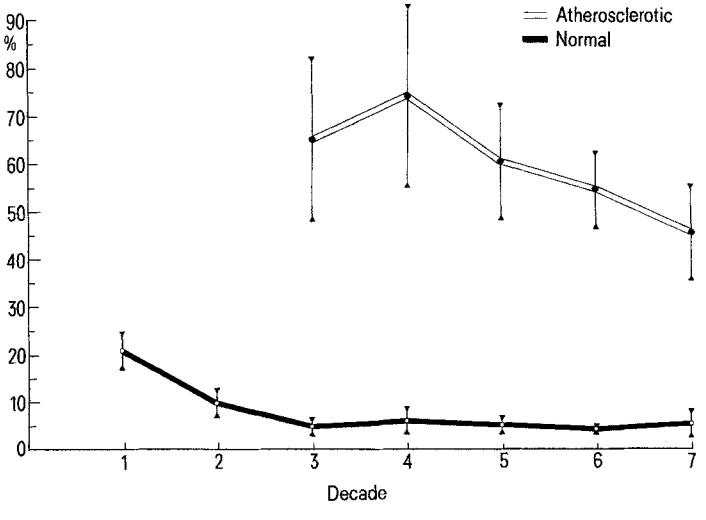

Figure 8. Change in intima-media-index in the various age groups; the data are given as percent change in comparison to the prior decade.

Indices	♂ (28)	p	♀ (39)
Proximal	231 ± 85	0.05	183 ± 63
	197 ± 76	–	164 ± 58
	181 ± 62	–	152 ± 36
Distal	166 ± 62	–	150 ± 42
Total	ε = 192 ± 64	–	162 ± 42
Inner circumference			
Proximal	2.1 ± 0.4	0.01	1.6 ± 0.4
	1.9 ± 0.4	0.01	1.5 ± 0.3
	1.8 ± 0.3	0.01	1.4 ± 0.3
Distal	1.6 ± 0.4	0.01	1.2 ± 0.3
	1.5 ± 0.4	0.05	1.1 ± 0.3
Total weight			Quarter weight
Proximal	124 ± 100	0.01	55 ± 42
	111 ± 88	0.01	48 ± 34
	102 ± 86	0.05	52 ± 46
Distal	89 ± 75	0.05	45 ± 36
True length	♂ 20.36 ± 6.8	> 0.05	
	♀ 17.06 ± 4.3		
Direct distance	♂ 10.7 ± 1.2		
	♀ 10.6 ± 1.4		
Total weight (g)	443.5 ± 326	> 0.01	
	205.6 ± 146		
Age			
> 50	214.9 ± 71	(32)	
< 50	183.5 ± 60	(42)	

dulation (1 in figure 9), local swelling (2), irregularity (3), areas of granularity (4), fragmentation (5), lysis (6), interruption (7) and reduplication (8). In the youngest age group alterations ranging from 5 to 20% can be seen. Loss of regular undulation (1 in figure 9) and interruption (7 in figure 9) are the alterations seen most frequently in the first decade. With aging, a continuous increase can be monitored for all the eight criteria examined. In the oldest age group a general involvement of IEM to nearly 50% is reached. As in the 1st decade, loss of regular undulation and interruption are the dominating features. Local swelling and the finding of areas of granularity are, in contrast, observed rather seldom.

Changes in IEM occur in a number of human arteries to an unimportant degree as soon as the membrane is completely developed. This stage is reached at about the 4th fetal month. The continuous increase with age is a more or less general phenomenon involving, particularly within the arteries, the eventual development of severe atherosclerosis. These IEM-alterations are most evident in the coeliac trunk; of the three branches, the SA shows the highest values; in addition, the changes during aging are more intensive in the SA than in the gastric or hepatic artery. Though a causal relation between IEM-alterations, the biochemistry of the arterial wall, and the existence of atherosclerosis has not been

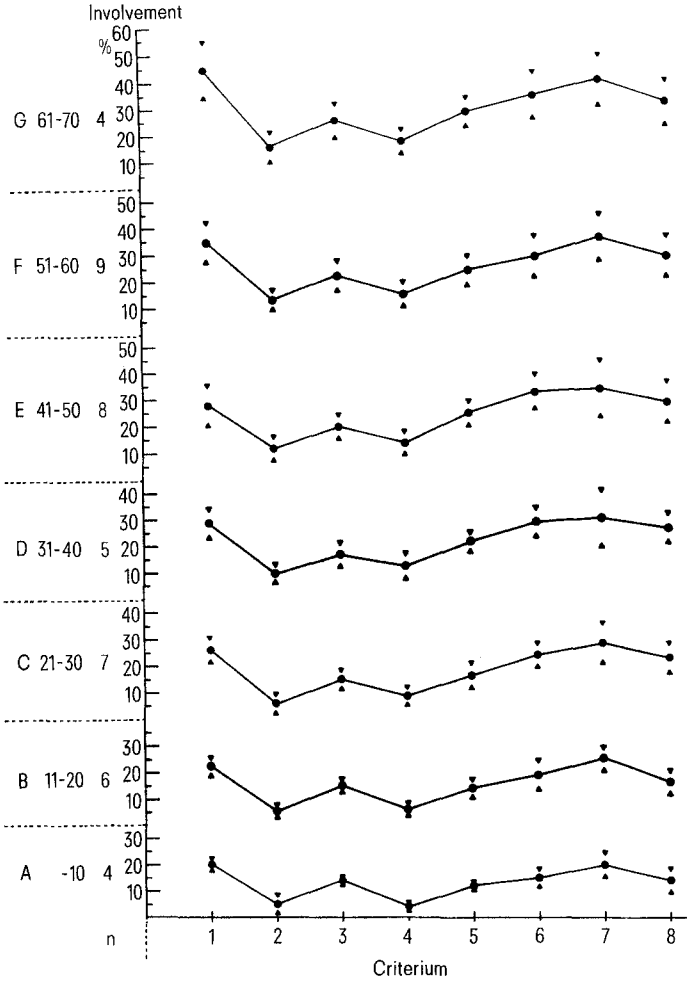

Figure 9. Alterations in various qualitative features of human internal elastic membrane.

verified up to now, it seems of great importance that, for example, in an earlier investigation in SA we were able to find a significant correlation between 'local swelling' of IEM and the IMI ($r = 0.54$; $p < 0.01$).

Role of smooth muscle cells and blood-borne elements

Besides the fact that it has now become more and more established that the vascular wall smooth muscle cells (SMC) are in the part derived from blood monocytes, their metabolic and functional stage is of essential importance during atherogenesis. In earlier work[5] we differentiated two distinct cell types: the activated one was characterized by a loss of specific organelles and an increase in unspecific ones, reflecting the high synthetic activity and the proliferative activity, in contrast to the contractile one with a dominating number of specific organelles. In this work[5,6], which studied the human splenic and femoral artery, we suggest that the higher the actual number of activated SMCs, the higher the proliferative activity and the activity of the vascular disease. Later studies did indeed reveal a much smaller number of activated SMCs in lesions of older patients than in patients dying at a young age of myocardial infarction, for example.

In SA the number of activated SMCs (ASMC) is very low in arteries showing no histological signs of advanced atherosclerosis. In tissue samples with significant atherosclerosis the ASMC number is significantly ($p < 0.001$) enhanced in all the age groups examined. The highest values are seen in the 4th decade (fig. 10) with a continuous decrease thereafter. In non-atherosclerotic arteries no age-dependence of the ASMC content has been observed. In atherosclerotic plaques from SA[6] the highest percentage of activated SMCs is seen in the intima and the inner third of the media. At the borders of the plaques the ASMC content was higher than in the center. In addition, in normal as well as in atherosclerotic SA a decrease in ASMC from the inner to the outer parts can be seen. The penetration of SMCs via the IEM into the intima has been seen only a few times in electron microscopy. Doing incorporation studies with ^{3}H-thymidine and ^{35}S-sulphate in human surgical specimens, one can see an age-dependent ^{3}H-thymidine-incorporation rate resembling exactly the changes in ASMC number in SA. Counting the ^{35}S grains after in-vitro incubation and comparing the number with the ^{3}H-thymidine positive cells reveals a correlation of $r = 0.35$; $p < 0.05$. In comparison to other human arteries, such as the coronary, femoral or radial artery, the number of ASMC is lower. A similar behavior can be found for the incorporation rate of ^{3}H-thymidine and ^{35}S, which points to the fact that the proliferative capacity of the SA is limited in comparison to the other vessels mentioned above. The continuous increase in intimal thickening seen in the SA might be due to an invasion of blood-derived monocytes, too. However, non of the available techniques, including esterase staining, allow quantification of these cells in human material derived from surgical specimens.

Role of parietal thrombus formation

That parietal thrombus formation is an early stage of atherosclerosis is widely accepted. Electron microscopic studies of SA offered no visual evidence for such early stages in any of the samples of various age groups studied. As thrombin and the platelet-derived growth factor (PDGF), liberated during thrombus formation, play an important role in SMC-proliferation, the morphological picture fits well with the finding of a lower number of ASMC in SA in comparison to the aorta, for example. It is impossible to decide which factors – hemodynamic, local metabolic factors or others – account for this difference.

Hemodynamic concept of atherosclerosis

The study of the human SA is of particular interest in that the atherosclerotic involvement is very severe; however, it never reaches clinical significance and practical importance. Due to the angularities, tortuosities and curving, the role of hemodynamics in this particular artery is of special importance. The rules of fluid mechanics apply to the natural conditions in the SA, and are a main determinant for the development and localization of lesions. Such specific predilection areas are curvatures, branchings, tapering or external attachment. At least for the human SA the role of external attachment can be neglected as up to now no alteration of the embedding of the artery has been detected. All the above-mentioned conditions result in one common feature; localized zones of diminished lateral pressure are an initial stimulus for production of intimal proliferation. Once the first curvings exist, others follow according to the basal laws of fluid mechanics, leading to the well-known tortuosity. However, the different intensity of

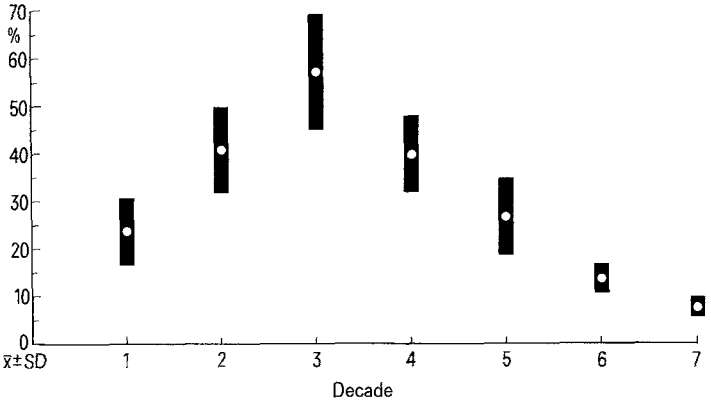

Figure 10. Quantitative distribution of activated smooth muscle cells in the splenic artery in various age groups.

curving seen in SA and other human arteries remains an open question.

Morphology and aging changes

It is extremely difficult to differentiate between those of the morphological changes described here which are normal aging or growth phenomena, and those which are a prerequisite of atherosclerosis. The age-dependent thickening of human SA (studied in nontortuous segments, in order to avoid confusion due to phenomena caused only by hemodynamics) is accompanied by qualitative and quantitative alterations in ground substance, especially an increase in collagen. The cellular density in the SA decreases with age and the enzymes of energy metabolism exhibit a decrease too. Thickening like that of the SA is also seen in femoral and renal arteries[9], accompanied by a significant increase in luminal diameter. Although an exact definition of atherosclerosis is given by the WHO criteria, it is not possible to define the earliest atherogenetic alterations in SA. In general, the SA is one of those human arteries which is rather severely affected.

Vascular hemostatic regulation

Prostaglandin system

Since prostacyclin (PGI_2) was discovered in 1976 by Moncada[14], and shown to be the most important inhibitor of platelet aggregation detected so far, and a very potent arterial dilator, a key role in maintaining hemostatic balance has been attributed to it. This hypothesis has attracted increasing importance after the finding that human atherosclerotic arteries generate much less PGI_2 than normal arteries do[25,26]. This might be one of the main regulatory mechanisms for preventing platelet deposition and thus the formation of parietal platelet thrombi.

As seen by high pressure liquid chromatography the human SA metabolizes ^{14}C-arachidonic acid, the fatty acid precursor of the 2-series prostaglandins predominantly to 6-keto-PGF_1 alpha, the main stable derivative of prostacyclin (fig. 11). The formation of PGI_2 in the human splenic artery in vitro, as measured by means of the platelet aggregation bioassay technique, is more or less constant in the different age groups studied, giving about 12 pg PGI_2/mg tissue wet wt per min in histologically unalterated tissue samples. However, in arterial samples showing signs of atherosclerosis, the in vitro synthesis of PGI_2 amounts to less than half of that in normal arteries (fig. 12). No age-dependent changes can be monitored here either.

Fibrinolytic activity

Using the fibrinolysis autography technique it can be seen that the intimal fibrinolytic activity in SA is extremely low. Positive areas can be detected only after

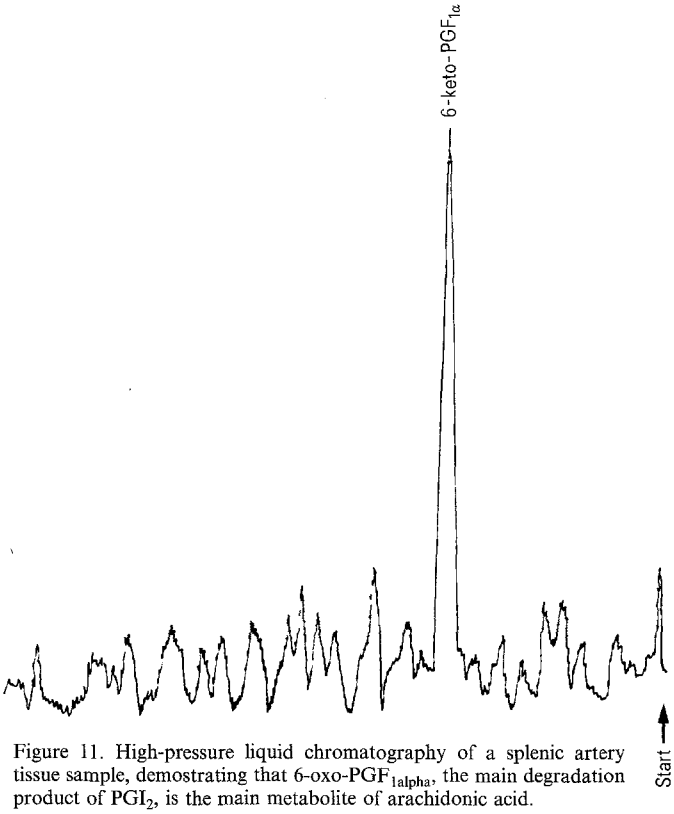

Figure 11. High-pressure liquid chromatography of a splenic artery tissue sample, demostrating that 6-oxo-PGF_{1alpha}, the main degradation product of PGI_2, is the main metabolite of arachidonic acid.

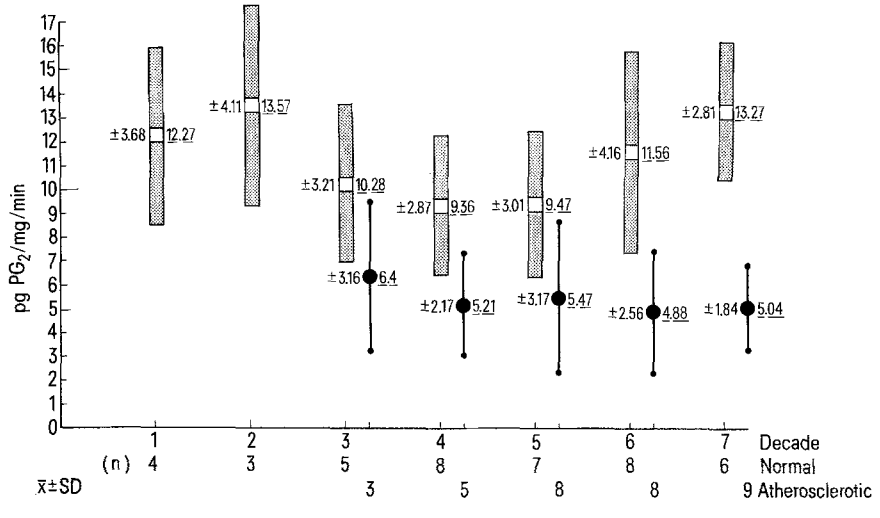

Figure 12. Splenic artery prostacyclin formation in normal and atherosclerotic splenic artery in various age groups.

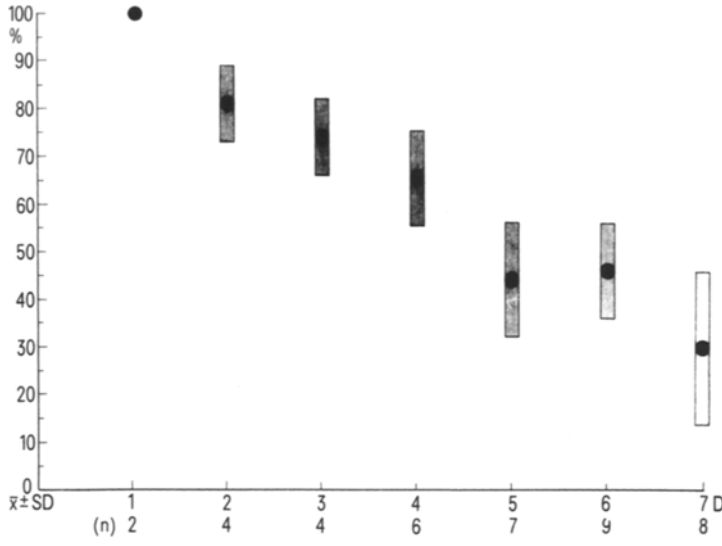

Figure 13. Fibrinolytic activity of human splenic arterial intima shows a continuous decrease with aging.

removal of the outer half of the media and the adventitia in order to avoid confusion due to adventitial fibrinolytic activity. After 2 h incubation it can be seen (fig. 12) that there is a marked decrease with age; in the 7th decade the activity is about one third of the starting value. However, no difference could be observed between the normal and the atherosclerotic tissue examined.

Proliferation of smooth muscle cells

It has been demonstrated that prostaglandins might play an important role in proliferation of vascular smooth muscle cells[23,24] via the cAMP stimulated by prostacyclin; this is one of the mechanisms accepted at present. The other one was discovered by Shechter[15], who demonstrated that malondialdehyde, a degradation product of thromboxane, together with low-density lipoproteins is able to cause proliferation of SMC and also foam cell formation, whereas the two compounds alone do not exert any action in this direction. This points to an important connection between the platelet and the lipid theories of atherosclerosis, particularly in the splenic artery of humans. The 3rd influencing component might be the PDGF, which is able to stimulate SMC proliferation in vivo and in vitro as well. It has been demonstrated that normal arterial prostacyclin formation is significantly enhanced in a dose-dependent manner by the addition of PDGF, whereas the response of atherosclerotic tissue is much less pronounced. This might account on the one hand for an increased proliferation of SMC via a decrease in cAMP, and on the other hand result in a vicious cycle by decreasing platelet cAMP and causing in consequence a further increase in the liberation of intraplatelet substances, such as β-thromboglobulin and the platelet-derived growth factor.

In summary, these findings demonstrate that the human splenic artery is subject at a very early stage to alterations which are normally found during atherosclerosis. It is of great interest that some findings, such the lengthening, the tortuosity, alterations in the internal elastic membrane, and the decrease in prostacyclin formation, are extremely pronounced. Later in life, hemodynamic alterations occurring at the well-known predilection sites are added to the degenerative ones, which leads to a very severe involvement of the artery.

To our knowledge, this review is the most comprehensive study done up to now with splenic artery material; however, the reason why this artery undergoes such large alterations, and the clinical implications of these changes, are not yet known. The findings support the view that each human artery develops its special morphological and functional spectrum of changes throughout life.

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Terminating arterial vessels in red pulp of human spleen: a transmission electron microscopic study

by L. Weiss, R. Powell and F.J. Schiffman

Department of Animal Biology, University of Pennsylvania School of Veterinary Medicine, Philadelphia (Pennsylvania 19104, USA) and Department of Internal Medicine, Brown University Program in Medicine, Providence (Rhode Island 02912, USA)

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The subject of the terminating arterial vasculature and its connections has been reviewed a number of times from our own laboratory and, in this multi-authored review, by Fujita and his colleagues and by the McCuskeys. We and they have concluded that the circulation in the red pulp is served by a vasculature in which there is no stable structural endothelial continuity, no mural continuity of a conventional sort, from the arterial terminal to the vein. But it has been amply documented by in vivo studies (see that of the McCuskeys and by the washout experiments of Groom, Song and their colleagues) that blood flow through the spleen may be as rapid and efficient as through other organs and tissues, yet offers several delayed circulations as well.

We shall return to rationalize the structural basis of blood flow through red pulp, but at this point, set out a number of transmission electron micrographs of red pulp of human spleen to demonstrate the nature of some arterial terminals. The material was obtained, with the aid of the Pathology Department at the Hospital of the University of Pennsylvania and with the cooperation of Professor John Glick of the Oncology Division, from patients splenectomized for staging of Hodgkin's disease. Only normal spleens or normal portions of minimally involved (stage I) spleens were used. The spleens were fixed by immersion according to routines already published within 20–30 min of clamping of the vascular pedicle. Well over 100 terminating arterial vessels were found in red pulp. Details are presented in the figures selected, provided with tracings and legends. Our general observations are as follows:

Metarterioles and arterial capillaries before and at termination characteristically contain dark and light endothelial cells, often alternating. Intermediate and microfilaments are present in abundance and stand out clearly in the light cells. Terminating vessels are capillary in character and possess a nonperforate basement membrane except where the endothelial cells separate, providing egress for luminal blood cells. These vessels also possess adventitial reticular cells which by branching