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Longitudinally orientated smooth muscle cells in rabbit arteries

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Abstract. Intima formation in vessels, spontaneous or experimentally induced, is generally characterized by the presence of longitudinally orientated smooth muscle cells (LSMC). During an experiment of neo-intima induction in carotid arteries in rabbits, by application of a non-constrictive silastic cuff, a study was performed to investigate the presence of LSMC in the systemic and pulmonary circulations, in both elastic and muscular arteries. Three patterns could be distinguished: intimal cushions in muscular arteries, single or small groups of LSMC in the intima in elastic and larger muscular arteries, and intra-medially located layers or columns of LSMC in the aorta, the pulmonary artery, at the bifurcation of the aorta and around orifices of branches. In order to understand this peculiar orientation a biomechanical approach was used: this showed that near the lumen the circumferential stress is 4.5 times higher than the longitudinal. Because the cell surface of the smooth muscle cells exposed to this stress per unit vessel length is much less in the longitudinal than in the circular direction we conclude that the LSMC align in the direction which allows them to cope most effectively with the mechanical stresses.

Key words: Smooth muscle cells – Intima – Arteries

Introduction

The application of a non-constrictive silastic cuff around the carotid artery in the rabbit (Booth et al. 1989) causes the formation of a neo-intima composed of longitudinally orientated smooth muscle cells (LSMC). In a previous study (Kockx et al. 1992) it was found that sham-operated contralateral arteries showed single subendothelial smooth muscle cells and discrete segmental intimal thickenings. These were composed of one to three layers of smooth muscle cells (SMC), predominantly but not exclusively longitudinally orientated and embedded in a network of collagen and elastic fibres. Similar lesions were found in the cuffed arteries, adjacent to or clearly separated from the neo-intima lesions. In these arteries these small lesions were considered as the minimal form of neo-intima formation, whereas in the sham-operated arteries their presence was attributed to a slight intimal reaction caused by the mechanical manipulation. However in control carotid arteries removed in animals whose organs were used for in vitro experiments and hence not exposed to any experiment in vivo, the same lesions were found. This finding prompted a search for the presence of spontaneous intimal lesions in different arterial locations where they could be expected to be found, particularly at bifurcations or ramifications. The presence of LSMC in the media and their possible relationship to neo-intima formation was also investigated.

Finally a biophysical approach to explain the longitudinal orientation was applied. In order to explain SMC re-orientation, it is necessary to consider the mechanics of the blood vessel wall. Materials such as arteries that undergo large deformations upon pressurization, can be described by an analytic method known as "finite deformation analysis". This method uses the concept of the strain energy density function. When a body is stretched by a given force, a certain amount of work (work = force × displacement) is done. Most of this work is stored in the body as "strain energy". This strain energy per unit volume of the deformed body is the strain energy density, denoted by W. If W can be determined for a material, then the elastic mechanical response of that material can be quantified, and moreover, the stress distribution within the wall can be calculated. Since these stress distributions cannot be measured directly, the finite strain analysis (Silver et al. 1989) is a very convenient way to study the stresses within the wall.

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Materials and methods

White rabbits of both sexes, weighing between 2.5 and 3.2 kg were examined. The animals were sacrificed by an overdose of Pentothal and the vessels under study were immediately dissected and fixed in situ by immersion in methacarn fixative. The different segments were removed after 30 to 60 min and immersion fixation was continued for up to 24 h. After processing to paraffin, the sections were stained with Sirius red haematoxylin which was used as a general survey stain. When indicated, Verhoef's elastica stain was used, generally in serial sections alternating with the Sirius red haematoxylin stain.

Immunohistochemical staining was performed on sections mounted on poly-L-lysine coated slides using a direct immunoperoxidase method with diaminobenzidine (Sigma) as chromogen. The following antibodies were used: monoclonal anti-alpha-smooth muscle actin (Sigma A-2547) diluted 1/2000, monoclonal anti-swine vimentin (Dako M-725) diluted 1/120, monoclonal anti-desmin II (Organon Technika) diluted 1/120 and monoclonal anti-proliferating cell nuclear antigen (PCNA; Dako pc 10), diluted 1/300.

Serial sections were made in many pieces in order to establish the spatial distribution and extent of those lesions composed of SMC which deviated from the circular direction and which were predominantly, and often exclusively, longitudinal.

The following segments were examined with the numbers examined indicated between brackets; carotid arteries (104): 3 fragments 1 cm apart in each artery, in total 312 fragments, bifurcation of the truncus brachiocephalicus (18), descending thoracic and abdominal aorta (45), bifurcation of the aorta in the common iliac arteries: transverse (31) and frontal longitudinal (18) sections. The left descending and right circumflex branch of the coronary arteries were examined in six cases, the bifurcation of the common iliac artery in the hypogastric and umbilical arteries in 10, the origins in the aorta of the coeliac axis (5), the superior mesenteric artery (5), the right renal artery (3), the left renal artery (5) and the ileolumbar artery (5). The orifices were cut at 4–5 levels in transverse aortic sections. The ascending aorta and adjacent stem of pulmonary artery were cut in 5 cases, the aortic arch between the origin of the carotid arteries and the left subclavian artery in 5, the end of the aortic arch beyond the left sublavian artery in 5, the stem of the pulmonary artery in (27), the bifurcation of the pulmonary artery in (5) the femoral artery in 10, fragments 2 cm apart in each artery.

From the lungs the lower lobes were examined in 4 segments in 27 animals and all the lobes (in 8 segments) in 25 animals. In addition the lungs of 138 animals which were used in a pharmacologic experiment and which were distended by injecting Bouin's fixative in the bronchi could be examined. The special interest of this group was that by distention of the bronchi the contraction of the arteries was much reduced, which allowed a comparison with the contracted arteries in the immersion-fixed tissues.

In addition 6 rabbits 1-day-old and 2 rabbits 7-day-old were examined. Fragments were taken from all the lung lobes, from the ascending aorta with the adjacent stem of the pulmonary artery, the carotid arteries, the thoracic aorta, the abdominal aorta with the branches of the coeliac axis, the superior mesenteric artery and the left renal artery. The aorta bifurcations were sectioned at three levels.

The animals with cuffed arteries belonged to three groups: the first covering a period between 6 h and 30 days after cuffing (34 animals) described in a previous publication (Kockx et al. 1992), the second of 27 animals after 7 days cuffing and the third of 14 animals after 14 days cuffing. In each animal the left carotid was cuffed and the right treated as sham.

For the calculation of the stress distribution in the wall, the experimental pressure radius data from rabbit carotid arteries (Fung et al. 1979) were used to determine the strain energy density function (Chuong and Fung 1983).

The stress distributions in the circumferential, longitudinal and radial directions in a blood vessel wall are given by the expressions:

$$\sigma_\theta(r) = c(1+2E_\theta)[b_1 E_\theta + b_4 E_z + b_6 E_r]\, e^Q + p(r)$$
$$\sigma_z(r) = c(1+2E_z)[b_4 E_\theta + b_2 E_z + b_5 E_r]\, e^Q + p(r)$$
$$\sigma_r(r) = c(1+2E_r)[b_6 E_\theta + b_5 E_z + b_3 E_r]\, e^Q + p(r)$$

with

$$p(r) = -c(1+2E_r)[b_6 E_\theta + b_5 E_z + b_3 E_r]\, e^Q - \int_{r_s}^{r} c\{(1+2E_r)[b_6 E_\theta + b_5 E_z + b_3 E_r] + (1+2E_\theta)[b_1 E_\theta + b_4 E_z + b_6 E_r]\}\, e^Q \frac{d\xi}{\xi}$$

which are based on the strain energy density function $W = c/2\, e^Q$ with $Q = b_1 E_{\theta 2} + b_2 E_z^2 + b_3 E_r^2 + 2b_4 E_\theta E_z + 2b_5 E_z E_r + 2b_6 E_r E_\theta$ (E_1: Greens strains, c, b_i: constants) first introduced by Chuong and Fung (1983). The experimental pressure radius data from rabbit carotid arteries (Fung et al. 1979) were used to determine this strain energy density function.

Results

The SMC lying in a longitudinal or in an oblique direction present three distinct patterns.

The first group is formed by focal accumulations of LSMC between the endothelial cells and a generally intact internal elastic lamina (IEL). The cells form 1–6 layers and are individually invested by collagen and elastic membranes. A new IEL, although thinner than the original one, is always present. Two varieties can be recognized. One is the localized cushion present at the ramification of muscular arteries: coronary arteries, branches of the carotid, mesenteric, renal, iliac and femo-

Fig. 1. Medium sized pulmonary artery with three intimal cushions and one branch. The internal elastic lamina (IEL) ist distinct and allows the cushions to be classified as intimal. ×230, anti-alpha smooth muscle actin antibody (anti-α-SMA Ab)

Fig. 2. Carotid artery with a neo-intima after 7 days cuffing. The longitudinal direction of the intimal smooth muscle cells (SMC) is obvious. ×290, anti-α-SMA Ab

Fig. 3. Control carotid artery from the same animal as Fig. 1. Single and small groups of longitudinal orientated SMC (LSMC) cover the luminal aspect. ×575, anti-α-SMA Ab

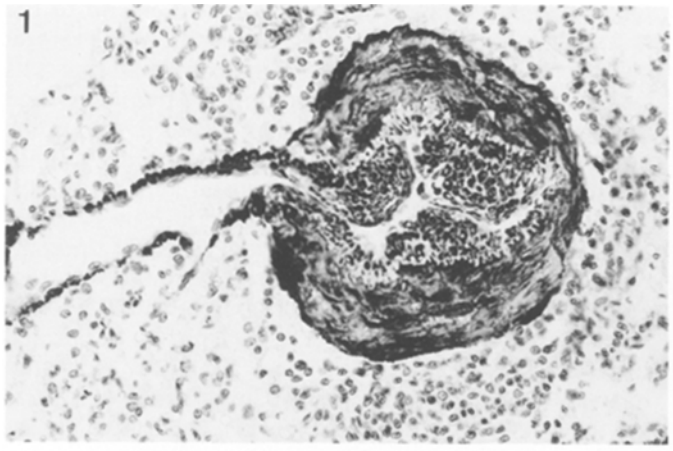
Fig. 4. Abdominal aorta showing several layers of LSMC embedded in a dense network of collagen and elastic fibres. ×460, anti-α-SMA Ab

Fig. 5. Aorta 2 mm above the bifurcation. Detail of a protruding column to illustrate the longitudinal direction of the SMC. ×150, anti-α-SMA Ab

Fig. 6. Elastica stain of the column showing the network of fibres in contrast to the circular fibres of the outer half of the media. ×150

Fig. 7. New born rabbit. Origin of superior mesenteric artery. The aorta contains slender columns of LSMC, (*boxed areas*). Notice the interruption between the media of the aorta and of the branch ("medial gap"). ×185, anti-α-SMA Ab

Fig. 8. Detail of one boxed area of Fig. 7. The column is well-individualized and is entirely surrounded by circularly oriented SMC. ×575, anti-α-SMA Ab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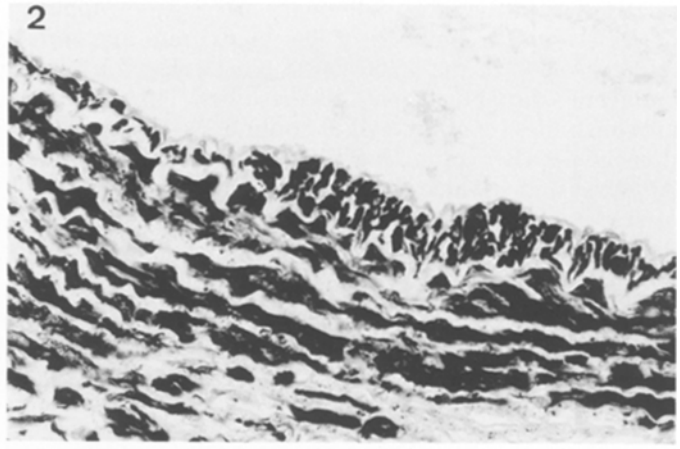
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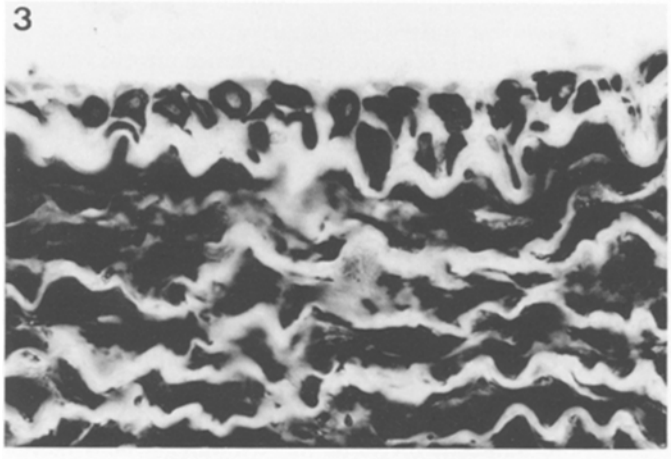
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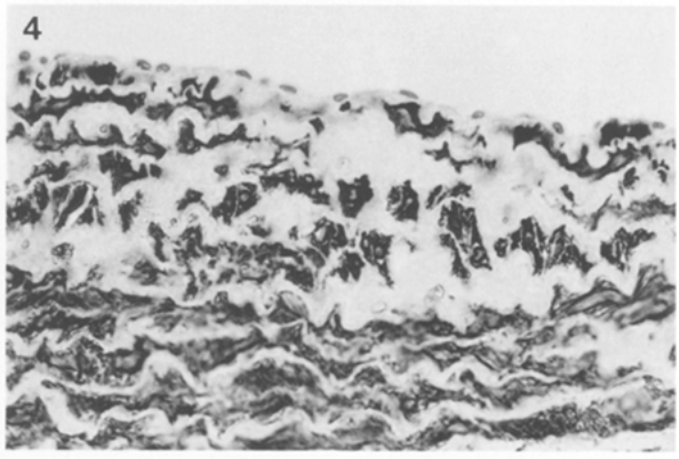
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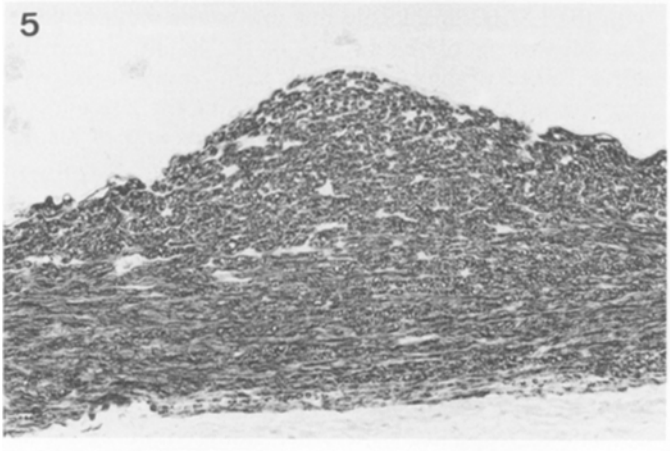
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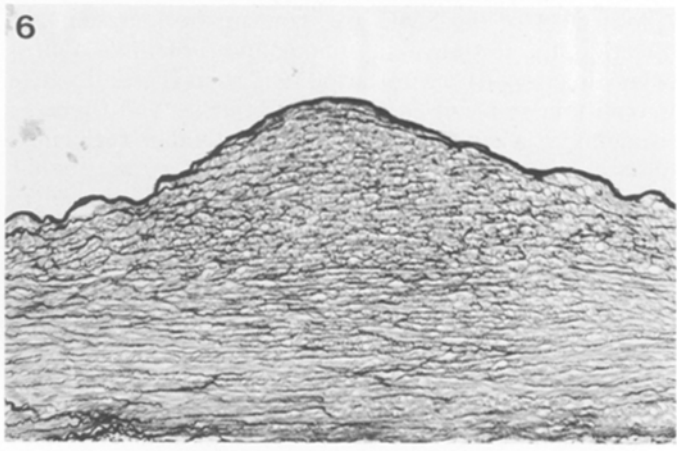
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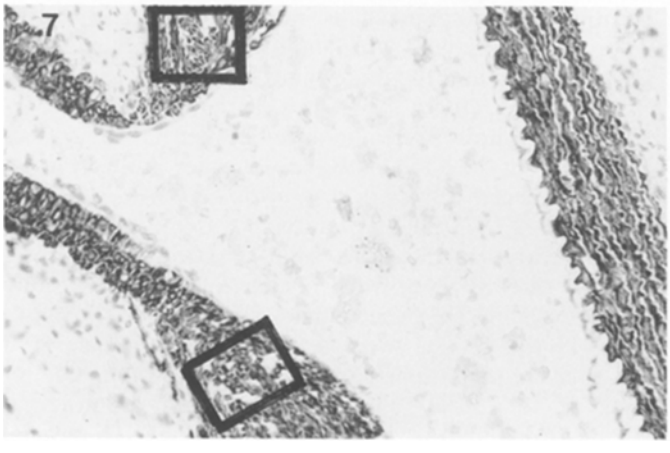
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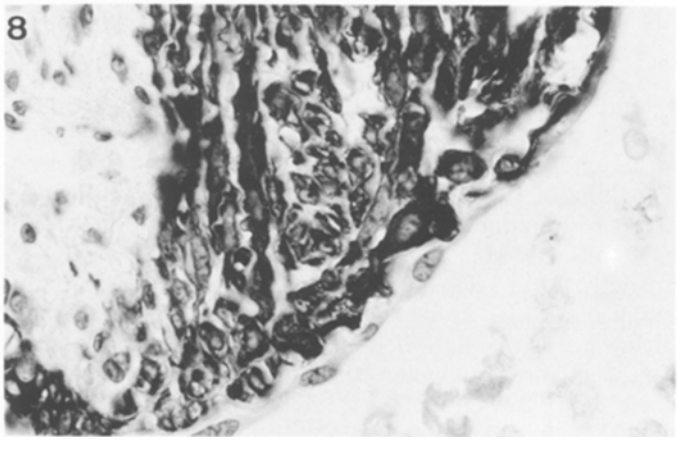
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ral arteries. In the intra-pulmonary arteries they appear in vessels with a diameter of less than 1 mm and were found in 90% of the 1,300 tissue blocks (Fig. 1.). They are evenly distributed over all the lobes. The cushions are sometimes superimposed or continuous with duplications of the IEL containing LSMC in the lung arteries. All the cushions which have been examined through serial sections were found to lie at junctions. It should be noted that in the systemic and the pulmonary circulation the cushions are found proximally and distally to ramifications, occasionally overriding the junction. The second variety has the same basic structure as the first but is thicker, has no relationship to junctions or bifurcations, extends over larger segments and may often be circular. It is associated with the experimental procedure of cuffing (Fig. 2.). It is the classic example of controlled neo-intima formation of known age. Lesions of this type have not been found in the new born or 7-day-old animals.

The second group consists of diffuse accumulations of SMC beneath the endothelium, between 2 to 20 in one section (Fig. 3.). They are generally embedded in a network of dense collagenous and elastic fibres. They often lie in irregular duplications of the IEL and are always bordered towards the lumen by an elastic membrane of very variable thickness (Fig. 4.). They are irregularly distributed and not particularly associated with bifurcations. They are present in systemic and pulmonary arteries of different sizes, generally with a diameter exceeding 200 μm. They may extend over junctions and cushions may develop on top of them, but they can always be clearly distinguished by the elastic fibre network. About 60% of the SMC are lying in the longitudinal direction, the rest have an oblique and sometimes a circular direction. In the aorta the IEL often shows irregular splitting resulting in alternating thicker and thinner segments in a circular direction. The thinner segments often show free ending curled extensions in a zone about 50 μm wide which contains stacks of SMC lying in a radial, oblique or longitudinal direction. Between the SMC irregular fragmented elastic fibres are present. On the abluminal side this zone is limited by the first well individualized thick elastic lamina. At birth and at 7 days these cells are found in the aorta, in the stem and in the larger lobar branches of the pulmonary artery.

The third pattern is characterized by localization in the media. Two varieties can be distinguished. The first are circular bands of LSMC, two to five layers thick, laying in the inner third of the media close to the IEL. They are found in the ascending aorta and in the arch, extending to the begin of the descending aorta. Similar bands lying in the outer third of the media are also found, although they are more irregular in size and distribution. The stem of the pulmonary artery contains alternating layers of longitudinally, obliquely or circularly orientated bands of SMC, representing an exaggeration of the aortic pattern. The second variety is constituted by columns of LSMC laying in the inner half of the media of the aorta in relation to the bifurcation and also at the origin of the smaller tributaries. In the abdominal aorta 2.5–3 mm cranial to the bifurcation small groups of LSMC appear in the middle of the media (Figs. 5, 6). They enlarge in caudal direction and extend to the IEL, bulge into the lumen and form a spur on the ventral and the dorsal aspect of the aortic wall. During this expansion they reach the outer third of the media and extend circumferentially with tapering ends in the middle of the media. They stop at the bifurcation itself and do not form a loop connecting the ventral and dorsal columns, rather they extend in a fan-like fashion caudally over 0.5 mm in the ventral and dorsal aspect of the common iliac arteries. Although generally the LSMC are separated from the endothelium by an intact IEL sometimes at the end of the slope of the spurs a duplicated ribbon of the IEL is present penetrating over 20–50 μm in the cell mass of the column. The columns of LSMC are surrounded by a dense network of collagen and elastic fibres, clearly separating individual cells.

An identical pattern is found at the bifurcation of the common stem of the carotid arteries, at the bifurcation of the brachio-cephalic trunk and at the bifurcation of the common iliac arteries in the hypogastric and umbilical arteries.

A similar, but less pronounced, pattern is present at the origin of the tributaries which form an angle between 60°–90° with the aorta: coeliac axis, superior mesenteric artery, renal arteries and ileolumbar arteries. Here the LSMC form slender columns which begin around the orifices in their distal half and end at the distal border, again forming no loop between the ventral and the dorsal columns as in the aorta bifurcation (Figs. 7, 8). The identification of the LSMC columns is often difficult because the adjacent SMC of the tributary which merge with the LSMC of the columns due to the section plane. The separation of the LSMC of the columns and the normal SMC of the tributaries is then based on the presence of collagen and elastic fibres, on the presence of thick bundles of SMC of the tributaries and of medial gaps. The intima at the junction may show accumulations of LSMC, forming a thin neo-intima.

The two varieties of this intra-medial pattern are present in the new born and 7-day-old rabbits, although quantitatively less pronounced.

The immunoreactivity of all the LSMC for a SMC actin in the three groups is of the same intensity as for the medial SMC. This clear and consistent positivity allows the easy identification of single LSMC, which are difficult to recognize with other stains. Staining for vimentin gave the same results; moreover endothelial cells were stained as well which allows a ready distinction between them and the underlying LSMC.

Immunoreactivity for PCNA in the naturally occurring lesions showed no difference between LSMC or medial SMC. In the adult rabbit evidence for multiplication of endothelial or SMC in arteries is very low, generally limited to 2 to 3 positive nuclei per tissue section. Because LSMC only form a small fraction of the total number of SMC a positive nucleus in LSMC is rarely encountered. In the experimentally induced neo-intima's however the LSMC showed many reactive nuclei and the adjacent media participated in this reaction. The results of the radial, circumferential and longitudinal stresses calculated at a luminal pressure of 120 mmHg,

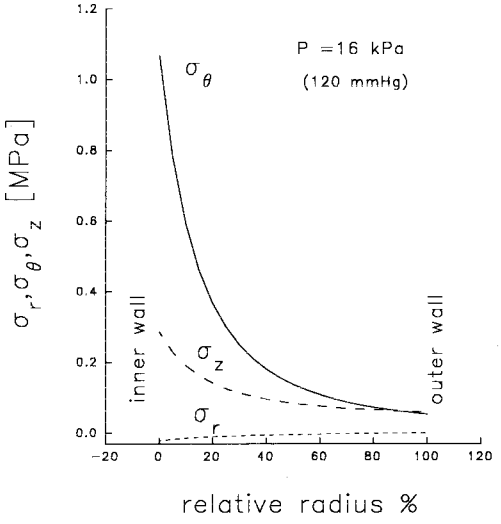

Fig. 9. Graph presenting the relationship between the 3 different stresses and their magnitude throughout the wall, calculated at a intra-luminal pressure of 120 mmHg, σ_r, radial; σ_θ, circumferential; σ_z, longitudinal stress

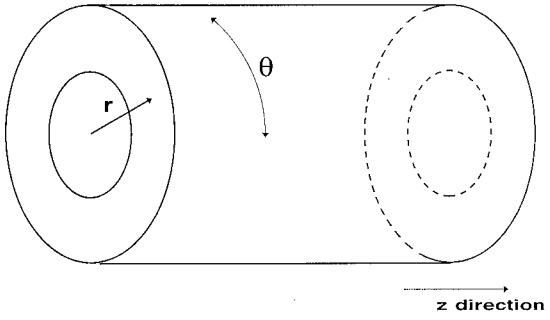

Fig. 10. Illustration of the three orthogonal directions in an artery: the circumferential (θ), radial (r) and longitudinal (z)

are presented in Fig. 9. They show that 1) the stresses are highest near the luminal side of the wall, 2) at the same radius the circumferential stress within the wall is much higher, up to 4.5 times, than the longitudinal stress, and the ratio always remains above unity throughout the full-thickness of the wall, 3) the stress distribution is not uniform throughout the wall.

Discussion

This study demonstrates the presence of LSMC in the arterial wall in different locations and under different conditions. Intra-medial LSMC are present at birth; subendothelial LSMC forming cushions develop after birth like the experimentally induced neo-intima. The small groups of subendothelial SMC associated with changes in the IEL are present at birth, although to a limited extent. They show a substantial post-natal increase. There is no difference in staining pattern or intensity between LSMC and circularly arranged SMC in any of the vessels under study. The identical reactivity for PCNA between LSMC and medial SMC indicates that the LSMC do not form a particular subset with respect to growth.

The naturally occurring structures have been described in detail in the older literature, the aorta by Thoma (1920) and Benninghoff (1930), the coronary artery by Lopes de Faria (1961) and the cerebral artery by Hassler (1961). More recent reviews also mention their existence (Meyer et al. 1980). Experimentally induced lesions are extensively discussed in the older literature by Langer (1924) and Jores (1924), and in the more recent by Buck (1963), Betz and Schlote (1979), Reidy (1985) and Prescott et al. (1989).

One of the advantages of the experimental approach is that the migration and longitudinal positioning of the SMC can be studied from the very beginning (Kockx et al. 1992). When the first SMC appear at 3 days after cuffing between the endothelium and the IEL they lie in a longitudinal direction and they remain so when they multiply and after multiplication when they are embedded in a network of collagen and elastic fibres. Even after 6–12 months this orientation is unchanged (Gebrane et al. 1982). This indicates that once the SMC lying under the endothelium have adopted this direction it is definitive. This conspicuous change in direction is sporadically mentioned in the descriptions of intimal lesions, but without any further comments. In the latest paper on intima formation by a panel of experts it is not mentioned (Stary et al. 1992).

There is a general impression that because the cells are so close to the blood stream they align in its directions, as we suppose endothelial cells do. How turbulence induces SMC which are normally circularly directed to adopt a longitudinal direction is not usually addressed. The presence of LSMC in the media of the aorta was particularly studied by Thoma (1920), using an elaborate mathematical approach, based on human autopsy material. Benninghoff (1930) also studied "tensions" in the vascular wall by a special unravelling technique. Both authors made a distinction between internal and external forces acting in the longitudinal direction. The presence of LSMC in the aortic arch and at the abdominal bifurcation are considered to be examples of the expression of two internal opposite longitudinal forces. It is noteworthy that Thoma himself did not consider the ventral and dorsal spurs as part of a loop, a kind of bridle opposing the downward pressure of the blood column on the crest of the bifurcation, because he did not find a muscular connection between the two, a finding which we can confirm.

An objection to this hypothesis is that in the aortic arch the LSMC bundles in our material are present over the full circumference and are not concentrated on the convex side as might be expected if the development of the LSMC was the result of intensive longitudinal stretch. Moreover the existence of the LSMC columns in very short bifurcations like the brachio-cephalic or in the orifices of branches whose direction is nearly at right angles with the aorta cannot be encompassed by this mechanism.

External longitudinal forces, due to the traction of

the surrounding tissue or organs, are much stronger than internal ones according to these authors. They result in the formation of a very thick adventitia mainly composed of longitudinally directed elastic and collagen fibres, mixed with a few SMC. In humans this pattern is particularly pronounced in the coeliac axis and in the superior mesenteric and renal arteries. We have found it in the rabbit in the same locations, and in the mesenteric artery the adventitia may become thicker than the media. In these animals the traction exerted by the abdominal organs is stronger, due to the horizontal position of the body.

These considerations are limited to the LSMC in the media. The reason why intimal SMC lie in the longitudinal direction are not addressed by these authors. Buck (1963) briefly discusses the contractile function of the LSMC. He admits that due to this direction it is hard to understand how the contraction could have an effect on the diameter of the vessels. He assumes that contraction may be a stimulus for the production and orientation of elastic and collagen fibres. In a later paper Buck (1979) explains that the longitudinal direction of the SMC is imposed upon them by the longitudinal direction of the fibrillary structures of the IEL. This theory could be invoked for the diffusely distributed LSMC, but cannot be applied to the cushions or the medial LSMC. Weibel (1958) in a study on the hyperplasia of intimal LSMC in bronchial arteries proposed that these structures were formed as a reaction to the longitudinal stress exerted on the lung tissue during respiration. Wagenaar and Wagenvoort (1978) in an attempt to verify this mechanism attached segments of mesentery to the diaphragm and arrived at the conclusion that the neo-intima which was formed was induced by the direct influence of the sutures and not by the traction.

The cushions at the branchings are sometimes referred to as muscular rings presumably acting as regulators of the vascular lumen diameter (Meyer et al. 1980), a concept which can not be entertained because of the longitudinal direction of the SCM. An interesting approach are the studies done on cultured SMC exposed to stretching of their artificial substratum (Buck 1983; Dartsch and Hämmerle 1986). They demonstrate that the cells align perpendicularly to the direction of the stretch. Although in vivo the conditions are far more complex, the value of this findings lie in the fact that they show, contrary to common belief, that the position of fusiform cells is not due to stress in the long axis of these cells.

Hence the evidence for a role of longitudinal forces in the development of LSMC is elusive.

If it is not a longitudinal stress, which force can be invoked to explain this change in orientation? When SMC migrate from the media to the subendothelial space they are not protected by the IEL. According to our calculations as shown in Fig. 9 they are subjected to a very high circumferential stress when compared with the longitudinal stress. When the residual stresses in the wall are taken into account, the stress distribution remains the same, although the circumferential stress is only 2.5 times higher than the longitudinal stress (Chuong and Fung 1986). When lying in circular direction they expose half of their surface to this stress, whilst in longitudinal direction they only expose a small fraction of their surface per unit vessel length. This implies that in order to cover a segment or the total luminal circumference they must increase their number which is obvious from the histological appearances. In fact they align in the direction with the least mechanical stress.

The existence of LSMC in the media could be explained by a similar mechanism, admitting that the jamming of the fluid column against the bifurcation causes distension of the vessel wall and an increase in circumferential stress which can become so high that it exerts its force beyond the IEL. The presence of bands of LSMC at the outer side of the aorta and the alternating bands of LSMC and circular SMC in the stem of the pulmonary artery are more difficult to understand.

There is however some circumstantial evidence from veins (Rhodin 1980). Normal veins contain variable amounts of LSMC: the wall of the inferior vena cava is composed of 70% LSMC, 5% circular SMC and 25% collagen and elastic fibres. It is generally accepted that this huge amount of LSMC serves to generate a longitudinal force which counteracts the transverse pressure of the viscera. In our view another explanation is possible: the inferior vena cava has a very wide lumen and a very thin wall, two conditions which will impose on the wall as a whole and on each of its constituents a high circumferential stress. By adopting a longitudinal direction and a concomitant increase in number like in the neo-intima, the LSMC expose a smaller fraction of area per unit vessel length and time to the pressure of the fluid column. The long saphenous vein contains 38% circular SMC, 55% collagen and elastic fibres and only 7% LSMC. The latter form a circular layer at the luminal side, in the inner media. With age or when the veins become varicose they show thickening of the wall (Milroy et al. 1989; Langes and Horst 1992): this is due to the development of an intima with collagen and elastic fibres mixed with LSMC, to a moderate increase in thickness of the media with its circumferentially oriented SMC, but above all to the presence of many coarse bundles of LSMC on the outer aspect of the media, the so-called third muscle layer. Hence the increase in hydrostatic pressure due to the valvular insufficiency is mainly counteracted by the development of LSMC and only to a small extent by hyperplasia of the circumferentially orientated SMC of the media. A similar and much more pronounced pattern occurs in the varicose ovarian veins and in the pampiniform plexus in varicocoeles: moreover in these locations the inner layer may be absent. However, the veins of the arm which do not become varicose and do not contain LSMC. From these findings it may be concluded that veins exposed to a high circumferential stress react by aligning SMC in a longitudinal direction.

Because the ascending aorta and the stem of the pulmonary artery are wide vessels with a relatively thin wall their reaction pattern may be analogous to that of the veins.

A final consideration on the small groups of LSMC connected with duplications of the IEL must be given.

It is clear that they form new elastic membranes and that the pre-existing IEL is broken and reduced. This suggests a function as a source for a new IEL which has been damaged by stretching during the longitudinal growth and by its continuous exposure to the blood pressure. This mechanism has also been described by Meyer et al. (1980) and Buck (1963).

We propose that the longitudinal direction of SMC in vessels in general is due to circumferential stress and not to longitudinal loads or to friction induced stress from the blood stream.

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