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Longitudinal smooth muscle in pulmonary arteries

Occurrence in congenital heart disease

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Summary. In lung biopsy specimens of 19 patients with congenital heart disease and pulmonary hypertension, in addition to the common features of plexogenic arteriopathy, longitudinal smooth muscle cells were found in small pulmonary arteries. These cells were arranged in bundles or layers, particularly in the intima but sometimes within the media or adventitia of the arteries. They often caused severe narrowing of the lumen. Corrective surgery of the cardiac defect was performed in 14 patients. The results suggested that even when these changes are widespread and severe, they do not stand in the way of a favourable postoperative course. In one patient who underwent a banding procedure of the pulmonary artery, virtually complete regression of the smooth muscle layers could be demonstrated in a second biopsy, taken 5 years later during a corrective operation.

Key words: Pulmonary arteries – Intimal thickening – Intimal smooth muscle – Congenital heart disease

Smooth muscle cells, arranged in a longitudinal fashion in the intima of pulmonary arterioles (Hicken et al. 1965) and to a lesser extent, in pulmonary venules (Wagenvoort and Wagenvoort 1976) are observed particularly in hypoxic pulmonary hypertension.

Patients with pulmonary hypertension due to congenital cardiac defects with a left-to-right shunt generally exhibit the pattern known as plexogenic arteriopathy in their lung vessels consisting of medial hypertrophy, cellular

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intimal proliferation and concentric-laminar intimal fibrosis. In the later stages of the disease fibrinoid necrosis, dilatation lesions and plexiform lesions appear in the pulmonary arteries. In some instances this picture may be complicated by a different form of intimal fibrosis, clearly resulting from organization of small thrombi. Longitudinally arranged smooth muscle cells do not normally belong to this picture.

In recent years we observed in lung biopsies taken from 19 patients with congenital heart disease and pulmonary hypertension, bundles or layers of longitudinal smooth muscle cells within the intima, and sometimes even within the media or adventitia of muscularized pulmonary arterioles. In most instances the development of these bundles was very striking and caused prominent narrowing or even total obstruction of the lumen.

The significance of this observation is related to the implications these vascular changes may have for the resistance of the pulmonary circulation and for regression of pulmonary hypertension following correction of the cardiac defect. Nowadays open lung biopsies are often taken in order to establish whether the state of the pulmonary vascular bed will allow closure of a defect or not. The feasibility of a corrective operation in these patients depends in part on the degree and extent of intimal thickening but also on its type. Concentric-laminar intimal fibrosis, as long as it is mild, will not preclude a favourable outcome of a correction but forms a contraindication when severe and wide-spread. A comparable degree of postthrombotic intimal fibrosis, however, need not be considered an objection to surgical correction of the cardiac defect (Wagenvoort et al. 1984).

Nothing so far is known about the consequences of intimal obstruction as a result of longitudinal smooth muscle bundles. The present study is an attempt to evaluate the significance of these unusual pulmonary vascular lesions, particularly with regard to their predictive value when observed in a lung biopsy.

Material and methods

Among approximately 300 open lung biopsy specimens taken from patients with congenital cardiac defects and submitted to us for evaluation of hypertensive pulmonary vascular disease, there were 19 in which bundles or layers of longitudinal smooth muscle cells were found in pulmonary arterioles. In all patients these biopsies were carried out either during corrective or palliative surgery or as a separate procedure. In the latter instances this was done in order to assess whether the lesions in the pulmonary vasculature would allow or preclude corrective surgery.

The 19 patients in the present study varied in age from six months to 28 years. Nine were male and ten female. They suffered from a variety of congenital cardiac defects with a left-to-right shunt, as listed in Table 1. In one patient (nr. 3) who suffered from a ventricular septal defect, a patent ductus arteriosus and a coarctation of the aorta, a biopsy specimen became available at the time of a banding of the pulmonary artery at the age of one and a half years and a second one five years later when corrective surgery was carried out. In most patients pulmonary arterial pressures were very high and close to or equal to systemic pressures.

The biopsy specimens were fixed or post-fixed in neutral 4% formaldehyde solution under vacuum in order to extract air bubbles and to achieve expansion of the lung tissue. Subsequently they were cut in slices approximately 4 mm thick. From the paraffin-embedded blocks sections

were cut at 5 μm and stained routinely with haematoxylin and eosin, Lawson's elastic-van Gieson stain and Perl's iron stain. In four instances relevant areas were cut out of histologic paraffin embedded sections. These were prepared for electron microscopic investigation using a simplified re-embedding procedure with only xylene as the intermediate step between paraffin and epoxy resin (Van den Bergh Weerman and Dingemans 1984).

Morphometric studies were carried out on those pulmonary arteries and muscularized arterioles that had an approximately circular cross-section in the histological slides. The medial thickness on either side of the vessel as well as the arterial diameter were measured. This was done with a calibrated eyepiece along a vertical line in the microscopic field when the cross-section was perfectly circular, and along an imaginary line through the shortest diameter when it was oval. The average medial thickness was subsequently expressed as a percentage of the external vascular diameter. In the presence of intimal thickening, irrespective of its type, this thickness was measured on either side of the vessel along the same lines and now expressed as a percentage of the internal vascular diameter. External and internal vascular diameters were measured from external, respectively internal elastic laminae on either side of the vessel. The number of arteries and muscularized arterioles meeting the requirements for measurement varied from 12 to 25 with an average of 19. The average medial and intimal thickness for each case is shown in Table 1.

Results

The muscular pulmonary arteries exhibited medial hypertrophy in all cases. This medial hypertrophy was mild, that is with a thickness between 7.0% and 9.9% of the external arterial diameter, in two patients, moderate (10.0%–14.9%) in five, and severe (15% or over) in twelve (Table 1). In all instances it was associated with muscularization of pulmonary arterioles of a size that normally are non-muscular.

Longitudinal smooth muscle cells were present in bundles or layers especially in small muscular pulmonary arteries and arterioles. In all 19 patients this was a regular finding and usually these changes were numerous. The bundles were particularly observed in the intima within a reduplication of the internal elastic lamina (Fig. 1). In this situation they regularly produced considerable narrowing or even total obstruction of the lumen. Occasionally these muscle cells appeared to be swollen with rather pale cytoplasm. In six cases additional longitudinal smooth muscle cells were present within the media (Fig. 2). In one of these cases (nr. 12) they were even confined to the media. These cells, either isolated or in bundles or layers, were lying between internal and external elastic laminae, sometimes adjacent to one of these membranes but often completely surrounded by the circularly arranged medial smooth muscle cells. Finally, there were four cases in which longitudinal smooth muscle cells were also found in the adventitia of pulmonary arteries and arterioles (Fig. 3). In as much as the site of the biopsy was known, no differences according to localization were observed.

Although the layers of smooth muscle cells were not traced in complete serial sections, it appeared that sometimes their lengthwise extension was considerable. Their overall presence in sections from subsequent blocks of tissue, suggested an uninterrupted occurrence over many millimeters at least in some cases.

Identification of these cells as smooth muscle fibres was done with the aid of electron-microscopy in four cases. These cells showed large amounts

Table 1. Sex, age in years, type of cardiac defect, medial thickness expressed as percentage of external vascular diameter (Med. Thickn.), intimal thickness as percentage of internal vascular diameter (Int. Thickn.), type of intimal thickening (Int. type), frequency of longitudinal smooth muscle cells (L.S.M.), frequency of pulmonary venous changes (Veins) and follow-up data in 19 patients

Nr.	Sex	Age (yrs)	Cardiac defect	P.A. press.	Med. thickn.	Int. thickn.	Int. type	L.S.M.	Veins	Follow-up
1	m	$\frac{1}{2}$	PDA	equal	25.0	12.0	pt +	+ + +	–	corr., did well
2	f	$1\frac{1}{2}$	TA I	equal	20.9	6.5	pt +	+	+ + +	corr., did well
3	m	$1\frac{1}{2}$	VSD, PDA, Coa	–	22.6	39.1	pt +	+ + +	+ + +	
		6		–	9.1	2.0	pt +	–	+ +	corr., did well
4	m	$1\frac{1}{2}$	VSD, Coa	85/35/60	15.1	20.7	cp + +, cl +, pt +	+	+	corr., no follow-up
5	m	2	PDA, Coa, MS	100/45/75	23.5	6.2	–	+ +	+	corr., did well
6	f	6	VSD	equal	15.7	11.0	–	+	+ +	corr., did well
7	f	6	AVSD	80/30/53	15.1	7.5	cp + +, cl +	+ +	–	corr., did well
8	m	7	AVSD	equal	15.2	10.6	cp + +, cl +, pt + +	+ +	+ +	corr., did well
9	f	9	VSD, MI	105/80/–	16.3	6.7	–	+ + +	+	corr., cardiac failure
10	m	9	ASD, VSD	120/60/–	7.3	8.2	–	+ +	–	corr., did well
11	m	11	TA I	110/78/90	10.7	54.2	pt + + +	+ + +	+	no operation
12	f	11	TA I[1]	(R.V. 150)	15.7	–	–	+ + +	–	corr., did well
13	f	12	Fallot, LPA from Ao Rt. Waterston Cooley	?	15.5	6.9	–	+ + +	–[2]	no operation
14	f	15	VSD, ASD, P.A. Banding	92/28/50	10.3	30.4	cp +, pt + + +	+ +	+	corr., no follow-up
15	m	16	VSD	100/63/75	13.0	19.1	cp + +, pt +	+ + +	+	no operation
16	m	16	TGA, VSD	60/40/–	7.5	60.1	pt + + +	+ + +	–	no operation
17	f	16	AVSD	90/60/–	16.4	5.8	dil?	+ +	+	corr., no follow-up
18	f	23	SV	equal	10.9	21.9	cp + +, cl +	+ + +	–	corr., did well
19	f	28	ASD, VSD	108/43/63	12.5	44.0	pt +	+ + +	+ + +[3]	no operation

[1] Multiple stenosis in left and right pulmonary arteries

[2] Data apply to left lower lobe. In left upper lobe severe plexogenic arteriopathy but no smooth muscle cells

[3] Also longitudinal smooth muscle cells in the walls of pulmonary veins

Abbreviations: m = male, f = female, PDA = patent ductus arteriosus; TA = truncus arteriosus persistens, VSD = ventricular septal defect, Coa = coarctation of aorta, MS = congenital mitral stenosis, AVSD = atrioventricular septal defect, MI = mitral incompetence, ASD = atrial septal defect, LPA from Ao = origin of left pulmonary artery from aorta, SV = single ventricle. Pulmonary arterial pressure is expressed as systolic/diastolic/mean; equal = equal to systemic pressures. pt = post-thrombotic intimal fibrosis, cp = cellular intimal proliferation, cl = concentric-laminar intimal fibrosis, dil = dilatation lesions, corr. = surgical correction of cardiac defect – –, +, + + and + + + indicate absence, respectively degree of vascular changes

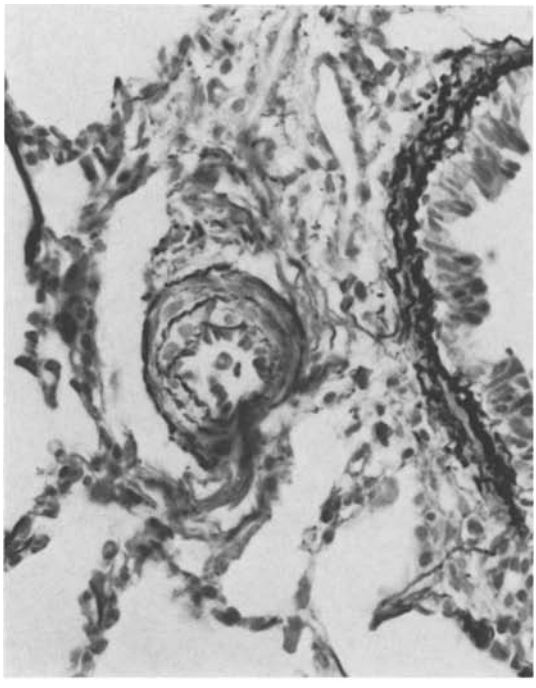

Fig. 1. Small muscular pulmonary artery with a layer of intimal longitudinal smooth muscle cells within a reduplication of the internal elastic lamina (El.v.G., ×220)

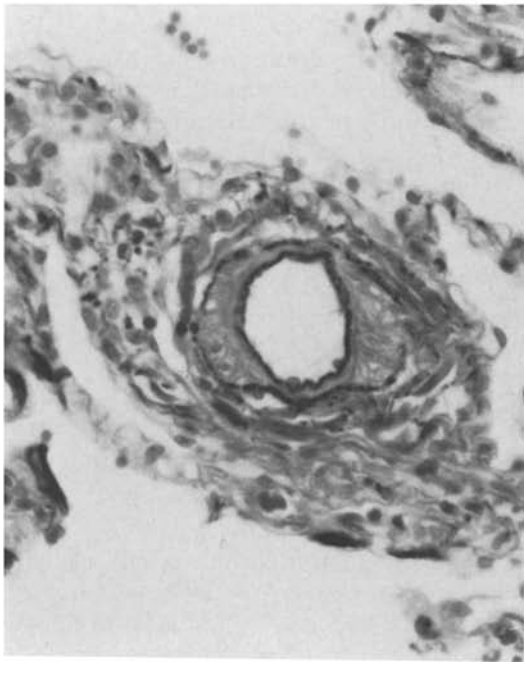

Fig. 2. Pulmonary arteriole with extensive longitudinal smooth muscle within the media bounded by internal and external elastic laminae (El.v.G., ×350)

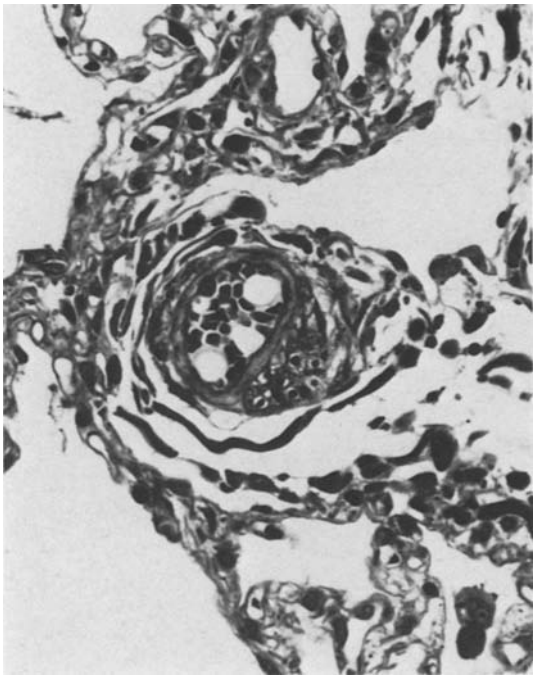

Fig. 3. Small muscular pulmonary artery with a bundle of longitudinal smooth muscle cells in the adventitia (El.v.G., ×220)

of intracytoplasmic filaments, attached to the plasma membrane at regular intervals, forming dense patches at the attachment sites, and fusiform densities in the cytoplasm. (Fig. 4).

Apart from intimal thickening on the basis of muscle bundles or layers, there were also other vascular lesions in 13 patients. Cellular intimal proliferation, usually in combination with mild, concentric-laminar intimal fibrosis as an expression of plexogenic arteriopathy, was found in seven patients.

The more advanced alterations of plexogenic arteriopathy were scarce. There were no plexiform lesions. In one patient (nr. 17), wide and fairly thin-walled segments of some small pulmonary arteries suggested the presence of dilatation lesions. In another patient (nr. 13) who suffered from a ventricular septal defect associated with an origin of the left pulmonary artery from the aorta, lung biopsies were available from both upper and lower lobe of the left lung. In the upper lobe there was, in addition to medial hypertrophy and concentric-laminar intimal fibrosis, fibrinoid necrosis of several arterial branches. Longitudinal smooth muscle bundles were absent here but numerous in arteries of the lower lobe where except for medial hypertrophy, it constituted the only lesion. The cause for the discrepancy in vascular pathology in both parts of the lung remained obscure.

Post-thrombotic intimal fibrosis was a strikingly common complication as it was present in ten patients; three of these had both types of intimal fibrosis, the concentric-laminar and the post-thrombotic. Occasionally, longitudinal smooth muscle cells were found within a fibrotic intimal thickening

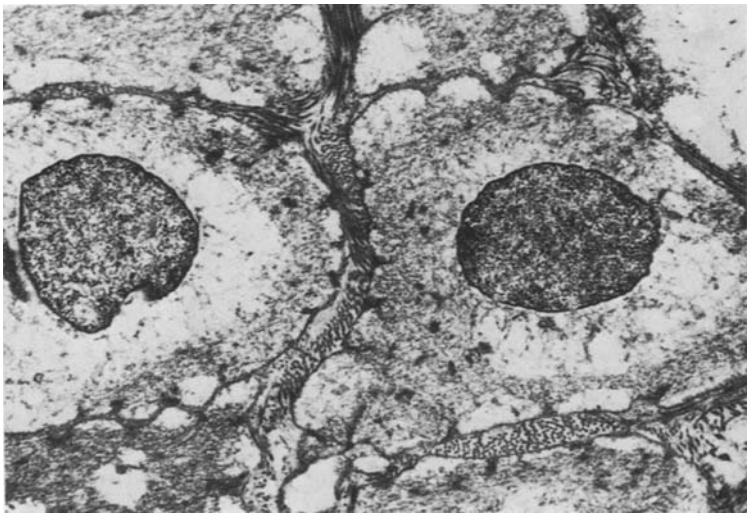

Fig. 4. Electronmicrograph of pulmonary arteriole with longitudinal smooth muscle. Dense patches and microfilaments are clearly recognizable (× 11,900)

which, in such instances, was exclusively of the post-thrombotic type. The average intimal thickness, irrespective of its type, is shown for each patient in Table 1.

Generally, the pulmonary veins are normal in plexogenic arteriopathy, although venous alterations are sometimes found in patients who have pulmonary venous hypertension resulting from mitral insufficiency for instance in cases of atrioventricular septal defect, or who developed left ventricular failure. In the present group of patients changes in the pulmonary veins were found in 12 cases. These consisted of hypertrophy of the media of the veins with arterialization of their walls meaning that the media becomes bounded by distinct internal and external elastic laminae so that it resembles that of an artery. Intimal fibrosis of the veins was sometimes present but usally mild.

In one patient (nr. 3) we had an opportunity to study the effect of abolition of pulmonary hypertension on the longitudinal smooth muscle in the intima, following an effective banding of the pulmonary artery. This boy had a ventricular septal defect in association with a patent ductus arteriosus and a coarctation of the aorta. At the age of one and a half years the coarctation was excised and a banding of the pulmonary artery was performed because of severe pulmonary hypertension. On that occasion a lung biopsy was taken. In the biopsy specimen there was severe medial hypertrophy of all arteries and arterioles and equally severe intimal thickening almost exclusively by longitudinal smooth muscle. Five years later a surgical correction of his cardiac anomaly was carried out and another biopsy was performed. Now the media of the pulmonary arteries was normal in thickness and all longitudinal smooth muscle had disappeared and was

replaced by thin layers of dense, collagen-rich intimal fibrosis. Pulmonary venous changes that were prominent in the first biopsy specimen had diminished though not completely disappeared.

Discussion

The development of bundles or layers of longitudinal smooth muscle cells in the intima of small muscular pulmonary arteries and arterioles is a characteristic feature of chronic hypoxic pulmonary hypertension. It has been described in patients with chronic bronchitis and emphysema, Pickwickian syndrome, kyphoscoliosis and other states of chronic hypoxia (Hicken et al. 1965; Hasleton et al. 1968; Heath 1963, 1970) and it also occurs in residents of high altitudes (Wagenvoort and Wagenvoort 1973). Similar alterations have been observed in pulmonary veins in these conditions (Wagenvoort and Wagenvoort 1976). Such longitudinal smooth muscle is a rather common finding in the pulmonary arterial intima and sometimes in the adventitia of patients suffering from mitral valve disease or recurrent pulmonary embolism but then it is usually found in medium-sized arteries and not in the smaller ones.

Arterial or arteriolar smooth muscle bundles are not a feature of plexogenic arteriopathy which is the usual pattern of hypertensive pulmonary vascular disease in congenital cardiac disease with a shunt and pulmonary hypertension. The common form of intimal thickening here is the concentric laminar, that is onion-skin type of intimal fibrosis. Far less commonly, eccentric postthrombotic intimal fibrosis is found particularly in cases of transposition of the large arteries where there is an increased tendency to thrombosis. The occasional occurrence of longitudinal smooth muscle in the arterial intima has been reported in congenital heart disease (Wagenvoort et al. 1964) but has been considered exceptional and of limited significance.

In the 19 patients of the present study multiple small arteries and arterioles were affected in this way. Usually these lesions caused severe narrowing or even obstruction of the lumina and sometimes they were also very widespread. Since these changes were found in several preoperative open lung biopsy specimens, submitted to us for evaluation of pulmonary vascular disease in order to decide whether the patient was a candidate for corrective surgery, it became of concern to know what the functional significance of these lesions was and whether they were reversible or not.

As Burton (1954) pointed out, it is likely that in the intima of small arteries and arterioles, longitudinal smooth muscle fibres, by their contraction, will enhance the effect of constrictive activity of the circular muscular coat. The same is true of those in the media and adventitia. In this respect it may be significant that almost all patients in this group had severe pulmonary hypertension, usually with a pulmonary arterial pressure close to equal or equal to systemic pressure. Moreover, medial hypertrophy of the pulmonary arteries and arterioles in these cases was judged severe in 12 patients,

moderate to fairly severe in 5 and mild in 2, suggesting a preference of longitudinal smooth muscle to develop in prominently contractile arteries.

At an ultrastructural level the morphology of the muscle fibres was normal. We are not well informed about the mechanism of development of these smooth muscle cells. It should be realized that the cells responsible for any form of intimal thickening have characteristics of smooth muscle cells or of myofibroblasts, when viewed with the electron microscope. However, their form as well as their arrangement is usually irregular and in light microscopic studies they can not be recognized as muscle fibres. They are probably derived from cells in the media that penetrate the internal elastic lamina (Balk et al. 1979). In contrast, the longitudinal smooth muscle cells are, even by light-microscopy, readily recognizable as such. There is reason to believe that, at least in some situations, they develop in response to damage to the vascular wall (Wagenaar et al. 1978).

There was no distinct relationship with other lesions of the morphologic pattern of plexogenic arteriopathy. Cellular intimal proliferation, concentric-laminar intimal fibrosis and fibrinoid necrosis, in combination or alone, were found in 7 patients. This is not more than could be expected in any group of patients with congenital heart disease and pulmonary hypertension. However, there was apparently an association of longitudinal smooth muscle with both post-thrombotic intimal fibrosis and with alterations in pulmonary veins. As we have seen before, both these types of vascular changes do not belong to the pattern of plexogenic arteriopathy, although they may become associated with it in complicated cases. In our present group of patients post thrombotic intimal fibrosis occurred in 10, and pulmonary venous alterations were present in 12 instances. The eventual significance of the combination of these changes with the development of longitudinal smooth muscle in pulmonary arterial walls remains speculative.

In five cases no correction of the cardiac defect was performed, either because it was refused by the patient or the patient's parents, or because such a correction was deemed too risky in view of advanced pulmonary vascular disease. In 14 patients surgical correction was carried out. In three of these the follow-up period following operation was too short for an adequate evaluation. Of the other 11 patients, one had residual pulmonary hypertension with mild cardiac failure; the remaining ten patients did very well after periods ranging from one to six years.

This suggests that the presence of longitudinal smooth muscle in the walls of pulmonary arteries does not form a contraindication for corrective surgery. Moreover, the complete disappearance of these lesions in one patient (nr. 3), in whom we had an opportunity to study lung biopsy specimens at the time of a banding procedure and again five years later when his cardiac defect was closed, demonstrates that this longitudinal muscle is an essentially reversible feature. In this respect it has the same significance as prominent medial hypertrophy with which it is usually associated. Its presence, even when widespread, should therefore not be a reason for concern with regard to reversibility of hypertensive pulmonary vascular disease as long as other irreversible changes are absent.

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