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Intramyocardial Microarteriopathy *

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Summary. 1. Two basic types of arterial vessels can be distinguished in the myocardium.

a) Compacta or Ventricular Wall Type. Intramyocardial microarteries with ring musculature of the media.

b) Papillary Muscle Type. Arteries with longitudinal musculature arranged as bundles in the broad media.

2. The manifestation of intramyocardial microarteriopathy differs in these vessel types.

PAS-positive and elastica-rich cushion-like thickening of the intima mainly occurs in the compacta type. Arterial vessels of the trabecular portion additionally show hyperelastosis of intima and media.

The degenerative lesions of the papillary muscle type are characterized by early degeneration of the smooth muscle cells and hyperfibroelastosis of intima and media.

3. Pathological vascular lesions in the compacta and papillary muscle type occur more frequently in the left ventricle, and increase with age.

4. Slight and medium lesions are in the majority. Severe vascular changes are seen in the 7th to 9th decade in about 5–10% (compacta type) and in 30–35% (papillary muscle type) respectively.

5. Hypertension seemed to raise the frequency of slight and medium lesions in the compacta type vessels. In the papillary muscle type the degenerative lesions frequently extend from the top to the bottom of the papillary muscles.

6. No significant difference between frequency and severity of vascular lesions in diabetics and in the control group could be demonstrated.

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** Dedicated to Professor Dr. A.J. Linzbach on the occasion of his 70th birthday

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7. It appears that pathological vascular lesions occur less frequently in compacta type vessels in cases of high-grade stenosis due to extramural coronary artery sclerosis.

8. Impairment of the quality of myocardial circulation is only encountered in the presence of severe pathological vascular lesions.

Key words: Intramyocardial microarteriopathy – Age – Frequency – Risk factors – Functional significance.

Introduction

Pathological damage to the intramyocardial vessels may occur from degenerative, metabolic, inflammatory, thrombotic or embolic disease. In its narrower sense the term "small vessel disease" of the heart is often used synonymously for intramyocardial arterial vascular lesions of degenerative origin. Other terms for such vascular alterations are arteriolar disease of the heart (Plaut and Kramer 1936; Lisa and Brown 1941; Jacobson and Rankin 1950), arteriolosclerosis of the myocardium (Wegelin 1944; Linzbach 1947), intramural coronary arteriosclerosis (Liebegott 1958), coronary sclerosis in small arteries (Okada et al. 1960), intramuscular coronary arteriosclerosis (Ueda 1962) or small vessel coronary disease (Rider et al. 1974). We prefer the term intramyocardial microarteriopathy.

In this area of arterial vascular lesions of a degenerative type our knowledge is still inadequate. The nature, localisation, frequency and functional significance of these pathological vascular alterations receive very different treatment in morphological investigations (Wegelin 1944; Linzbach 1955; Blumenthal et al. 1960; Baroldi 1962; Ueda 1962; Richardson et al. 1966; Haerem 1969a, b; Schoenmackers 1969; Ratcliffe and Redfield 1972; Factor 1976; Ledet 1968, 1976; James 1965, 1967, 1977; Rahlf and Vaupel 1977; Crall and Roberts 1978).

The investigations made by Bucher (1944, 1945, 1947) showed the great variations possible in the normal anatomy of intramyocardial arteries. For this reason we determined to carry out a systematic investigation of the normal anatomy of intramyocardial arteries, to analyse pathological vascular lesions and to attempt a classification of vascular lesions occuring in various vessel types.

Furthermore we tried to correlate the vascular lesions found with age and sex and investigated the influence of risk factors in coronary heart disease, particularly hypertension and diabetes mellitus.

Material and Method

Tissue samples of the anterior and posterior wall of the left and right ventricle from 1,000 hearts in rigor mortis, taken from men and women aged between 4–100 years (Table 1), were systematically

Table 1

Decade		♂	♀	Total
1	1–10 years	37	22	59
2	11–20 years	19	14	33
3	21–30 years	37	9	46
4	31–40 years	48	15	63
5	41–50 years	71	39	110
6	51–60 years	89	58	147
7	61–70 years	169	83	252
8	71–80 years	121	108	229
9	81–90 years	26	29	55
10	91–100 years	1	5	6
		618	382	1,000

Table 2

Negative	No vascular alterations
slight	< 25% of the vessels with pathological wall alterations without stenosis of the lumen
medium	25–50% of the vessels with pathological wall alterations without significant stenosis of the lumen and < 25% of the vessels with stenosis of more than half the lumen
severe	> 50% of the vessels with pathological wall alterations without significant stenosis of the lumen and > 25% of the vessels with stenosis of more than half the lumen

investigated. The tissue was always removed in such a way that the complete wall cross-section with papillary muscle could be examined. The heart muscle tissue was normally fixed in 4% formalin solution and, in a few cases, in Bouin's solution as well. Frozen and paraffin sections were made in each case. We stained the frozen sections with Oil-Red-0 and the paraffin sections with Hematoxylin-Eosin, PAS, Elastica, Congo red, Methyl violett, van Gieson stain and Goldner's Trichrome method. In some cases fibrin staining was also carried out using the Ladewig and Lendrum method, or PTAH.

The intramyocardial arteries were classified into:

1. arterioles (with one muscle layer of the media);
2. small arteries (with 2–3 muscle layers) and
3. arteries (with more than 3 muscle layers).

The evaluation of the degenerative alterations was made according to the differing degrees of vascular damage (Table 2).

In grading the degree of stenosis of the large extramural coronary arteries we followed the WHO recommendation (1958):

Nil = No stenosis.
< 50% = Stenosis of less than half the lumen
and
> 50% = Greater degree of stenosis.

Risk factors in coronary heart disease such as diabetes mellitus and hypertension were collated from clinical records. Diabetic patients always required insulin. Hypertension was defined at a minimum blood pressure of 95 mm Hg diastolic and 160 mm Hg systolic. Diabetes mellitus was also presumed in cases where histological examination of the kidneys revealed diffuse or nodular glomerulosclerosis. Advanced concentric pressure hypertrophy (in the absence of aortic stenosis) was attributed to hypertension.

As a control group we took a sample of hearts from 240 men and women, in which no factors seemed to be present which might have led to pathological vascular alterations in the arterial intramyocardial vascular system.

We were not able to take the risk factors of smoking or hyperlipoproteinemia into consideration, as there were only a limited amount of clinical records available.

Results

A. Normal Anatomy of the Small Intramural Coronary Arterial System

In the postmortem contracted myocardium two basic types of arterial vessels can be distinguished:

1. Compacta or Ventricular Wall Type.
2. Papillary Muscle Type.

1. Compacta or Ventricular Wall Type. The compacta type is an arterial vessel with a thin intima and a well formed single layered elastica interna. The media contains smooth muscle cells arranged in a circle or flat helix, so that the media possesses a layer of ring muscle seen in cross-section. The adventitia is thin and consists of only slightly collagenous fibrous tissue. This type of vessel is most commonly found in the ventricular walls and the atria (Fig. 1).

In the trabecular portion of the myocardium arteries can be observed which have an inner layer of smooth muscle cells running lengthwise and an outer layer of circular musculature. Rarely vessels occur which show a more or less well-developed threefold layered muscular wall consisting of one inner circular, one medial longitudinal and one outer circular muscle layer. We believe that most of these vessels are compacta types in different stages of contraction. Some of them seemed to be arteries with incomplete transformation into papillary muscle type vessels.

2. Papillary Muscle Type. This is an arterial vessel with an intima of varying breadth and a single or occasionally double-layered elastica interna. The media is very broad with bundles of smooth musculature bunched into steep helices or running lengthways. The adventitia contains dispersed collagenous fibrous tissue. This vessel type is found mainly in the papillary muscles and less often in the trabecularis or in the compacta of the ventricles or atria (Fig. 2).

Serial sections from papillary muscles show that infants and small children have arterial vessels with a ring muscle layer in the media, and more rarely vessels whose smooth muscle cells changes directions lengthways towards the intima or adventitia. Between 5th and 10th years the arterial vessels change their shape in such a way that the vessel wall aquires more and more bundles of longitudinal musculature only. This transformation becomes more marked especially at the tip of the papillary muscles. We have found the most striking

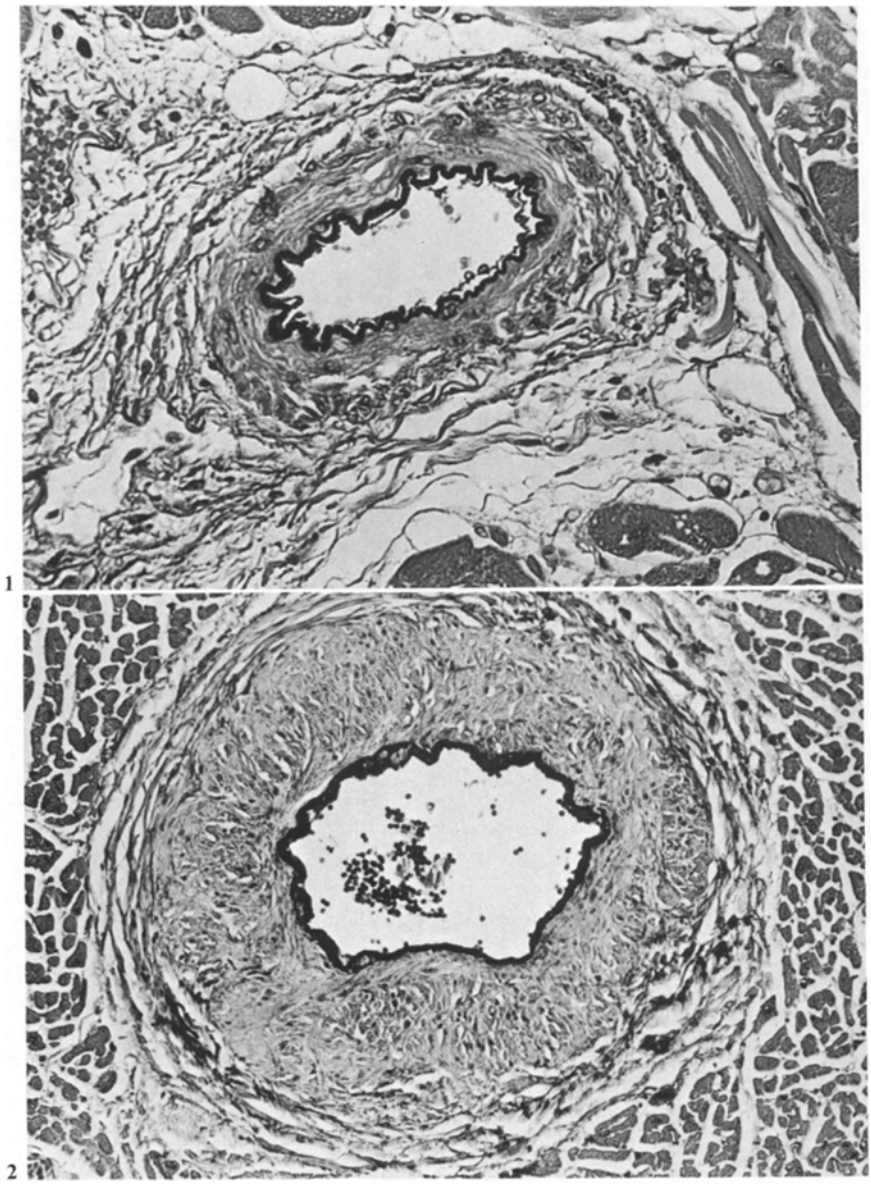


Fig. 1. Compacta type with ring musculature of the media. × 350 HE-Elastica

Fig. 2. Papillary muscle type with longitudinal musculature arranged as bundles in the broad media. × 140 Elastica-Goldner

cases of transformation of the smooth muscle cells in the vascular wall of arteries in the right papillary muscles. In the left papillary muscles, these typical transformations are often masked by the development of premature degenerative damage (Rahlf and Bruns 1978).

B. Degenerative Vascular Lesions in the Small Intramural Coronary Artery Branches

1. Degenerative Vascular Lesions in the Compacta or Ventricular Wall Type. In the compacta type excentric hyaline homogenous areas of thickening can be found subendothelially in the intima (Fig. 3). The hyaline PAS-positive deposits can develop into button-, cushion- or pad-shaped growths that lead to considerable displacement of the lumen. These pads can be shown up with elastica staining, revealing thickening of the elastica interna and also sometimes merging or lumpy deterioration and local fragmentation (Fig. 4). Fibrin staining using the Ladewig and Lendrum method is usually negative. Fat staining reveals only occasional pieces of fat-positive material in these pads. Spreading of the pads leads to narrowing and degeneration of the media. In large pads cellular elements can be seen with round or oval nuclei which partly resemble lymphoid cells or degenerated smooth muscle cells (Fig. 5). These vascular alterations are only of a local character and the pad formation develops particularly commonly at or near vascular branching areas (Fig. 6).

A second less common type of hyaline pad formation due to parietal microthrombosis can be found in the compacta-type. The elastica interna sometimes runs over the pad-like thickening of the intima without any distension, fragmentation or multiplication of the elastic material. Fibrin and fat staining are usually positive. These pads can be completely replaced by fibrous tissue.

These two pad formations are different from pads which are mainly built of regular smooth muscles cells caused by post mortem contraction of the arteries.

In the trabecular portion of the ventricular wall the pathological alterations of intramural arteries are additionally characterized by hyperelastosis of the intima (Fig. 7) and media (Fig. 8). Sometimes small arteries occur without an elastica interna and a predominant multiplication of the elastica externa (Fig. 9).

Rarely we found arterioles with focal or concentric hyaline transformation of the wall accompanied by disappearance of the smooth muscle cells.

2. Degenerative Vascular Alterations in the Papillary Muscle Type. In the papillary muscle arterial type, disintegration of the elastic lamina in the intima can be seen even in young persons (Fig. 10). With increasing age, destruction of the smooth muscle cells occurs in the variably broad media accompanied by fibrosis and hyperelastosis (Fig. 11). The intima can also reveal simultaneous or separate oedema. Increasing fibrosis accompanied by continual narrowing of the lumen can lead to a practically complete replacement of the intima and media by connective tissue (Fig. 12). At the same time fibrous tissue increases in the adventitia. Fibrosis and hyperelastosis of the whole vascular wall can develop so severely that intima and media become practically indistinguishable (Fig. 13).

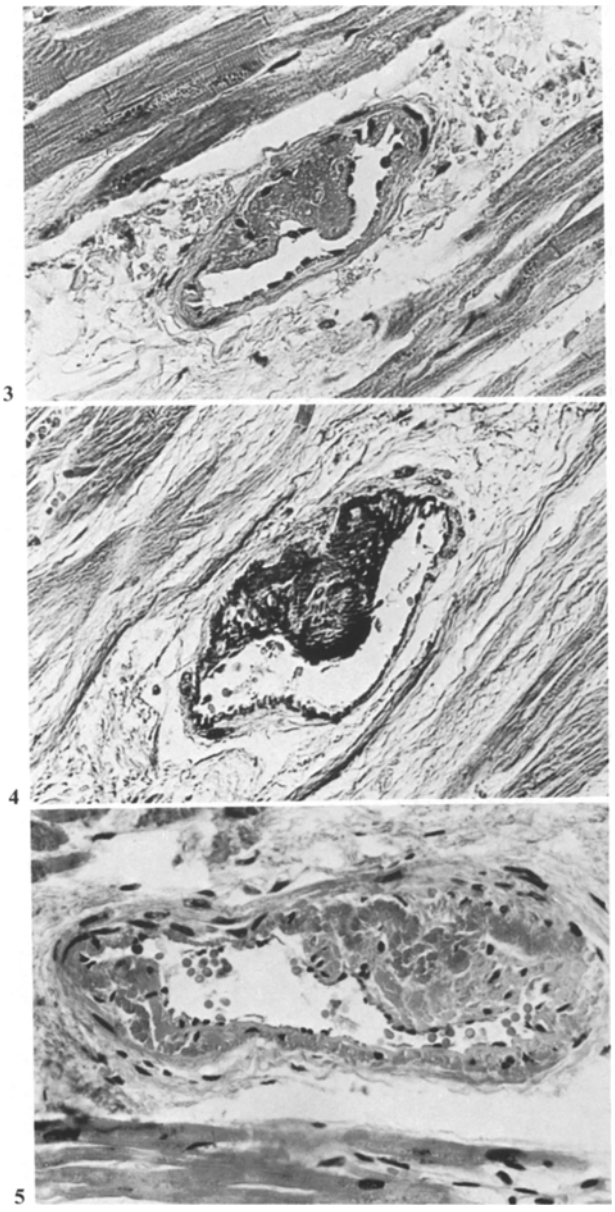


Fig. 3. Excentric thickening of the intima with cushion-like formation in a compacta type artery. ×450 Hematoxylin-Eosin

Fig. 4. Thickening and fragmentation of the elastica interna in a cushion pad of the compacta type arteries. ×450 Elastica

Fig. 5. Compacta type artery with cellular elements in a cushion-like lesion. ×450 Hematoxylin-Eosin

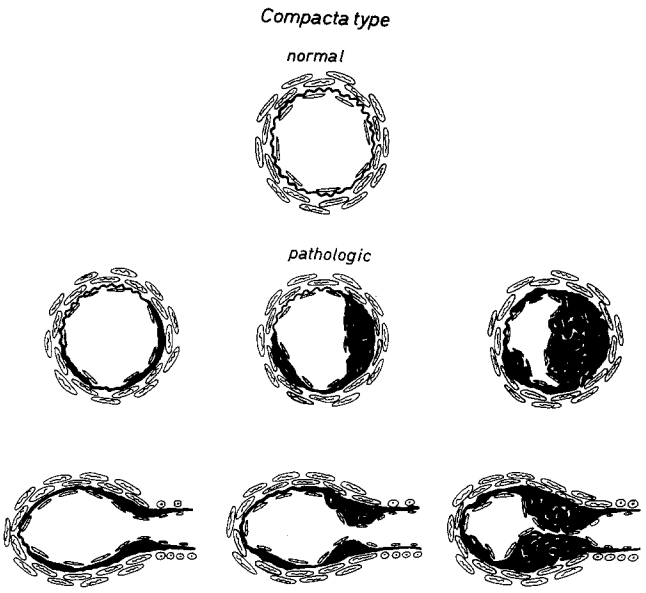


Fig. 6. Graphic representation of the pad-like formations in compacta type arteries near or at branching areas.

In the papillary muscle arterial type, finely distributed fatty deposits are seen in the intima, media and adventitia. This fat lies in the smooth muscle cells, and partly also in the collagenous fibrous tissue. Finely distributed fatty deposits are also found in the surrounding scarred tissue of the myocardium. The typical changes that take place in papillary muscle arteries with hyperfibroelastosis are usually much severer in the vessels of the left papillary muscles than in those of the right ventricle. Vascular lesions are usually more severe near the tip than the bottom of the papillary muscles.

Scarring of the myocardium of the left papillary muscles is frequently seen in cases with severe degenerative lesions of the papillary muscle arteries.

C. Frequency and Severity of Vascular Damage

Pathological vascular lesions in the compacta and papillary type mainly occur in the left ventricle. The vascular alterations increase with age (Fig. 14). In the papillary muscles they occur even during the first 10 years of life with a frequency of about 30%. It is not until the second decade that pathological lesions in the compacta type appear, in 21% of cases. From the 6th decade onwards, it is hard to find a heart that reveals no pathological vascular changes. In the compacta it is almost without exception vessels with 2–3 circular muscle layers of the media that are affected (Fig. 15). Arterioles with one muscle layer do not show any pathological alteration until the 4th decade of life (4%). With advancing age we find that alongside the pathological damage to vessels

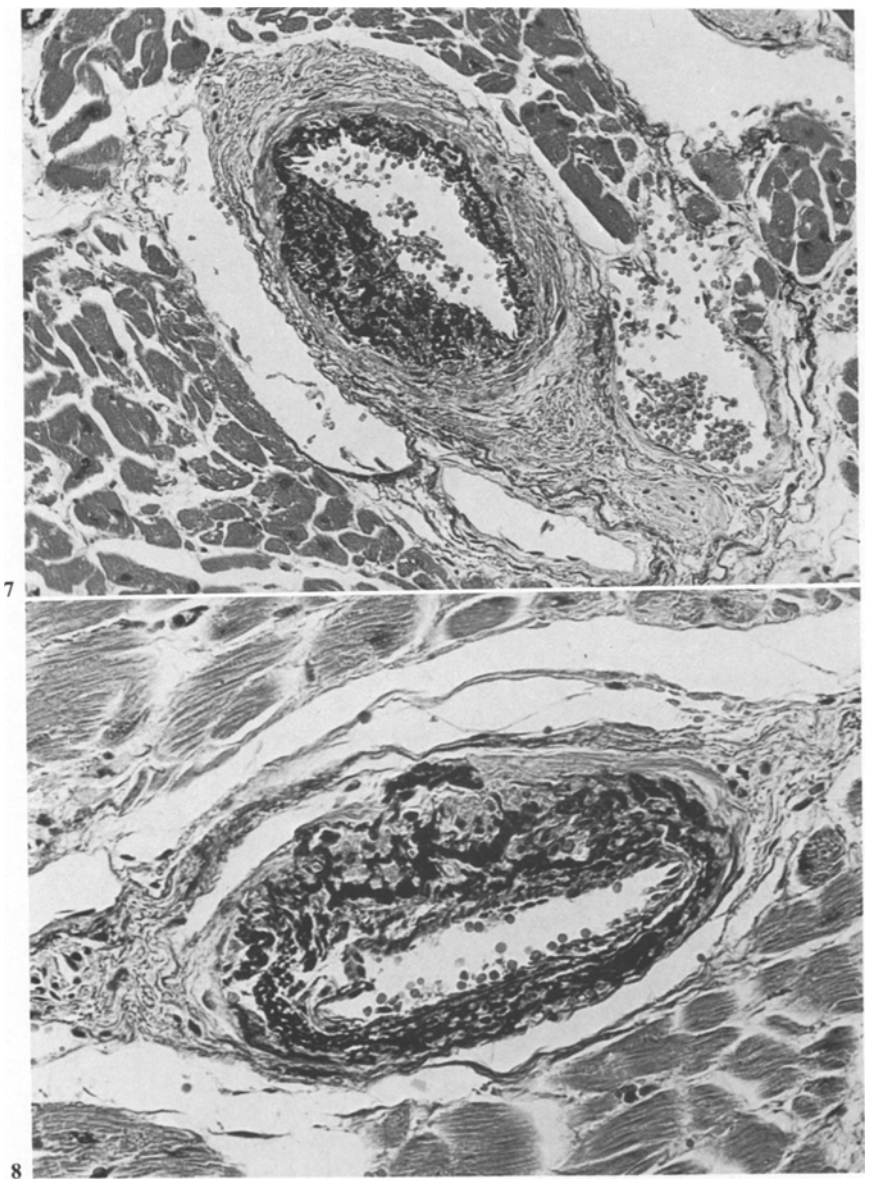


Fig. 7. Ventricular wall artery of the trabecular portion with predominant hyperelastosis of the intima. ×225 HE-Elastica

Fig. 8. Ventricular wall artery of the trabecular portion with hyperelastosis of the intima and media. ×350 HE-Elastica

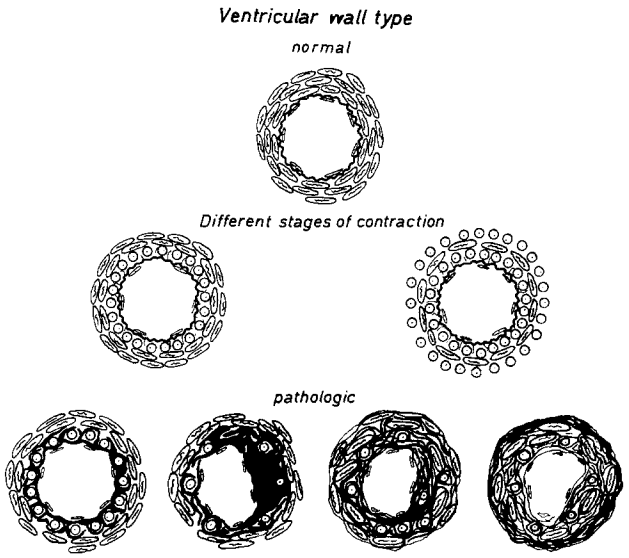


Fig. 9. Graphic representation of pathologic lesions in ventricular wall arteries of the trabecular portion

with 2–3 muscle layers, an increasing percentage of lesions in arterioles and vessels with more than 3 muscle layers takes place.

The pathological vascular alterations in the compacta type vessels occur in men earlier and more extensively than in women (Fig. 16).

When one categorises the severity of intramyocardial microarteriopathy in different degrees, it is evident that slight lesions comprise the majority (Fig. 17). The change-over to medium and severe impairment is completed in the papillary muscle arteries sooner and more severely than in the wall arteries. Men and women in the 7th to 9th decade of life show severe pathological vascular lesions in the compacta-type, in about 5–10% of cases, whereas in the papillary muscle type the figure lies between 30–35%.

D. Influence of Hypertension and Diabetes Mellitus on the Occurrence of Intramyocardial Microarteriopathy

We were able to use for our investigation the hearts of 240 hypertensive patients. There exists no special type of hypertension-dependent vascular damage in the intramyocardial microarteries. It can be seen from Fig. 18 that in the 4th and 5th decade slight vascular damage occurs in the compacta type more frequently in the hypertension than in the control group. This remains valid for lesions of medium severity especially in the 6th and 7th decade of life. Comparisons are harder to come by earlier and later than this as fewer subjects are available for random sampling.

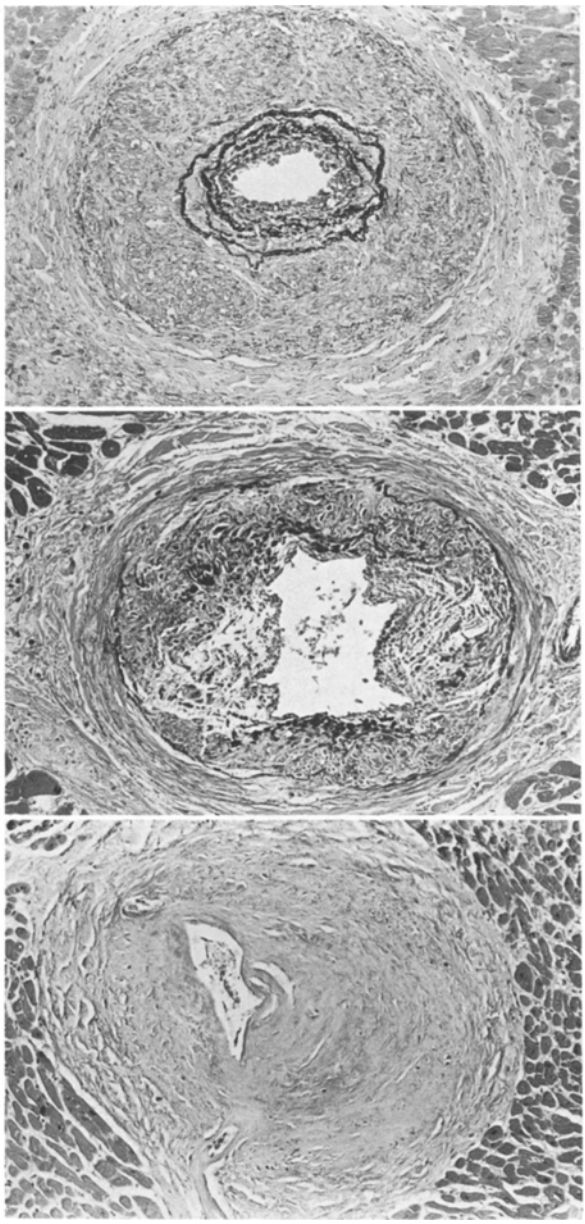


Fig. 10. Slight hyperelastosis in a papillary muscle type artery (right anterior papillary muscle). × 225 HE-Elastica

Fig. 11. Severe hyperelastosis in a papillary muscle type artery (left anterior papillary muscle). × 180 HE-Elastica

Fig. 12. Complete replacemant of intima and media by connective tissue with narrowing of the lumen of a papillary muscle type artery (left posterior papillary muscle). × 140 Hematoxylin-Eosin

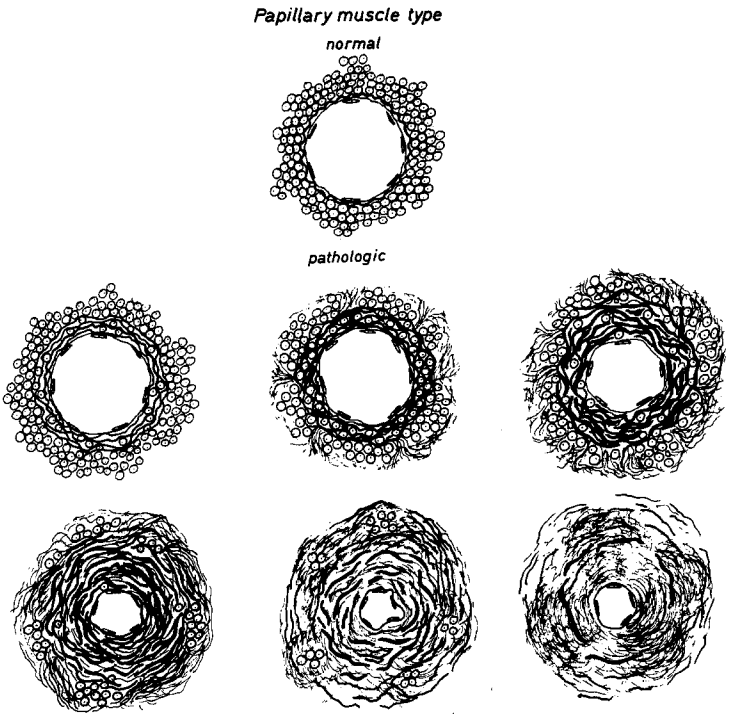


Fig. 13. Graphic representation of the degenerative lesions in the papillary muscle artery type

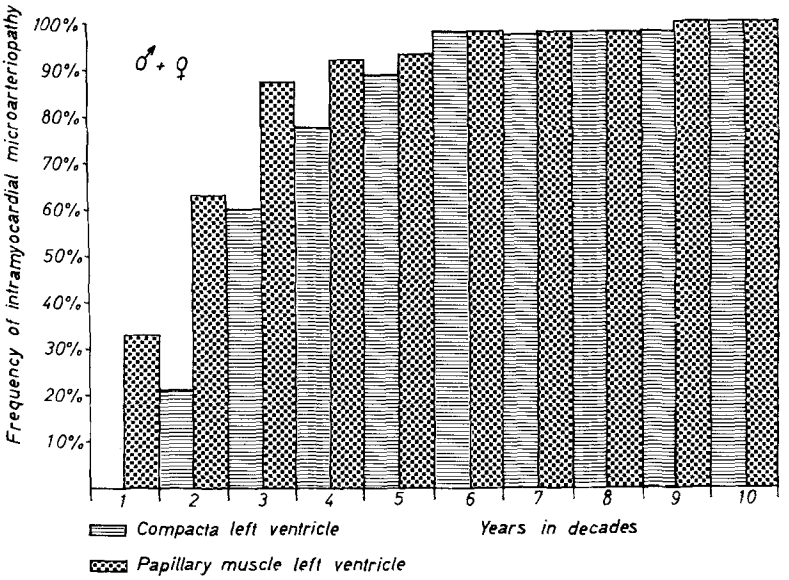
In the papillary muscles the influence of hypertension on the occurrence of vascular alterations is more difficult to explain on the evidence we collected. It seems that the typical changes in papillary muscle arteries with hyperfibroelastosis are rather more pronounced in hypertension cases. The transition from slight or medium to severe impairment is completed at the top and bottom of the left papillary muscles.

The most impressive result of our investigations on the influence of hypertension or hypertrophy on microarteriopathy is the fact that we found much more evidence of micronecrosis or microscars in the myocardium of the left ventricle, especially of the trabecularis and the papillary muscles, when severe microarteriopathy is accompanied by hypertension or advanced concentric hypertrophy.

We examined 119 cases of diabetes mellitus. No significant difference between the severity of compacta and papillary muscle type vascular lesions in this and in the control group could be demonstrated from our material (Fig. 19). The increase of slight and medium ventricular wall type lesions in diabetics in the 4th and 5th decade is not significant because of the different numbers of cases in diabetics and controls.

E. Effect of the Degree of Stenosis of the Extramural Coronary Arterial System on Pathological Lesions of the Intramyocardial Coronary Arteries

We cannot draw any statistically clear conclusions from our material; one can only regard it as probable that there might be an inverse ratio between



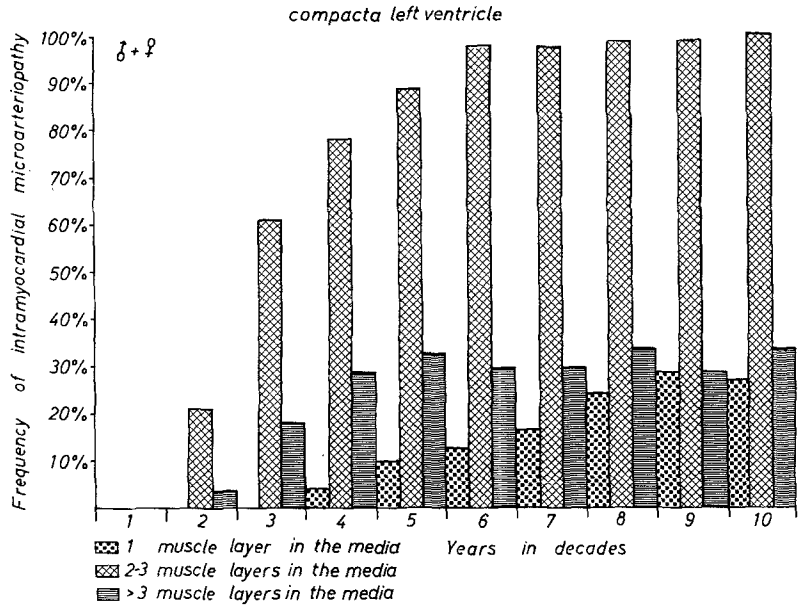
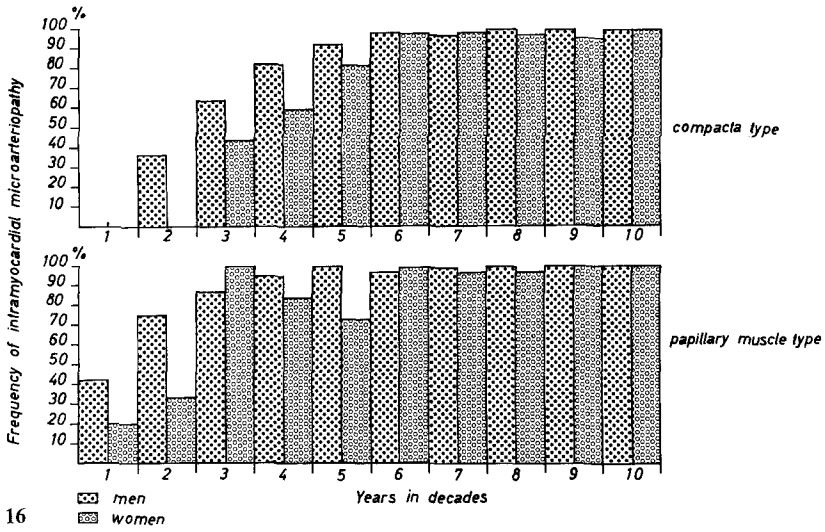


Fig. 14. Frequency of pathological changes in intramyocardial arteries of the compacta and papillary muscle type

Fig. 15. Frequency of pathological changes in the compacta type arteries according to the number of muscle layers in the media



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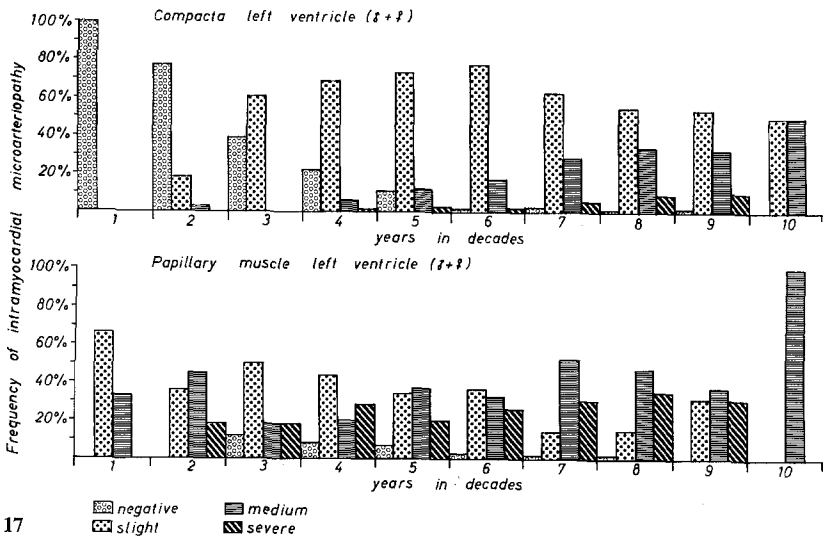

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Fig. 16. Frequency of pathological changes in microarteries of the left ventricle. Distribution according to sex

Fig. 17. Grading of pathological changes in the intramyocardial microarteries of the compacta type and papillary muscle type

the severity of extramural coronary arterial sclerosis and the occurence of intramyocardial vascular wall lesions in the compacta type. Severe pathological intramyocardial vascular lesions are more marked in cases with only up to 50% extramural stenosis (Fig. 20).

In our evaluation of the results, the degree of intramyocardial microarteriopathy in both test areas of the left ventricle was taken together, regardless

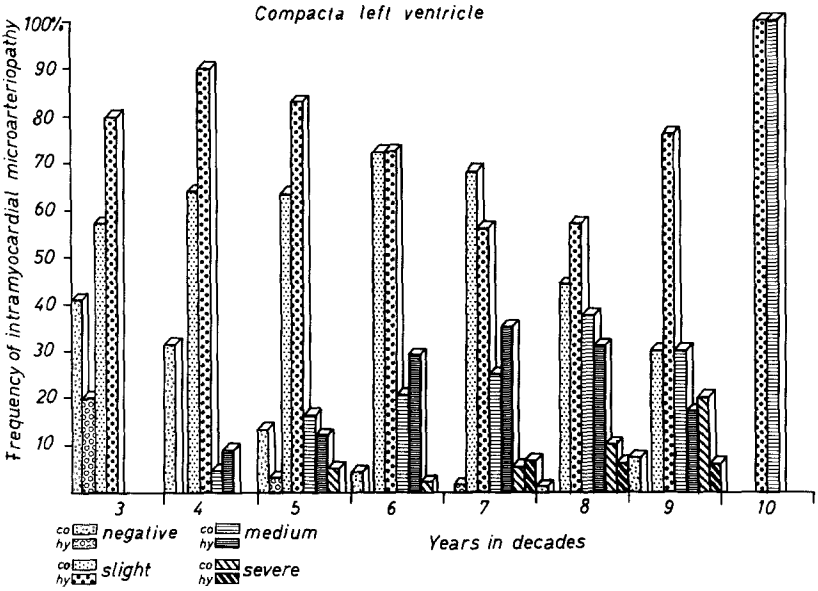


Fig. 18. Comparison of the degree of intramyocardial microarteriopathy (compacta type) in cases of hypertension with controls. *co* control, *hy* hypertension

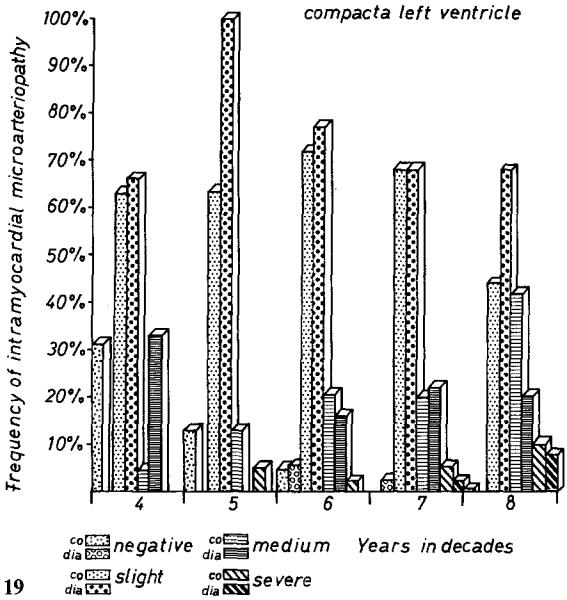
of whether only one or more extramural coronary arteries were stenosed. However, when we compare the intramural damage to the compacta type vessels in one single heart, we often see that slight intramyocardial microarteriopathy occurs in the supply area of a severely stenosed extramural coronary artery, whereas in the supply area of a patent coronary artery the degree of intramural vascular damage is severe.

The vascular lesions of the papillary muscle type arteries develop independently from extramural coronary sclerosis.

F. Functional Significance of the Vascular Lesions

In the regulation of blood flow resistance and thus the supply of blood to the heart, an important role is played by the intramural small coronary vessels. It is not only the compacta type vessels but also the papillary muscle type that show in post mortem contracted hearts a considerable narrowing of the lumen. Preliminary studies in hearts which have been perfused at 100 mm Hg for 5 min, however, show that the degree of stenosis in pathologically altered intramural arteries is much less than in the postmortem contracted and not perfused hearts (Fig. 21).

We suppose that severe vascular lesions (in advanced age 5–10% for compacta type lesions and 30–35% for papillary muscle type lesions) can lead to irregular disturbances in the supply of blood to the myocardium. This may be supported by the fact that in cases of non-stenotic extramural coronary sclerosis but



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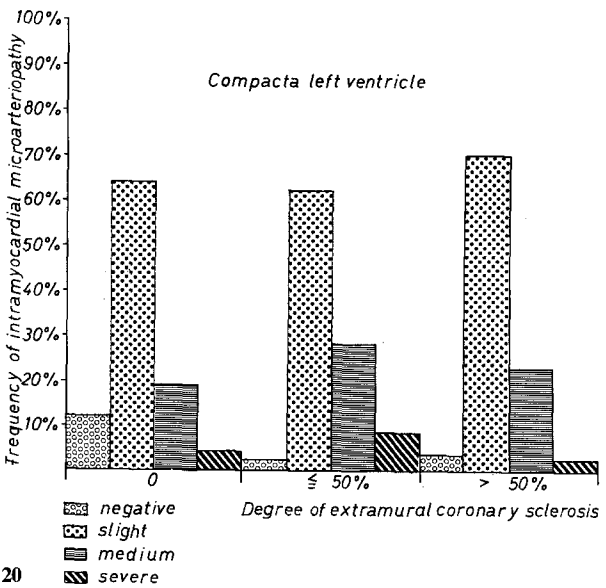

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Fig. 19. Comparison of the degree of intramyocardial microarteriopathy (compacta type) in cases of diabetes mellitus with controls. *co* control, *dia* diabetes mellitus

Fig. 20. Degree of intramyocardial microarteriopathy in relation to the degree of extramural coronary sclerosis (♂+♀)

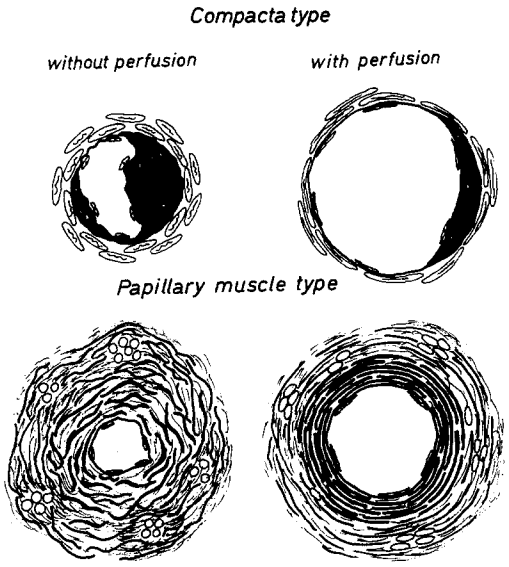

Fig. 21. Graphic representation of the degenerative lesions in the compacta and papillary muscle type in hearts with and without post-mortem perfusion

having obvious severe degeneration of the papillary muscle arteries micronecrosis and scarring can be found in the myocardium of the left papillary muscles. Furthermore, we found disseminated micronecrosis and scars in the ventricular wall and papillary muscles of the left ventricle predominantly in some of our cases where a concurrence of both microarteriopathy and hypertrophy or hypertension existed.

Scarring of the left papillary muscles may play an important role in dysfunctions of papillary muscles or the development of a relative mitral insufficiency, especially in hypertrophied left ventricles.

In our investigations there is no evidence for major infarctions of the myocardium caused by intramyocardial degenerative microarteriopathy. In all cases of subendocardial or transmural infarctions we found high grade coronary sclerosis with or without thrombosis of extramural coronary branches.

Discussion

Investigations on the normal histology of the small intramyocardial vessels have been chiefly carried out by Bucher (1944, 1945, 1947). He noted four seperate types in the intramyocardial arterial vessel system. These types could be distinguished from a vessel with ring musculature in the media, corresponding to our typical wall or compacta type. Some of the vessel types described by Bucher should be seen as compacta type arteries in different stages of contraction. The smooth muscles cells of the media are normally arranges in helices (Fischer 1951; Goerttler 1953). The helices can change their shape in dilated or contracted vessels. In cross-sections of the arteries it is possible to see more smooth muscle cells of the flat part of the helix (circular muscle layer), of

the steeper part (longitudinal muscle layer) or of both (circular and longitudinal muscle layers). One of Bucher's artery types with marked longitudinal musculature of the wall is similar to our papillary muscle type. We think that in this type of artery there is a real change in organisation of the muscular wall which is not due to the effects of wall thickening in arteries with smooth muscle cells, which are normally arranged in helices of varying pitch. Longitudinal or steep helices of muscle bundles in a vessel wall are used in conjunction with externally operating forces to stretch the vessels lengthwise (Bucher 1947; Ratzenhofer 1952). Weibel (1958) was able to show in the experiments on the mesenteric arteries of animals that when these vessels had been fixed by operation to the diaphragm, the diaphragm movements in respiration, consisting of rhythmic expansion and contraction, led to the growth of longitudinal muscle bundles in the vascular wall. These cells derived from the circular muscle layers of the media by mitotic division.

Our investigations show that statements concerning the incidence of pathological alterations to the small intramyocardial coronary arteries can only be made if the pathological lesions in the compacta and papillary muscle type vessels are analysed seperately.

Wegelin (1944) and Haerem (1969b), who have mainly concerned themselves with pathological alterations in the compacta type, interpret the pad and cushion formations in the compacta type as the consequence of ongoing, frequently recurring vascular damage. According to Haerem (1969b), these alterations are said to appear more often at vascular branch-areas, since the laminal stream can become turbulent here, which is known to be able to cause endothelial damage (Fry 1968). Haerem (1969b) supposed that the PAS-positive material that he found in the cushions or pads, which can partly be identified as elastin, can largely be produced from components of the vascular wall.

We only interpret fibrin and fat rich pad formations as parietal microthromboses. Haerem (1969a, b, 1972) was sometimes able to find small aggregates of thrombocytes at the intima in intramyocardial microarteries.

Pad formations by regular smooth muscle cells mostly should be seen as a phaenomenon of postmortem contraction of the vessels. Baráth et al. (1966) and Benisch and Wisniewski (1971) interpret pad formations with smooth muscle cells as a sphincter at arteriovenous anastomoses. Intramyocardial arteries with cushion-like smooth muscle cells that run lengthways were seen by Zinck (1940) as compressor arteries.

Our results show that intramyocardial microarteriopathy in papillary muscle arteries is characterized by alterations of the intima, elastica interna, media and adventitia. Wolff (1929) noted fibrosis of the media as being the most obviously striking pathological alteration to the papillary muscle arteries. Gross et al. (1934) found that it was more often in the left posterior papillary muscle than in other spots that vessels with longitudinal musculature occured in which large quantities of fibrous tissue had developed in the media and intima accompanied by hyperelastosis.

Alavaikko et al. (1970) particularly described the strong tendency to fatty degeneration of the smooth muscle cells of the media in the papillary muscle arteries.

In accordance with our results an increasing degeneration in small intramural arteries and arterioles with age was observed by Wolff (1929); Gross et al. (1934); Wegelin (1944); Linzbach (1955); Blumenthal et al. (1960); Schwartz and Mitchell (1962); Boucek et al. (1965); Sośnierz and Wieczorek (1968); Haerem (1969b); Alavaikko et al. (1970); Höpker et al. (1975) and Naeye and Liedtke (1976).

Wegelin (1944) found pathological vascular changes in about 50% of cases in the 6th decade of life, and in 80% of cases in the 9th decade. He examined mainly arterioles with a diameter of 25–50 μ. The changes were observed to be more severe and occur earlier in men than in women. He did mention the fact that the proportion of severe vascular damage in his sample averaged 8,6%, with a peak of 11,1% in the age group 41–60. From the age of 50 onwards Haerem (1969b) found no heart that did not reveal pathological changes in the small intramyocardial arteries of the compacta types. No direct comparison with our results can be made, due to the different basis of age group division.

Linzbach (1955) examined 56 hearts aged between 60 and 94. He graded the vascular alterations into the categories slight, medium and severe. His fingings showed that slight vascular changes grew less with age while medium ones increased, and severe damage reached a peak in the 8th decade. Going by positive findings alone Linzbach was able to show pathological changes in 80% of cases in the 7th decade of life and 100% in the 9th, but Linzbach did not distinguish between papillary muscle and compacta type.

Hypertension has been described as a contributory factor in the occurance of pathological intramyocardial vascular lesions (Odel 1940; Kathke 1955; Neubuerger and Denst 1955; Liebegott 1958; Blumenthal et al. 1960; Volkova 1961; Schwartz and Mitchell 1962; Sośnierz and Wieczorek 1968; Haerem 1969b; Alavaikko et al. 1970; Doerr 1970). In experimentally – induced acute hypertension Kunz et al. (1973) and Olsen (1978) have demonstrated increased permeability in small intramyocardial arteries and arterioles. The small arteries showed a distinct deposit of plasma components in the intima and media as well.

However, Fishberg (1925); Wegelin (1944); Baroldi (1962); Ueda (1962); Ledet (1968) and Knežević et al. (1970) found no correlation between the severity of the intramyocardial vascular lesions and the presence of hypertension.

According to our results hypertension is associated with a rise in the frequency of slight and medium lesions in the vessels of the compacta type in the 4th–7th decade. In the papillary muscle arteries the transition from slight or medium to severe impairment is completed in hypertensive cases not only at the top but also at the bottom of the left papillary muscles; it is mainly the extension of the lesions that is influenced by hypertension.

We have found not specific hypertensive lesions in the intramyocardial microarteries (Rahlf 1979). However, without histometrical investigations we were not able to make statements concerning medial hypertrophy or hyperplasia in cases with hypertension. When we compare the findings in the literature relating to pathological-anatomical vascular changes in hypertension, we find that references are frequently made to lesions in the elastic lamella and media. It is possible that with this type of lesion we are dealing with degenerative rather than hypertension specific vascular lesions especially in the papillary muscle types. Among the hypertensive cases we examined we were not able to find any increase in arteriolosclerosis (hyalinosis of the smallest intramural

arterial vessels with only one muscle layer of the media) as described by Kathke (1955) in a total of 7 hearts.

Investigations on nephrosclerosis and blood pressure, however, show that nephrosclerosis can undergo arrest or reversal (Tracy and Toca 1974). Even the most densely fibrous intimal lesions appear to be capable of reversal. Duration and severity of hypertension seemed to be very important factors if one tries to study the influence of hypertension and the occurrence of hypertensive specific vascular lesions. In our investigation we did not, however, attempt any further analysis of clinically diagnosed hypertension in terms of duration or severity.

We never saw so-called glomoid or plexiform lesions in intramyocardial coronary arteries as described by Salyer and Hutchins (1974) in cases of malignant hypertension.

Diabetics according to the findings of Saphir et al. (1956); Blumenthal et al. (1960); Cicala and Marin (1960); Jonáš et al. (1966), Ledet (1968, 1976, 1979); Halkin and Ravid (1972); Rubler et al. (1972); Pearce et al. (1973); Hamby et al. (1974); Crall and Roberts (1978) and Zoneraich et al. (1978) are particularly likely to show pathological wall and papillary muscle type vessel alterations. Strongly PAS-positive staining was seen especially in the smallest intramyocardial vessels, in which the lumen diameter ranged between 15–50 μ (Ledet 1968, 1976). The pathological myocardial changes were additionally characterised by periarterial collagen build-up, which is evidently much commoner in diabetics (Ledet 1976; Regan et al. 1975, 1977).

During post-mortem injection studies Factor et al. (1980) observed microaneurysms in the hearts of diabetics.

In contrast to these findings Haerem (1969b), Ratcliffe and Redfield (1972) and Höpker et al. (1975) saw no causal connection between diabetes mellitus and the occurrence of intramyocardial arterial vessel damage.

We did not find any noteworthy increase in the frequency of pathological changes in the compacta or papillary muscle type vessels in diabetics. One explanation for our negative result may be that we included in our statistical analysis all ventricular wall type vessels irrespective of diameter. However, even in small arteries or arterioles we found no increase of PAS-positive material in the vessel walls. Another reason may be that we mainly considered clinically diagnosed cases of diabetes mellitus, and also did not limit our investigation to cases where diabetes mellitus was accompanied by diffuse or nodular glomerulosclerosis.

Wegelin (1944); Baroldi (1962); Schwartz and Mitchell (1962); Ueda (1962); Sośnierz and Wieczorek (1968); Alavaikko et al. (1970), were not able to show any relationship between severity of stenosis of the extramural main vessels and the occurrence and frequency of intramural vascular alterations in their studies. The changes seemed to take place independently of one another in both areas.

However, Ratcliffe and Redfield (1972) found a positive correlation between atherosclerotic stenosis of the extramural coronary arteries and stenotic lesions of the intramural coronary arteries.

Very different results were obtained by Linzbach (1955); Haerem (1969b) and Hatani (1977) who found that severe stenosis of the extramural coronary

artery branches were accompanied only by a small degree of intramural arterial degeneration. Where there was little or no stenosis of the extramural vessels, they found an increased severity of degeneration in the intramural arterial vessel branches. This is an accordance with our results regarding the ventricular wall type lesions.

Wegelin (1944); Volkova (1961); Baroldi (1962) and Baroldi and Scomazzoni (1967) consider that intramural vascular alterations are of little significance in the function and maintenance of the myocardium.

In contrast to this opinion Ueda (1962) and Donomae et al. (1962, 1965) believe that severe intramural damage can lead to chronic heart insufficiency without attacks of angina pectoris so-called "silent heart failure" or "chronic cardiac failure". Similar views are held by Ratcliffe and Redfield (1972) and Naeye and Liedtke (1976). Severe microarteriopathy of the myocard can according to Linzbach (1972) lead to manifest coronary insufficiency even without sclerosis of the extramural arteries. It is particularly in old age that intramyocardial microarteriopathy becomes of functional importance.

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References

Alavaikko M, Hirvonen J, Räsanen O (1970) Fatty change in papillary heart muscle and in its arterioles. Acta Pathol Microbiol Scand [A] 78:458–472

Baráth J, Veres J, Csörgey M (1966) The role of functional factors and special vascular sphincter apparatuses in myocardial infarction. Acta Med Acad Sci Hung 22:111–116

Baroldi G (1962) Histopathological study of the intramural artery vessels in relation to the pathology of extramural coronary arteries and myocardial damage. Cardiologia 41:364–380

Baroldi G, Scomazzoni G (1967) Coronary circulation in the normal and in the pathologic heart. Office of the Surgeon General/Department of the Army Washington, D.C.

Benisch MB, Wisniewski M (1971) Muscular cushions of intramyocardial arteries: Their relationship to coronary arteriosclerosis. Angiology 22:304–310

Blumenthal HT, Alex M, Goldenberg S (1960) A study of lesions of the intramural coronary artery branches in diabetes mellitus. Arch Pathol 70:27–42

Boucek RJ, Takeshita R, Brady AH (1965) Intimal hypertrophy in coronary arteries and considerations of the papillary muscle arteries (Man). Anat Rec 153:243–254

Bucher O (1944) Polsterbildungen in den Arterien des Myokards (Polsterkissen und Polsterarterien). Schweiz Med Wochenschr 74:522–523

Bucher O (1945) Sondervorrichtungen an Kranzgefäßen. Schweiz Med Wochenschr 75:966–969

Bucher O (1947) Über den Bau der Blutgefäße des menschlichen Herzens. Acta Anat 3:162–189

Cicala V, Marin A (1960) Ricerche istologiche ed istochimiche sulla coronaropatia diabetica e arteriosclerotica. Riv Anat Pathol 18:755–786

Crall FV, Roberts WC (1978) The extramural and intramural coronary arteries in juvenile diabetes mellitus. Am J Med 64:221–230

Donomae I, Matsumoto Y, Kokubu T, Koide R, Kobayashi R, Ikegami H, Ueda E, Fujisawa T, Fujimoto S (1962) Pathological studies of coronary atherosclerosis especially of sclerosis of intramuscular coronary arteries. Jpn Heart J 3:423–441

Donomae I, Matsumoto Y, Ueda E (1965) Significance of coronary arteriosclerosis in the intramuscular coronary arteries. Geriatrics 20:179–193

Doerr W (1970) Allgemeine Pathologie der Organe des Kreislaufes. In: Handbuch der allgemeinen Pathologie, Bd III/4, Springer, Berlin Heidelberg New York, S 205

Factor SM (1976) Intramyocardial small vessel disease in chronic alcoholism. Am Heart J 92:561–575

Factor SM, Okun EM, Minase T (1980) Capillary microaneurysms in the human diabetic heart. N Engl J Med 14:384–388

Fischer H (1951) Über die funktionelle Bedeutung des Spiralverlaufes der Muskulatur in der Arterienwand. Gegenbaurs Morphol Jahrb 91:394–445
Fishberg AM (1925) Anatomic findings in essential hypertension. Arch Intern Med 35:650–668
Fry DL (1968) Acute vascular endothelial changes associated with increased blood velocity gradients. Circ Res 22:165–197
Goerttler K (1953) Die funktionelle Bedeutung des Baues der Gefäßwand. Dtsch Z Nervenheilk 170:433–445
Gross L, Epstein EZ, Kugel MA (1934) Histology of the coronary arteries and their branches in the human heart. Am J Pathol 10:253–273
Haerem JW (1969) Cushion-like intimal lesions and platelet aggregates in intramyocardial arteries of man. Acta Pathol Microbiol Scand 77:73–89
Haerem JW (1969) Cushion-like intimal lesions in intramyocardial arteries of man. Acta Pathol Microbiol Scand 77:598–608
Haerem JW (1972) Platelet aggregates in intramyocardial vessels of patients dying suddenly and unexpectedly of coronary artery disease. Atheroclerosis 15:199–213
Halkin H, Ravid M (1972) Involvement of the intramural coronary circulation in diabetic angiopathy. Isr J Med Sci 8:773–774
Hamby RI, Zoneraich S, Sherman L (1974) Diabetic cardiomyopathy. JAMA 229:1749–1754
Hatani H (1977) Angiographic, histochemic and histopathological studies on the intramural coronary arteries in the infarcted heart. Acta Pathol Jpn 27:511–526
Höpker W-W, Nüssel E, Weiler J (1975) Ausbreitungsmuster der Arteriosklerose: Alter und Risikokriterien bei epicardialen und intramuralen Veränderungen der Coronargefäße bei Patienten mit Herzinfarkt. Verh Dtsch Ges Pathol 59:348–354
James TN (1965) Anatomy of the coronary arteries in health and disease. Circulation 32:1020–1033
James TN (1967) Pathology of small coronary arteries. Am J Cardiol 20:679–691
James TN (1977) Small arteries of the heart. Circulation 56:2–14
Jacobson SA, Rankin ThJ (1950) Arteriolar disease of the heart. Angiology 1:477–483
Jonáš V, Chlumská A, Kozák P (1966) Změny intramurálních koronárních cév u diabetiků. Acta Univ Carol [Med] (Praha) 12:379–384
Kathke N (1955) Die Veränderungen der Coronararterienzweige des Myokards bei Hypertonie. Beitr Pathol 115:405–422
Knežević M, Knežević-Kirvak Š, Rode B (1970) Beitrag zur Kenntnis der Pathologie der intrapapillären Koronararterienästchen am linken Herzen. Verh Dtsch Ges Pathol 54:348–355
Kunz J, Keim U, Braselmann H, Kreher Ch, Nitschkoff St (1973) Intramurale und perivasale Ablagerung von Plasmaproteinen bei der experimentellen Hypertonie. Exp Pathol (Jena) 8:294–302
Ledet T (1968) Histological and histochemical changes in the coronary arteries of old diabetic patients. Diabetologia 4:268–272
Ledet T (1976) Diabetic cardiopathy. Quantitative histological studies of the heart from young juvenile diabetics. Acta Path Microbiol Scand [A] 84:421–428
Ledet T, Neubauer B, Christensen NJ, Lundbaek K (1979) Diabetic cardiopathy. Diabetologia 16:207–209
Liebegott G (1958) Die intramurale Coronarsklerose bei Hypertonie. Med Klin 35:1465–1466
Linzbach AJ (1947) Mikrometrische und histologische Analyse hypertropher menschlicher Herzen. Virchows Arch 314:534–594
Linzbach AJ (1956) Das Greisenherz. Deutscher Internistentag 1955, Leipzig; Verlag Volk und Gesundheit, Berlin, S 324–332
Linzbach AJ (1972) Das Altern des menschlichen Herzens. In: Altmann HW, Bücher F, Cottier H, Grundmann E, Holle E, Letterer E, Masshoff W, Meessen H, Roulet F, Seifert G, Siebert G (Hrsg) Handbuch der allgemeinen Pathologie, Bd VI/4. Springer, Berlin Heidelberg New York, S 369
Lisa JR, Brown ChR (1941) Arteriolar disease of the heart. Ann Intern Med 14:2147–2156
Naeye RL, Liedtke AJ (1976) Consequences of intramyocardial arterial lesions in aortic valvular stenosis. Am J Pathol 85:569–580
Neubuerger KT, Denst J (1955) Les lésions artériolaires des piliers du coeur au cours du rhumatisme cardiaque chronique. Arch Anat Cytol Pathol 31:76–81
Odel HM (1940) Structural changes in the arterioles of the myocardium in diffuse arteriolar disease with hypertension group 4. Arch Intern Med 66:579–602

Okada R, Harumi K, Nomura M, Murao S (1960) A case of coronary sclerosis in small arteries associated with diffuse myocardial fibrosis. Jpn Heart J 1:348–356
Olsen F (1978) Akute hypertensive damage of arterial vessels of the heart. Acta Pathol Microbiol Scand [A] 86, 199–200
Pearce MB, Bulloch RT, Kizziar JC (1973) Myocardial small vessel disease in patients with diabetes mellitus. Circulation 48, suppl IV:6
Plaut A, Kramer ML (1936) Arteriolar disease of the heart. Arch Pathol 22:393–397
Rahlf G, Vaupel H-A (1977) Die Pathologie der kleinen intramuralen Coronararterienäste. Verh Dtsch Ges Pathol 61:345
Rahlf G, Bruns M (1978) Normale und pathologische Anatomie der Papillarmuskelarterien. Verh Dtsch Ges Pathol 62:387
Rahlf G (1979) Microscopic pathology of intramural coronary arteries and arterioles of the left ventricle in arterial hypertension. International Symposium: "Heart in Hypertension", Munich (in press)
Ratcliffe HL, Redfield E (1972) Atherosclerotic stenosis of the extramural and intramural coronary arteries of man. Virchows Arch [Pathol Anat] 357:1–10
Ratzenhofer M (1952) Zur Bildung von Längsmuskulatur in Blutgefäßen. Verh Dtsch Ges Pathol 36:267–278
Regan TJ, Ahmed SS, Levinson GE, Oldewurtel HA, Ahmad MR, Haider B, Lyons MM (1975) Cardiomyopathy and regional scar in diabetes mellitus. Trans Assoc Am Physicians 88:217–221
Regan TJ, Lyons MM, Ahmed SS, Levinson GE, Oldewurtel HA, Ahmad MR, Haider B (1977) Evidence for cardiomyopathy in familial diabetes mellitus. J Clin Invest 60:885–899
Richardson HL, Graupner KI, Richardson ME (1966) Intramyocardial lesions in patients dying suddenly and unexpectedly. JAMA 195:254–260
Rider AK, Billingham ME, Harrison DC (1974) Small vessel coronary disease: Biopsy evidence of intramyocardial arteriopathy. Circulation 49/50, Suppl III:109
Rubler S, Dlugash J, Yuceoglu YZ, Kumral T, Branwood AW, Grisham A (1972) New type of cardiomyopathy associated with diabetic glomerulosclerosis. Am J Cardiol 30:595–602
Salyer, WR, Hutchins GM (1974) Glomoid lesions in systemic arteries in malignant hypertension. Arch Pathol 97:104–106
Saphir O, Ohringer L, Wong R (1956) Changes in the intramural coronary branches in coronary arteriosclerosis. Arch Pathol 62:159–170
Schoenmachers J (1969) Die Blutversorgung des Herzmuskels und ihre Störungen. In: Lehrbuch der speziellen pathologischen Anatomie. Ergänzungsband I/1, 59–224. Walter de Gruyter+Co., Berlin
Schwartz CJ, Mitchell JRA (1962) The relation between myocardial lesions and coronary artery disease. Brit Heart J 24:761–786
Sośnierz M, Wieczorek M (1968) Morphological lesions of intramyocardial arteries in 100 cases examined post mortem. Pol Med J 7:839–844
Tracy RE, Toca VT (1974) Nephrosclerosis and blood pressure. II. Reversibility of proliferative arteriosclerosis. Lab Invest 30:30–34
Ueda E (1962) Pathological studies of coronary atherosclerosis, especially of sclerosis of intramuscular coronary arteries. Med J Osaka Univ 13:117–137
Volkova KG (1960) The arterioles of the myocardium in hypertension. Exerpta med (Amst) Sect XVIII 5 (1961) 688–689. Arch Pathol 22/11:13–18
Wegelin C (1944) Über Arteriolosklerose im Myokard. Schweiz Med Wochenschr 74:57–60
Weibel E (1958) Die Entstehung der Längsmuskulatur in den Ästen der A. bronchialis. Z Zellforsch 47:440–468
Wolff K (1929) Die Längs- und Spiralanordnung der Muskulatur in der Media der Papillarmuskelschlagadern. Virchows Arch 276:259–278
World Health Organization (1958) Wld Hlth Org techn Rep Ser:143
Zinck KH (1940) Sondervorrichtungen an Kranzgefäßen und ihre Beziehung zu Coronarinfarkt und miliaren Nekrosen. Virchows Arch [Pathol Anat] 305:288–297
Zoneraich S, Silverman G, Zoneraich O (1978) Small stiff heart in diabetes mellitus. Am J Cardiol 41:426

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