REVIEW

Clinical picture of arteriolosclerosis

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Abstract

Arteriolosclerosis is a generalised systemic vascular disease which is characterised by hyalinisation of intima (hyalinosis) as well as proliferation and hypertrophy of the media in the arteriolar part of the arterial system (so-called benign arteriolosclerosis). However, the patients suffering from accelerated and malign hypertension develop also fibrinoid necrosis (so-called malign arteriolosclerosis, arteriolonecrosis). Arteriolosclerosis as well as other similar stenotic (obliterating, obstructive, occlusive) diseases of the arterial system, have one single common consequence — ischemia. Currently, angio-organic ischemic syndromes in the whole world most frequently result from atherosclerosis which, however, is not the only nosologic unit of the group of arterial diseases having the tendency to develop arterial wall sclerosis. The latter group is briefly referred to as arteriosclerosis. In addition to atherosclerosis, this group includes also Mönckeberg's medial arteriosclerosis, diabetic angiopathy and arteriolosclerosis.
The authors of this study, on the basis of their analysis of their own large set of patients (71,662 angiologic consultant examinations performed during the period of 25 years of the existence of the Angiologic Department of the Medical Faculty Hospital of Comenius University in Bratislava) attract attention to the fact that the clinical picture of this disease is multiform, and that it occurs frequently in clinical practice. Therefore, angiology is a separate specialisation which is above the structure of internal medicine. ***(Tab. 5, Fig. 3, Ref. 46.)***
Key words: arteriolosclerosis, arteriosclerosis, angio-organic ischemic syndromes, internal medicine, angiology.

The Angiologic Department of the II Internal Clinic of the Medical Faculty Hospital, Comenius University in Bratislava is probably the oldest angiologic department. It was established in 1974, after the angiologic laboratory of the Balneologic Institute of the Medical Faculty of the Comenius University, and since then it has been providing continuous angiologic health care as a separate department of the Faculty Hospital (23, 24, 25, 26, 27, 37).

All consultant angiologic examinations which were subject to the analysis, were personally carried out by the first author of this study, who was the head physician during the first century quarter of the existence of the Angiologic Department of the II Internal Clinic of the Medical Faculty Hospital, Comenius University in Bratislava (1974—1999). Out of their total number of 71,662, the diseases of distributive vascular bed (especially the ischemic disease of lower limbs) were involved in 13,045 examinations (18.2 %), disorders of microcirculation in 2,219 examinations (3.1 %), diseases of the venous system in 47,574 examinations (66.4 %), impairments of the lymphatic system in 861 examinations (1.2 %) and other impairments of the circulation system were involved in 7,963 examinations (11.1 %). This represents probably the largest set of angiologic patients which has ever been analysed in the Slovak Republic. Arteriolosclerosis has occurred in 9,384 patients of this set (13.09 %). These data are stated on the base of funduscopy (ophthalmoscopy). However, the author has not performed this examination in all angiologic patients, just in those suffering from arterial hypertension or other risk factors of arterial diseases, as well as in patients with angio-organic ischemic syndromes (23—27).

Arteriolosclerosis is a separate nosologic unit of the group of organic stenotic (obliterating, obstructive, occlusive) diseases of the arterial system with the tendency of vascular wall sclerosis (2, 11, 12, 14, 21, 23, 24, 27, 33—35, 42, 45), briefly referred to as arteriosclerosis (Tab. 1).

Organic stenotic (obliterating, obstructive, occlusive) diseases of the arterial system have one common cardinal consequence — ischemia (2, 3, 11—14, 19—27, 33—37, 42). They represent the basic etiopathogenic condition of the development of angio-organic

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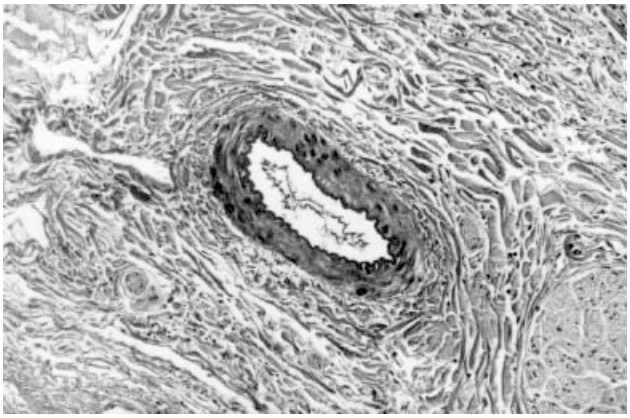

Fig. 1. Structure of normal arteriole. Wavy black line lining lumen is internal elastic lamina. Smooth muscle cells sorround the elastic lamina. H.E. x300.

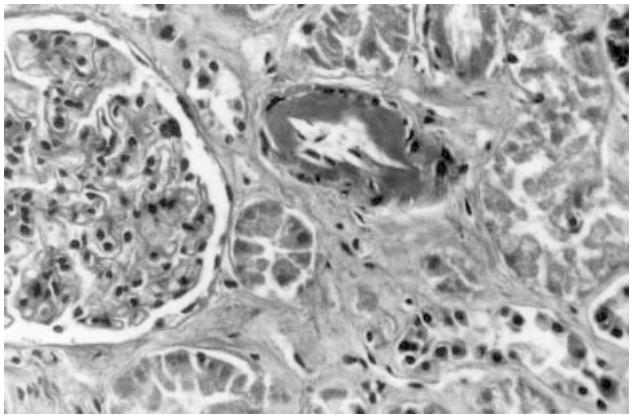

Fig. 2. Hyaline arteriolosclerosis of renal arteriole. Round dark mass to right of glomerulus. H.E. x400.

ischemic syndromes (angio-tissular ischemic syndromes) (Tab. 3). The most frequent current cause of these syndromes in the world is undoubtedly atherosclerosis, which, however, is not the only nosologic unit of diseases with the sclerotic tendency of arterial wall (reducing the elasticity, roughening and hardening the vascular wall) briefly referred to as arteriosclerosis (2, 14, 21, 23, 24, 33, 42). In addition to atherosclerosis, arteriosclerosis includes Mönckeberg's medial arteriosclerosis (Mönckeberg's sclerosis, mediocalcinosis), diabetic angiopathy (diabetic macroangiopathy and diabetic microangiopathy) and arteriolosclerosis (Tab. 1).

In addition to several nosologic units of arteriosclerosis, the angio-organic ischemic syndromes can be caused (Tab. 1) also by inflammatory diseases of the arterial system (arteritis, vasculitis, angiitis), external compression of artery (compressive syndromes) and other obliterating diseases of the arterial system (e.g. fibromuscular dysplasia of arteries, cystic degeneration of arterial adventitia, arterial thrombosis, arterial emboli, and other less frequent diseases and disorders) (23, 24, 37).

Hence, stenosis or even occlusion of vessels can generally result not only from an intramural cause (e.g. inflammation of arterial wall in vasculitis), but also from extramural causes (e.g. external compression of artery by means of any pathologic process), intraluminal causes (e.g. thrombus, embolus), most frequently though, from their combinations (23, 24, 33, 37).

The intima of arterioles in patients with arteriolosclerosis is afflicted by hyalinisation and hypertrophy of the media in the arteriolar part of the arterial system (the so-called benign arteriosclerosis). Some authors distinguish two subforms: 1) hyaline arteriolosclerosis — when hyalinisation of intima prevails, and 2) hyperplastic arteriolosclerosis — when hyperplasia and hypertrophy of media prevail (2, 21, 23, 24, 27, 33, 39, 45) (Fig. 1, 2).

In some patients with accelerated and malign hypertension, however, the affliction of arterioles is faster and more serious. This condition is histomorphologically characterised as fibrinoid necrosis (the so-called malign arteriolosclerosis, arteriolonecrosis) (2, 23, 24, 27, 33—35, 37, 42) (Fig. 3).

The acceleration of hypertension develops in coincidence with primary, as well as secondary arterial hypertension with long-term and insufficiently treated high diastolic blood pressure. Currently, due to the availability of modern antihypertensive drugs, this phenomenon is fortunately rare. The malign arteriolosclerosis (arteriolonecrosis) incurs failure of regional circulation of vitally important organs (malign revulsion of hypertension) (1, 2, 11, 20—29, 33—46).

Tab. 1. Main organic disorders and diseases of the arterial vascular system.

1. Non-obstructive (non-occlusive, non-obliterating) diseases
   a) Arterial aneurysm
   b) Arteriovenous fistula
2. Obstructive (stenotic, occlusive, obliterating) diseases
   a) Diseases with the tendency of arterial wall sclerosis
      – Atherosclerosis
      – Mönckeberg's medial arteriosclerosis (mediocalcinosis)
      – Arteriolosclerosis
      – Diabetic angiopathy
   b) Inflammatory diseases (arteritis, vasculitis, angiitis)
   c) Compressive syndromes of arteries
   d) Other obstructive diseases and disorders of arteries
      – Fibromuscular dysplasia of arteries
      – Cystic degeneration of arterial adventitia
      – Arterial thrombosis
      – Arterial emboli
      – Rare obstructive diseases and disorders of arteries

Tab. 2. Main signs of accelerated and malign arterial hypertension.

Diastolic blood pressure: usually over 140 mmHg	
Heart:	hypertensive cardiomyopathy, failure of the left heart
Brain:	hypertensive encephalopathy
Kidneys:	malign nephroarteriolosclerosis with renal insufficiency (with rapidly decreased glomerular filtration and the development of uraemia)
Eyes (funduscopy):	hypertensive angioretinoneuropathy (the oedema of the papilla)
Terminal state:	syndrome of disseminated intravascular coagulation (DIC)

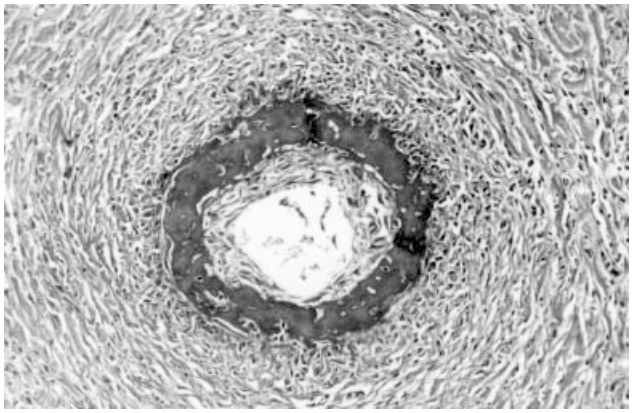

Fig. 3. Fibrinoid necrosis of arteriole in malignant hypertension. H.E. x300.

The main signs of accelerated and malign hypertension are given in Table 2. Its treatment requires to decrease urgently the blood pressure while monitoring the vital functions. The slower effort to bring down the blood pressure to normal values is to be put forth later (1—46).

Pathogenic coincidence of arteriolosclerosis with arterial hypertension is not unambiguously clear and concluded. Probably it is the consequence, and not the cause of hypertension. Similarly to atherosclerosis and other organic obliterating diseases of the arterial system, also in arteriolosclerosis, the stage of endothelial dysfunction takes place prior to the development of structural changes, the fact of which brings about an increased tendency to arteriolar spasms (arterioloconstrictions), thrombosis and other changes (1—46).

The clinical picture results from both the primary disease (arterial hypertension) and individual angio-organic ischemic syndromes (Tab. 3) based on arteriolosclerosis (1—46).

The term of *angio-cardial ischemic syndrome determined by arteriolosclerosis* is probably more known than the cardiologic syndrome X, angina pectoris with normal coronarogram, microvascular angina pectoris, small vessel disease, etc. These are archaic and inexact terms which have originated probably in result of poor knowledge. The term of arteriolosclerotic hypertensive cardiomyopathy is used also in coincidence with the concomitant cardiac decompensation with heart dilatation.

The clinical picture usually displays the signs of stable or unstable angina pectoris or even non-Q infarction, or a painless form of angio-cardial ischemic syndrome (Tab. 4). Coronarography, however, reveals normal findings in large arteries, but a "slow flow" in some areas of the vascular bed. The presence of the "small vessel disease of the heart" can be objectively proved by abnormal coronary reserve, e.g. by dipyridamole test, the proof of myocardial hypoperfusion. However, in addition to arteriolosclerosis, this picture can be caused by other vascular diseases of microcirculation, e.g. diabetic microangiopathy, vasculitis, thrombosis, etc. (Tab. 1), the fact of which can be definitely confirmed in vivo only by endomyocardial biopsy (5, 6, 7—10, 13—18, 22—35, 37—46).

The suspicion of ischemic disease of the heart determined by arteriolosclerosis (arteriolosclerotic cardiac ischemic syndrome, angio-cardial ischemic syndrome based on arteriolosclerosis) can be signalled by the absence of signs and symptoms of atherosclerosis, and vice-versa by the presence of arteriolosclerotic signs in other organs in patients with arterial hypertension without other risk factors of atherosclerosis and other vascular diseases (23, 24, 27).

The angio-cerebral ischemic syndrome based on arteriolosclerosis is unusually variable, clinically manifested mainly by the picture of progressive subcortical periventricular arteriolosclerotic encephalopathy (leuko-araiosis, Binswanger's disease) or by multifocal (multiinfarction) ischemia (24—41), which is determined also by the fact that arterioles are afflicted by microaneurysms (so-called Charcot-Bouchard aneurysms) representing the potential bleeding sites. Disseminated foci (partially isolated or conflu-

Tab. 3. The most frequent angio-organic (angio-tissular) ischemic syndromes and their synonyms.

1. Angio-cardial ischemic syndrome, vascular myocardial ischemic syndrome, coronary-cardial ischemic syndrome, etc.
   – Vascular ischemic disease of the heart
2. Angio-cerebral ischemic syndrome, carotico-cerebral ischemic syndrome, vertebrobasilar cerebral ischemic syndrome, etc.
   – Vascular ischemic disease of the brain
3. Angio-ischemic syndrome of extremities
   – Vascular ischemic disease of extremities,
4. Angio-renal ischemic syndrome
   – Vascular ischemic disease of the kidneys
5. Angio-ocular ischemic syndrome
   – Vascular ischemic disease of eyes
6. Angio-gastrointestinal ischemic syndrome, vasculo-mesenteric ischemic syndrome, etc.
   – Vascular ischemic disease of digestive organs
7. Angio-genital ischemic syndrome
   – Vascular ischemic disease of genitals (vasculogenic impotency and other diseases)

Tab. 4. Clinical forms and subforms of vascular ischemic disease of the heart (IHD).

Painful form	Painless form
Acute:	
	Asymptomatic
Unstable angina pectoris	
	Symptomatic
Acute infarction of the heart	(IHD with heart insufficiency)
Chronic:	Dysrhythmia (arrhythmia)
Stable angina pectoris	Mors subita
	(Sudden coronary death)
States subsequent to myocardial infarction	

ent) afflict mostly the basal ganglia and the periventricular white matter (corona radiata). From the histomorphological aspect, the arteriolosclerotic cerebral ischemic syndrome is involved, resulting in status lacunaris cerebri (23, 24, 33, 41, 42).

The clinical manifestation of angio-cerebral ischemic syndrome based on arteriolosclerosis is particularly represented by sings and symptoms of small pyramidal and extra-pyramidal lesions which partially withdraw, but reappear again ("minor strokes"), and those of diverse manifestations of angiogenic (vascular) dementia. CT (MR) examinations reveal acute ischemic lesions depicted by their transitory oedema. Older post-necrotic pseudocysts are depicted as a disseminated partially confluent hypodensity in the given brain area of "butterfly shape" (23, 24, 33—35, 41, 42).

The differential diagnosis has to exclude also the cerebral autosomal dominant (recessive) arteriopathy with subcortical infarctions and leukoencephalopathy (CADASIL, CARASIL) (23, 24, 41).

Hypertensive encephalopathy develops due to sudden or progressive elevation of blood pressure (diastolic blood pressure over 140 mmHg) with the origin of cerebromeningeal oedema (Tab. 2). The initial prodromal manifestations of hypertensive encephalopathy include cephalgia, nausea, vomiting, sight disorders, psychical changes. Tonic and clonic convulsions, and quantitative and qualitative disorders of consciousness can develop. The most severe complications are represented by intracerebral haemorrhage, sometimes in frame of disseminated intravascular coagulation (DIC) (1, 3, 23, 24, 36, 37, 44, 46).

The angio-ischemic syndrome of extremities based on arteriolosclerosis (arteriolosclerotic ischemic syndrome of extremities) is particularly manifested by trophic changes on the ventral side of the crus, most frequently on the interface of its middle and lower thirds. In the beginning, the changes are manifested as petechial bleeding foci and develop rapidly into very painful skin lesions (ulcers) achieving 2—4 cm in diameter (Martorell's syndrome) (23, 24, 36, 39).

The angio-renal ischemic syndrome based on arteriolosclerosis (arteriolosclerotic renal ischemic syndrome) is most frequently referred to as benign vascular nephrosclerosis (it would be more appropriate to refer to it at least as angionephrosclerosis, while nephroarteriolosclerosis is comprehensible). The main manifestations include proteinuria up to 2 g per 24 hours, the urine sediment displays normal findings. The values of glomerular filtration decrease, the fact of which coincides also with clinical manifestations of chronic renal insufficiency). The patients with accelerated (malign) hypertension, however, develop malign arteriolosclerosis with fibrinoid necrosis (arteriolonecrosis), most frequently referred to as malign vascular nephrosclerosis (malign nephroarteriolosclerosis or malign nephroarteriolonecrosis are more appropriate terms).

Urine contains large amount of proteins, the sediment contains a large number of casts and erythrocytes. The glomerular filtration quickly decreases and renal insufficiency deepens into the terminal uremic stage (1, 3, 23, 24, 33, 35, 37, 42).

The angio-ocular ischemic syndrome based on arteriolosclerosis (arteriolosclerotic ocular ischemic syndrome) can be precisely diagnosed by funduscopic examination. Therefore, it is necessary not only for ophthalmologists, but also for all internal physicians, and naturally, for angiologic specialists to be skilled in the latter examination. (23, 24, 27).

Regarding the recent WHO classification of arterial hypertension as from 1999 (46), various previous classifications of so-called "hypertensive changes" are losing their sense. Internal physicians specialised in angiology must be especially interested in funduscopic signs of the disease, initially detectable on vessels, later also on the retina, and eventually by changes in the optic disk (23, 24, 27).

Should the examined state involve changes situated only in vessels, it should be referred to as latent angio-ocular ischemic syndrome based on arteriolosclerosis ("hypertensive angiopathy"). In the beginning, the course of arterioles is normal, thereafter they become mildly curved and ultimately tortuous. During arteriolo-constrictions, the arteriolo-venular ratio changes to 1:3, the fact of which can be observed already in the initial stage of endothelial dysfunction. The development of structural changes in the walls of arterioles (endothelial hyalinosis and proliferation and hypertrophy of the media) cause that the A-V ratio changes to 1:2, sometimes to 1:1. At the beginning, the vascular lumen is only transitorily, reversibly irregular, later it becomes permanently, irreversibly irregular (rosary-shaped). The size of stenosis is usually evaluated by percentage. The angle of arteriolar branching increases, becoming obtuse, rectangular even acquiring the shape of the Greek letter omega ("omega sign"). In the beginning, the vascular reflexes are more marked, more accentuated and dominant, or even have the appearance of a silver wire (silver wire phenomenon). In the sites of arteriolo-venular crossing (A-V crossing) the transparency of the vascular wall of arterioles retreats, thus causing that the portion of venule beneath the arteriole in sites of A-V crossing stops being noticeable (Pines' sign). Later on, the so-called Gunn's sign appears (the venule before its crossing with the arteriole is widened and in the site of their crossing, it is "pushed down" and narrower. Thereafter its normal width is regained. In the beginning, the Gunn's signs can be noticed sporadically, later their number increases. Severe cases of arteriolosclerosis display the Salus' sign, where the venule is shifted from its original site, as if it was getting out of the way, and we see it as an arch or a saddle-shaped curve of venules beneath arterioles (Salus' phenomenon — I stage), or the venule "completely disappears" within the retinal tissue (Salus' phenomenon — II stage).

In addition to vascular changes, the manifesting angio-ocular syndrome based on arteriolosclerosis ("hypertensive angio-retinopathy") displays changes in the retina. Especially the area of the posterior pole exhibits small disseminated ischemic "cotton-wool" foci (microinfarctions) and solitary petechial bleedings. The progression of arteriolosclerosis accrues the number of ischemic "cotton wool" foci together with intraretinal haemorrhages which are either dot or flame-shaped, or flat, according to the particular layer of the retina they have originated in. The sites, where ischemic foci and haemorrhages have been resorbed, bear minor scars with pigment appearing in result of glial proliferations (severely reflecting foci). In the surrounding of macula, their aggregates form a picture resembling a star-shaped figure. Macula lutea is granulated and without reflection. The bleedings in cases of marked angio-ocular syndrome are necessary to be distinguished from those present in coincidence with other diseases.

Tab. 5. Main auxiliary instrumental non-invasive angiologic examination methods.

1. Phonoangiography
2. Claudication distance
3. Thermodiagnosis
   a) Thermometry
      – Acral transverse thermometry
      – Longitudinal thermometry
   b) Thermography
      – Thermovision
      – Fluid crystals
4. Oscillometry
5. Oscillography and sphygmography
6. Ultrasound examination of arteries and other vessels (Echovasculography):
   a) Imaging echovasculography (vascular imaging, vascular scan)
   b) Doppler echovasculography:
      – Continual wave (CW) Doppler technique
      – Pulse, impulse Doppler (PD) technique
      – Colour-coded Doppler-flow-imaging
7. Radioisotope method of the measurement of blood flow
8. Examination of the arterial part of microcirculation
9. Funduscopy
10. Haemorrheologic examinations
11. Transcutaneous monitoring of blood gases
12. Plethysmographic examination of vessels
    a) Simple plethysmography
    b) Plethysmography with venous occlusion, etc.

The complicated course of angio-ocular ischemic syndrome based on arteriolosclerosis ("hypertensive angio-retino-neuropathy") in coincidence with accelerated and malign arterial hypertension brings about vascular changes (malign arteriolosclerosis with fibrinoid necrosis and thrombotic occlusions — arteriolonecrosis), retinal changes, as well as the signs of ischemic oedema (ischemic neuropathy) of the optic disk, the fact of which is manifested by its inaccurate border, mild elevation (to +3D), greyish pink colour, or by minor haemorrhages (23, 24, 27).

It is necessary to remember that funduscopy enables to observe directly, simultaneously and in vivo practically all types of blood vessels: arteries, arterioles, pre-capillaries, capillaries, venules and veins. In this sense, funduscopy represents an irreplaceable ophthalmologic as well as angiologic non-invasive examination tool (23, 24, 27).

Diagnosis and differential diagnosis. Despite the fact that these particular and some further clinical forms (Tab. 3) are distinguished according to organ localisation, it is necessary to bear in mind that arteriolosclerosis is a generalised, systemic disease, and that the narrowing of arteriolar lumen or even its obliteration, result in ischemia and other structural and functional changes in practically all tissues and organs of organism. These can have an impact on the level of the systemic arterial blood pressure and in this way an unfavourable vicious circle can develop.

Funduscopy and some other angiologic examination methods of microcirculation (Tab. 5) play a crucial diagnostic role in clinical practice (23, 24, 27).

Arteriolosclerosis is a disease with the second highest mortality among vascular diseases, but we are witnessing the fact, that the physicians have insufficient knowledge of it. It is necessary to distinguish arteriolosclerosis particularly from all organic obliterating and non-obliterating diseases and functional diseases of the arterial system (Tab. 1) (23, 24).

Prevention and therapy. Arteriolosclerosis is a typical case of diseases of the arterial system, where the direct invasive angiologic or angiosurgical therapy cannot be considered (24). Basically, it involves non-medicamentous and medicamentous prevention and therapy of the arterial hypertension (1, 3, 4, 23, 24, 29, 34, 38, 44, 46), as well as complex angioprotective prevention and therapy (23, 24).

Currently, atherosclerosis is the most frequent disease causing angio-organic ischemic syndromes. However it is not the only nosologic unit, and in the clinical practice it is necessary to be aware that other organically determined diseases of the arterial vascular system can be involved, including arteriolosclerosis. Arteriolosclerosis is a generalised, systemic vascular disease, characterised by hyalinisation of the intima (hyalinosis) and proliferation and hypertrophy of the media of the arteriolar part of the arterial system (so-called benign arteriolosclerosis). The patients with accelerated and malign arterial hypertension develop fibrinoid necrosis (so-called malign arteriolosclerosis, arteriolonecrosis).

Arteriolosclerosis has, similarly to other stenotic (obliterating, obstructive, occlusive) diseases of the arterial system, one common consequence — ischemia. Angio-organic ischemic syndromes determined by arteriolosclerosis can have multiform structural and functional impacts, including fatal consequences.

The management of arteriolosclerosis and angio-organic ischemic syndromes based on arteriolosclerosis should be coordinated by internal physicians specialised in angiology who should be skilful in all angiologic diagnostic methods, including funduscopy (ophthalmoscopy) and basic angiologic therapeutic methods.

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