Coronarographic and Pathomorphological Characteristics of Unstable Atherosclerotic Plaques in Acute Coronary Syndromes

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The proximal segments of the main coronary vessels are the most often localization of "soft" unstable atherosclerotic plaques. The maximum number of plaques developed in the anterior descending branch of the left coronary artery. Pathognomonic relationship was found between the type of these plaques (with ulceration, rupture, thrombosis) and certain acute coronary syndrome. It was shown that the criteria of the plaque instability correlated with clinical manifestations of coronary syndromes. The bases and effects of "pathological" vascularization of unstable atherosclerotic plaques on the angioarchitectonics and hemodynamics of the heart were determined. Dissociation between myocardial vascularization degree and myocardial blood supply index was detected, which underlies the development of "unstable" myocardium in patients with acute coronary syndromes.

Key Words: *atherosclerotic plaques; acute coronary syndromes; coronarography; histopathology; morphometry*

Acute coronary syndromes (ACS) developing as a result of solitary manifestations of coronary atherosclerosis characterize unstable angina, myocardial infarction, and sudden cardiac death [5]. The pathogenetic basis of all ACS forms is a clear-cut morphological substratum: unstable atherosclerotic plaque (UAP). Due to fine fibrous cap and large lipid core, these UAPs (soft, yellow, vulnerable) are most often complicated by cracks, ulceration, ruptures with subsequent parietal or intramural thrombosis and development of the total spectrum of clinical manifestations of ACS. The notions of "unstable blood" (highly liable to clotting) and "unstable myocardium" (extremely liable to the development of fatal arrhythmias) are used in this context [1].

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We studied the incidence and location of different UAP types in three main coronary arteries (CA) and their effects on the volume and type of vascularization of the left cardiac ventricle and its relationship to the level of blood supply to the myocardium in ACS. The definition of criteria of atherosclerotic plaque instability and the characteristics of patho- and thanatogenesis of various ACS are interesting in this respect.

MATERIALS AND METHODS

The study was carried out on 240 hearts of subjects dead from ACS: unstable angina, myocardial infarction, and sudden cardiac death (80 per group). The main group consisted of 166 males and 74 females (mean age 52.6±0.4 years). A control observation, matched for age and sex, was selected for every other observation. The control group included 120 hearts of subjects dead from casual

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causes, without UAP and clinical manifestations of ACS.

The objective status of the coronary system was studied by postmortem polypositional coronarography in all cases [2]. Combined coronarographic and standard anatomic method proposed by WHO were used [3]. Each branch of the main CA (right, anterior interventricular, and circumflex branch of the left artery) was planimetrically divided into 4 segments with equal area of the intima surface and compared with the corresponding segments on coronarograms. This methodological approach ruled out the "unrecorded" coronary atherosclerosis and showed the location of each UAP in the vascular map of the heart.

The incidence and location of UAP in different ACS were studied in the segments of 3 main CA. The data were compared with the degree of vascularization (volume density of vessels) the left cardiac ventricular walls by the 3 studied main CA. Thanatological significance of changes in the angioarchitectonics of the hearts of dead subjects was evaluated by the myocardial blood supply index [3]. Micropreparation of UAPs and their detailed microscopic examination were carried out on isolated CA after their special dissection. The type of UAP was evaluated with consideration for the type of destruction of its fibrous cap (with ulceration, rupture, or thrombosis) and the status of the lipid core ("arm" or "isthmus") [5].

Transverse sections (5-7 μ) of the targeted segments of not dissected CA were stained (after fixation in formalin-calcium mixture and paraffin treatment) with hematoxylin and eosin, oil red O (for lipid detection), after Masson (for collagen), with picrofuchsin after van Gieson with poststaining of elastic fibers with Weigert's resorcin-fuchsin and after Coss (for detection of calcium incorporations). Pathomorphological criteria of instability of atherosclerotic plaques were compared with the clinical and paraclinical findings.

Quantitative data were statistically processed using Student's *t* test and alternative variations.

RESULTS

The incidence of UAP in different segments of the 3 main CA was in a certain pathognomonic relationship with ACS type (Table 1). The highest incidence of UAP was detected in segment 1 of the anterior interventricular CA branch in all ACS types predominating in patients with unstable angina. The percent of UAP typically decreased in the distal direction of this CA segments. Patients with myocardial infarction ranked second by the incidence of UAP, while in sudden cardiac death UAP were most rare. Study of the right CA revealed UAP only in segments 1 and 2 in patients with unstable angina and in 3 segments in sudden cardiac death. Similar location of UAP was recorded in 3 segments of the left circumflex CA branch. No UAP were detected in any of these CA segments in patients dead with myocardial infarction.

The mean values for 3 studied CA clearly indicate that UAP were located primarily in the proximal segments, while 4 distal segments remained intact. This was associated with clinical manifestation of ACS in the form of unstable angina and sudden cardiac death.

Analysis of the relationship between the incidence and location of "soft" UAP and signs of their destruction or instability (damaged cap of the plaques separating the atheroma core from its surface layers) included identification and characterization of the main types of destruction of the plaque cap (ulceration, rupture, and thrombosis) in the main CA in relation to the developing ACS. Pathognomonic relation between the UAP type and ACS was noted (Table 2). Study of the 3 main CA showed that UAP with ulceration were more incident than other destructions and constituted the pathogenetic base of unstable angina. Plaques with rupture of the cap underlying the ethiopathogenesis of sudden cardiac death, ranked second, while UAP with thrombosis were most rare and occurred mainly in myocardial infarction. The anterior interventricular left CA branch was the main location of all UAP types in ACS.

Hence, instability is the key factor in the relationships between the incidence, location, and types of UAP, on the one hand, and ACS, on the other. Importantly that the strength of "soft" UAP cap is determined by the presence of extracellular matrix proteins (particularly collagen), formed by smooth-muscle cells in the CA wall. Increased content of proteoglycan-associated lipids in the UAP "isthmus" or "arm" and active development of inflammatory process in the atheroma are also essential for the development of instability. This process is caused by interactions of inflammatory cells with endothelial and smooth-muscle cells in CA. Initiation of inflammation is largely caused by oxidation of LDL in UAP lipid core [11].

An extremely important factor promoting instability and determining its progress is the so-called "pathological" vascularization of UAP linked with the effects of various growth factors stimulating angiogenesis in a peculiar way [8]. Analysis of vascularization degree in functionally overloaded left ventricle showed the highest volume density of

TABLE 1. Incidence (%) and Location of UAP in CA Segments in Different Types of ACS

CA		ACS	Segment of artery			
			1	2	3	4
Right						
		Unstable angina	4.6	1.2	—	—
		Myocardial infarction	—	—	—	—
		Sudden cardiac death	4.2	1.4	1.2	—
Left	anterior interventricular branch					
		Unstable angina	18.2	10.4	4.6	1.2
		Myocardial infarction	10.2	4.4	2.2	—
		Sudden cardiac death	10.2	2.6	1.8	—
	circumflex branch	Unstable angina	8.4	2.6	1.2	—
		Myocardial infarction	—	—	—	—
		Sudden cardiac death	6.8	1.4	1.2	—
Summary values for 3 arteries		Unstable angina	10.4	4.7	1.9	0.4
		Myocardial infarction	3.4	1.5	0.7	—
		Sudden cardiac death	7.1	1.8	1.4	—

vessels in all its walls in cases with UAP location in the anterior interventricular branch of the left CA (Table 3). The plaques in this CA were detected in the maximum number of cases. The degree of left ventricular vascularization ranked second, if UAP were located in the circumflex branch of the left CA. The minimum vascularization of left ventricular walls corresponded to minimum incidence of UAP in the right CA. Hence, the degree of left ventricular wall vascularization decreased from the anterior wall to the cardiac apex and septum (in the presence of UAP located in all segments of the studied CA).

Serial analysis of polypositional coronarograms showed characteristic changes in the cardiac angioarchitectonics in subjects dead from various ACS in the presence of UAP in the main CA. Frequent presence of UAP in the anterior descending branch of the left CA led to pronounced restructuring of the left coronary basin with the formation of angiographic changes, close to the myocardiogram intensification or intense coronarogram symptom [3].

TABLE 2. Incidence (%) of UAP Types in Different ACS

CA		UAP	ACS		
			unstable angina	myocardial infarction	sudden cardiac death
Right		With ulceration	5.8	—	—
		With rupture	—	—	6.8
		With thrombosis	—	—	—
Left	anterior interventricular branch	With ulceration	34.4	—	—
		With rupture	—	—	14.6
		With thrombosis	—	16.8	—
	circumflex branch	With ulceration	12.2	—	—
		With rupture	—	—	9.4
		With thrombosis	—	—	—
Summary values for 3 arteries		With ulceration	17.4	—	—
		With rupture	—	—	10.3
		With thrombosis	—	5.6	—

TABLE 3. Incidence (%) of UAP in the Main CA, Degree of Vascularization (Volume Density of Vessels) of Cardiac Left Ventricle, and Myocardial Blood Supply Index in Patients Dead from ACS (*M*±*m*)

CA	UAP incidence	Volume density of vessels in left ventricular walls, %				Myocardial blood supply index, g/mm^2	
		anterior wall	posterior wall	lateral wall	apex and septum	main group	control group
Right	12.6	40.2±1.2	36.6±1.6	34.4±1.2	32.4±1.4	22.2	17.6
Left							
anterior interventricular branch	65.8	68.2±1.2	54.2±0.8	50.8±1.4	50.2±0.6	24.4	17.8
circumflex branch	21.6	42.4±1.2	38.8±1.4	36.8±1.2	36.2±1.6	23.2	18.0
Summary values for 3 arteries	100	150.8±1.2	129.6±1.3	121.4±1.3	119.4±1.2	—	—

Clearly seen uneven lumen of the descending branch of the left CA was combined with zones of small vascular networks, forming borderline "compensatory-reactive" fields. They were most pronounced mainly in the anterior wall of the cardiac left ventricle (Fig. 1, *a*).

The presence of numerous UAP in the circumflex branch of the left CA caused pathognomonic changes in the cardiac angioarchitectonics in subjects with uneven lumen of the main CA in the presence of pronounced myocardial hypervascularization and individual re-calibration of vessels of the left and right coronary basins. Small vascular "compensatory-reactive" fields in these cases were characterized by predominant location in the posterior and lateral walls of the left cardiac ventricle (Fig. 1, *b*).

The presence of UAP in the right CA promoted angiographic detection of uneven lumen and plaque foci in it. These changes were paralleled by adjacent zones of "vascular devastation" and pronounced small vascular hypervascularization of the left coronary basin regions (Fig. 2).

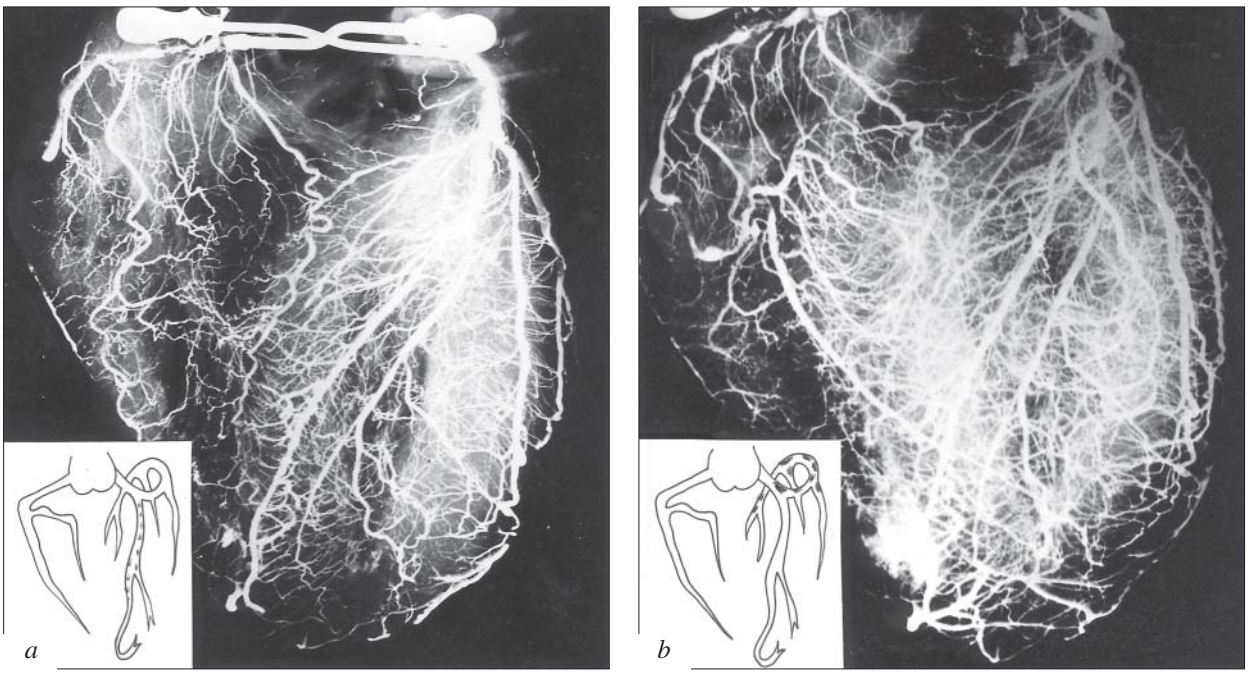

Fig. 1. Left CA. *a*) uneven lumen of left descending CA branch with intense coronarogram symptom in the left coronary basin and manifest small-vascular "compensatory-reactive" fields in the marginal zones in patient (male) K., 68 years; *b*) uneven lumen of circumflex left CA at an appreciable length in the presence of pronounced myocardial hypervascularization and individual re-calibration of left and right coronary vessels in patient (male) V., 58 years.

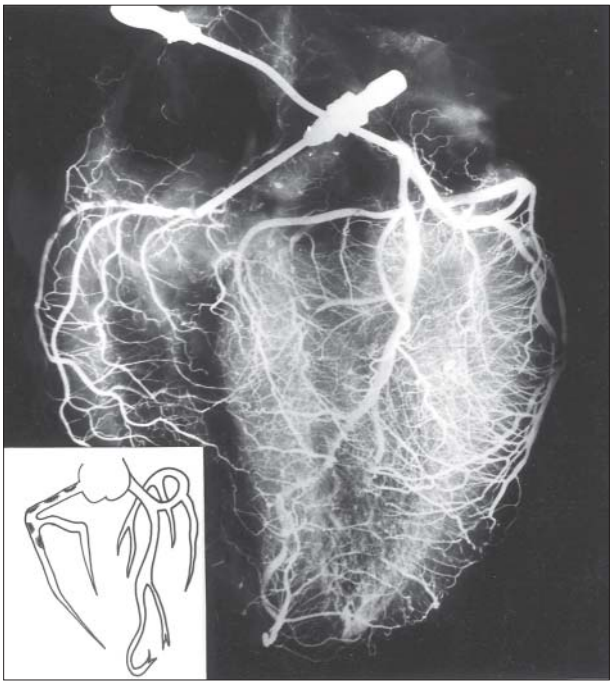

Fig. 2. Uneven lumen and focal plaques in the right CA, combined with the marginal "vascular devastation" zone and pronounced small-vascular hypervascularization in zones of the left coronary basin in patient (male) A., 52 years.

Characteristic histological and histochemical manifestations of UAP corresponded to the detected changes in the cardiac angioarchitectonics in subjects dead from ACS. Intact compact caps of UAP surrounding large atheromas were detected. The atheromas had an inflammatory necrotic foci in the center with pronounced inflammatory reaction in the isthmus (Fig. 3, *a*). Along with this, there were UAP with clearly seen detachment of the atheromatous substance core from the internal surface of the cap and formation of empty pouches (Fig. 3, *b*). In addition, there were UAP with sharp ulcerative necrotic degradation of atheromas and rupture of fibrous cap, with thrombotic substance by the inner surface of the cap and in pouches under the cap (Fig. 3, *c*). Pathohistological changes in UAP of the main CA corresponded to lipid and degenerative necrotic UAP in some cases in subjects dead from various ACS types [6].

The detected differences in the vascular map in subjects dead from ACS in the presence of UAP in the main CA presented as a combination of moderately pronounced obstructive syndrome with a complex of coronarographic manifestations (hypervascularization syndrome, individual re-calibration of coronary vessels, "vascular devastation" zones,

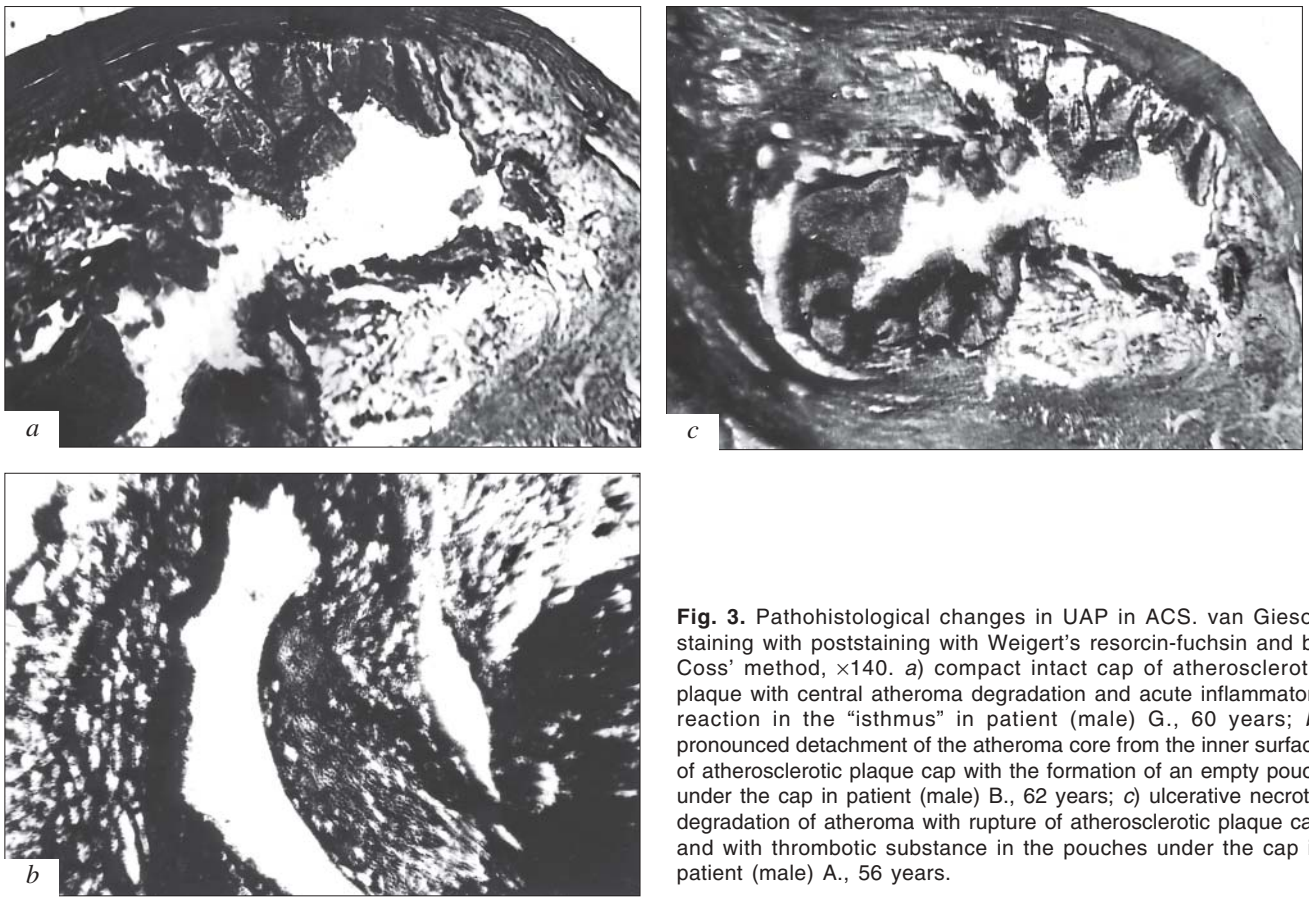

Fig. 3. Pathohistological changes in UAP in ACS. van Gieson staining with poststaining with Weigert's resorcin-fuchsin and by Coss' method, ×140. *a*) compact intact cap of atherosclerotic plaque with central atheroma degradation and acute inflammatory reaction in the "isthmus" in patient (male) G., 60 years; *b*) pronounced detachment of the atheroma core from the inner surface of atherosclerotic plaque cap with the formation of an empty pouch under the cap in patient (male) B., 62 years; *c*) ulcerative necrotic degradation of atheroma with rupture of atherosclerotic plaque cap and with thrombotic substance in the pouches under the cap in patient (male) A., 56 years.

small-vascular "compensatory-reactive" fields) of the intercoronary stealing syndrome. These changes related to a significant increase in vascularization volume in regions of individual segments of the main CA with UAP, favored the increase in leukocyte migration inside UAP. In turn, leukocytes releasing various inflammation mediators sharply stimulated the atherogenesis process and attracted stem cells of the bone marrow origin differentiating into endothelial cells and actively promoting angiogenesis [9,10].

The detected close relationship between the incidence of UAP in the main CA and degree (volume) of left-ventricular vascularization (Table 3) under conditions of increasing bloodflow velocity and pressure gradient was paralleled by the development of the Venturi's effect, promoting activation of coronary bloodflow [4]. However, the intercoronary stealing syndrome creating the situation of anatomical insufficiency of coronary circulation did not provide its functional adequacy in the presence of UAP in the main CA. This was objectively shown by myocardial circulation indexes, which evidenced higher than normal values of net weight of cardiac muscles per mm^2 of the involved CA lumen (Table 3). This integral parameter differed significantly in the studied subgroups. These data persuasively confirm the differences in the clinical picture of different ACS types and characterized in a way the main components of their ethio- and pathogenesis in connection with the development of the so-called "unstable myocardium" [7,12].

Hence, combined study of the clinical coronarographic and pathomorphological relationships between UAP and ACS revealed significant incidence and pathognomonic location of UAP in separate segments of the main CA. A relationship between the most grave UAP types with ACS forms was detected. Typical changes in the cardiac angioarchitectonics in subjects dead with "soft" UAP in the main CA were detected and the volume density of vessels in the wall of functionally overloaded left ventricle was evaluated. This latter value was in sharp dissociation with the myocardial blood supply index, forming the pathogenesis of "unstable myocardium". The data help to evaluate the criteria of atherosclerotic plaque instability by clinical coronarographic and pathomorphological data simultaneously and the main factors of ACS patho- and thanatogenesis.

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