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Parietal centripetal and centrifugal thickening neovascularization in the descending anterior coronary artery

Possible relations with the problem of collateral circulation

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Summary. Left coronary arteries of 30 human hearts, obtained at autopsy, were injected with contrast medium. A control group was formed from anterior descending coronary arteries free of atherosclerosis and a study group from anterior descending coronary arteries with areas of atherosclerotic injury. The following differences in the two groups were noted. The control group did not show successfully injected vessels in intima and media, while cases with atherosclerotic injury have them; the number of injected vessels in presence of atherosclerotic injury was three times greater than in healthy coronary arteries; there was a decreasing gradient from outside to in, in the number of injected vessels in both groups; and finally in atherosclerotic vessels we noted a lack of balance between parietal thickening and the residual lumen (conspicuous thickening was accompanied by a small reduction in the lumen). We interpret centrifugal thickening as a possible compensatory mechanism in the major branches for an inadequate canalization of vessel, and suggest possible formation of coronary collateral circulation from vasa vasorum by a process of neovascularization.

Key words: Coronary arteries – Coronary collateral circulation – Neovascularization – Intimal thickening – Vasa vasorum

Introduction

The idea of possible coronary parietal thickening with neovascularization originated from pioniering work by Winternitz et al. (1938). These authors demonstrated the presence of rich vascular channels surrounding and penetrating sclerotic lesions and suggested that these new vessels might play an important role as source of parietal haemorrhages and in the genesis of the late complications of atherosclerosis. Paterson (1936, 1938) studied the vascularization of the intima of coronary arteries and correlated it with intimal haemorrhage, atherosclerosis and coronary thrombosis, while Morgan (1956) observed neovascularization coming from intima into the deep portions of thrombi. Other authors, including Giampalmo and Antoci (1959), studied the occurrence, in vascularized atheromas, of haemorrhages responsible for acute stenosis by means of oedematous thickening and Barger et al. (1984) pointed out that in coronary arteries free of atherosclerosis, vasa vasorum were rarely seen, and, when present, were sparse and did not form a capillary plexus. In contrast, in areas with atherosclerotic injury, a dense plexus of microvessels was frequently observed, suggesting marked neovascularization. Such microvessels typically extended from the adventitia through the media and into the thickened intima.

Later Diaz-Flores and Dominguez (1985) showed penetration of vasa vasorum and formation of intra-arterial granulation tissue which produced myointimal thickening. Transitional forms between pericytes and myointimal cells were found, suggesting that intimal thickening comes from cells from the vasa vasorum, in particular from pericytes. Zamir and Silver (1985) obtained casts of the entire lumen of the coronary network: many casts showed inprints of atherosclerotic plaques, remnants of calcified masses, and fine vascular meshes near the lumen of the major coronary arteries. The authors asked four questions as about the role of the neovasculature in coronary artery disease: was the neovasculature present to an extent exceeding that of normal vasa vasorum; was it associated with the pathogenesis of atherosclero-

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Table 1. Control group, i.e., cases with anterior descending coronary arteries free of atherosclerosis

Sex	Age	Heart Weight (gr)	Injected vessels			
			INT	MED	ADV	PADV
m	22	380	0	0	2	3
m	75	600	0	0	0	14
m	39	480	0	0	8	7
m	23	360	0	0	1	1
m	23	370	0	0	0	1
m	23	400	0	0	0	4
m	46	440	0	0	0	4
f	58	540	0	0	0	7
m	34	480	0	0	0	3
Mean	38	450	0	0	1	5
min	22	360	0	0	0	1
max	75	600	0	0	8	14

sis; was it associated with intramural hemorrhage; and were neovascular beds associated with vascular spasm.

In this study we have addressed these questions and the possible relations between vasa vasorum and the problem of collateral circulation.

Materials and methods

The material used for this study came from the Pathological Anatomy and Histopathology Institute of S. Maria della Misericordia Hospital (Udine, Italy).

Thirty human hearts were obtained at autopsy from two groups of subjects: a control group with anterior descending coronary arteries free of atherosclerosis (on a histological basis); and a study group with anterior descending coronary arteries presenting areas with atherosclerotic injury, as evidenced by intimal thickening or frank calcification.

The control group included 9 cases, 8 male and 1 female ranging in age from 22 to 75 years (mean 38); heart weight ranging from 360 to 600 g (mean 450) (Table 1). The study group included 21 cases, 17 male and 4 female ranging in age from 43 to 78 years (mean 65); heart weight ranging from 320 to 780 g (mean 485) (Table 2).

The standard method for each heart (modified from Silver et al. 1980 and from National Researche Council 1980) was the following: after removing the heart from body it was weighed, x-rayed in the antero posterior position and subjected to postmortem angiography by injection, through cannulas placed in the left coronary ostia, a radiopaque medium (barium sulfate and gelatine [3:1] with addition of crome yellow dye). The heart was then fixed for at least 15 days in 10% buffered formalin solution.

The anterior descending coronary artery was removed from the heart and cut trasversly into 1-cm thick slices. The heart was cut into 2-cm thick slices parallel to the posterior atrioventricular groove, proceeding from the apex to the base.

Histological sections, prepared from the anterior descending coronary arteries and a selection from heart slices of various sites (left ventricle: anterior, middle and posterior wall; right ventricle: anterior and posterior halves) were stained with haematoxylin and eosin, van Gieson and Weigert (for elastic fibers). We studied the following variables on anterior descending coronary arteries:

Table 2. Group at study, i.e., cases with anterior descending coronary arteries presenting areas with atherosclerotic injury

Sex	Age	Heart weight (gr)	Injected vessels			
			INT	MED	ADV	PADV
m	78	440	0	0	5	11
f	54	320	0	2	4	15
m	71	480	1	0	7	26
m	56	400	0	0	2	13
m	56	465	3	0	5	10
m	68	575	0	1	3	15
f	62	760	0	0	6	27
f	53	400	1	0	2	10
m	76	560	0	0	12	13
m	70	460	0	1	2	18
m	43	480	0	0	2	15
m	56	540	14	0	6	13
m	78	450	0	0	4	18
m	62	370	3	0	11	34
m	68	440	4	1	2	11
m	56	780	0	0	4	5
f	76	440	0	0	3	12
m	64	340	1	0	5	11
m	74	420	3	4	2	9
m	66	600	0	1	1	8
m	77	450	0*	0*	0*	0*
Mean	65	484	1,5	0,5	4	14
min	43	320	0	0	0	0
max	78	780	14	4	12	34

* injection of contrast medium unsuccessful

Real luminal area (RLA) – the area of the lumen directly measured on cross sections of the vessel, using millimetered paper.

Parietal Thickening (PT) – the area inside media minus the real luminal area.

Number of vessels injected by contrast medium, as evidenced on histological slides, in: intima (INT); media (MED); adventitia (ADV); periadventitia (PADV).

Results

The study group was divided in two subgroups in considering the results. Group 2A was a subgroup inclusive of the sections free of atherosclerotic injury; Group 2B was a subgroup inclusive of the sections presenting areas with atherosclerotic injury.

The control group (9 cases), composed of 136 coronary cross sections, had 55 injected vessels, 44 in the periadventitia (80%) and 11 in adventitia (20%); no vessels were present in the media and the intima (Fig. 1). The average anterior descending coronary artery in the control group therefore possesses 6 injected vessels, 5 in periadventitia and 1 in adventitia.

The study group (21 cases), composed of 285 coronary cross sections, had 422 injected ves-

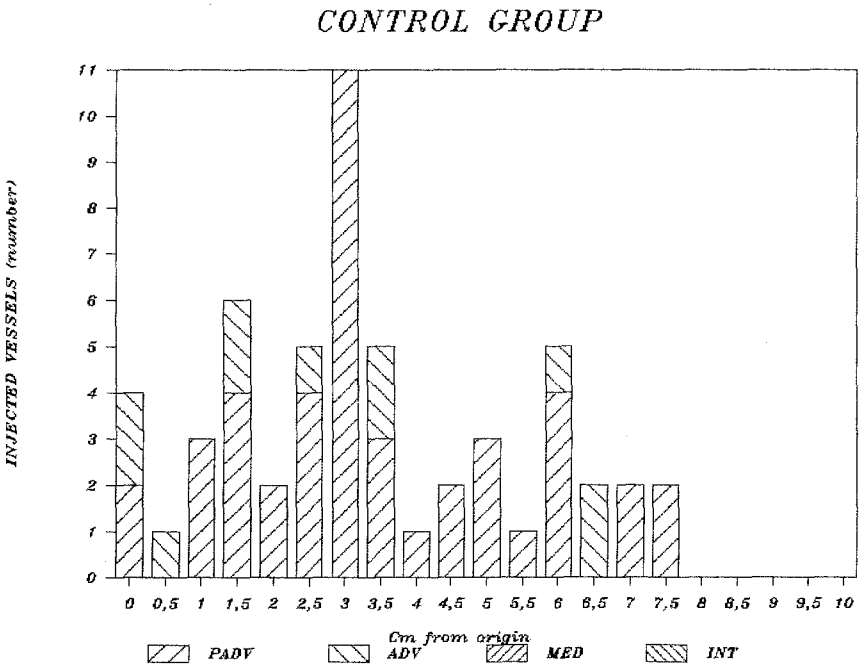

Fig. 1. Distribution of injected vessels along anterior descending coronary artery in control group. There are no injected vessels in intima and media; injected vessels are present in adventitia and periadventitia

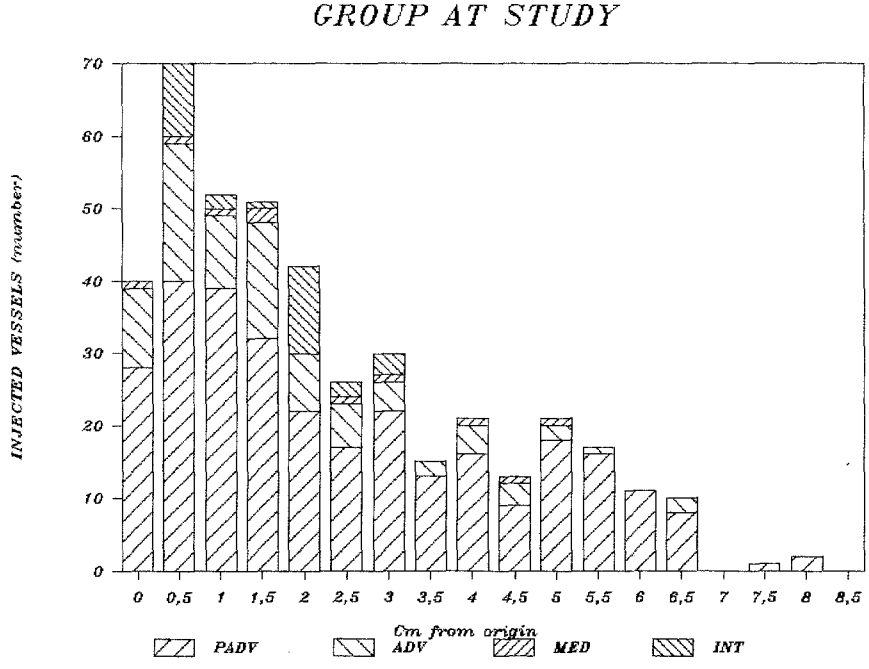

Fig. 2. Distribution of injected vessels along anterior descending coronary artery in the group at study. Injected vessels are present in the periadventitia and adventitia, but also in intima and media

sels; 294 were in the periadventitia (70%), 88 in the adventitia (21%), 10 in the media (2%) and 30 in the intima (7%) (Fig. 2). The average anterior descending coronary artery in this group therefore possesses 20 injected vessels, 14 in periadventitia, 4 in adventitia, 0.5 in media and 1.5 in intima.

We observed a quantitative difference in the two groups in periadventitia (14 injected vessels in the study group and 4 in the control group) and in adventitia (4 injected vessels in the study group agaist 1 in the control group); and a qualitative difference in media and intima (control anterior descending coronary arteries have no injected vessels while study cases have them).

The number of injected vessels was three times greater in presence of atherosclerotic injury than in its absence. The subgroup which included the sections of anterior descending coronary arteries free of atherosclerosis, composed of 133 coronary cross sections (mainly from the distal sections of

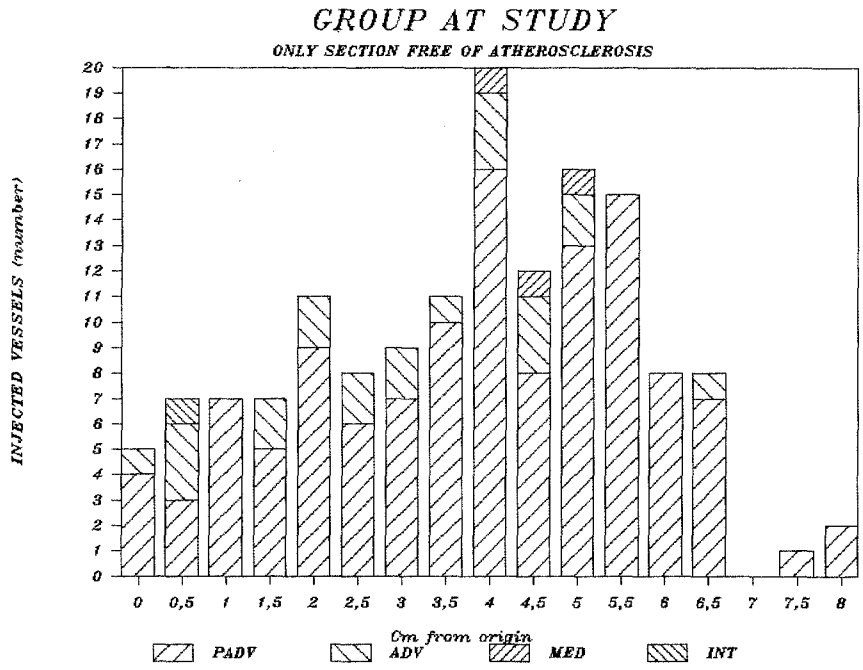

Fig. 3. Distribution of injected vessels along the anterior descending coronary artery in the subgroup inclusive of the sections without atherosclerotic injury of atherosclerotic vessels

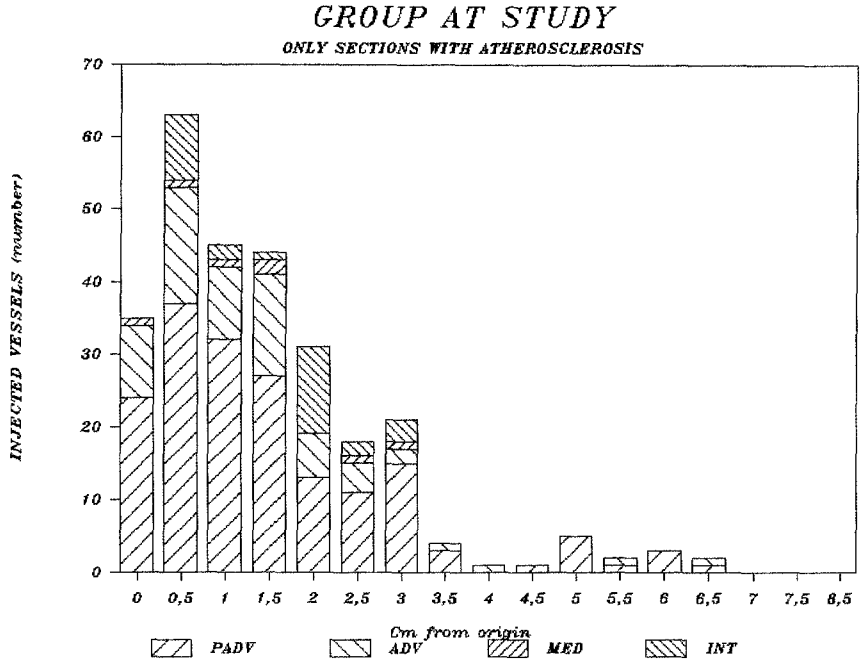

Fig. 4. Distribution of injected vessels along anterior descending coronary artery in the subgroup inclusive of the sections with atherosclerotic injury of atherosclerotic vessels

the vessel) had 147 injected vessels (35%), 121 in the periadventitia (82.3%), 22 (15%) in the adventitia, 3 (2%) in the media and 1 (0.7%) in the intima (Fig. 3).

A hypothetical average anterior coronary artery, formed only by sections free of atherosclerosis, should possess 12 injected vessels, 9 in the periadventitia, 2.5 in the adventitia, 0.4 in the media and 0.1 in the intima; values twice those of control group. The subgroup including sections of anterior descending coronary arteries presenting areas with atherosclerotic injury, composed of 152 coronary cross sections (prevailing in proximal sections of vessel), had 275 injected vessels (65%), 173 (63%) in the periadventitia, 66 (24%) in the adventitia, 7 (2.5%) in the media and 29 (10.5%) in the intima (Fig. 4).

A hypothetical median anterior coronary artery formed only by sections of the vessel with atherosclerotic injury should possess 26 injected

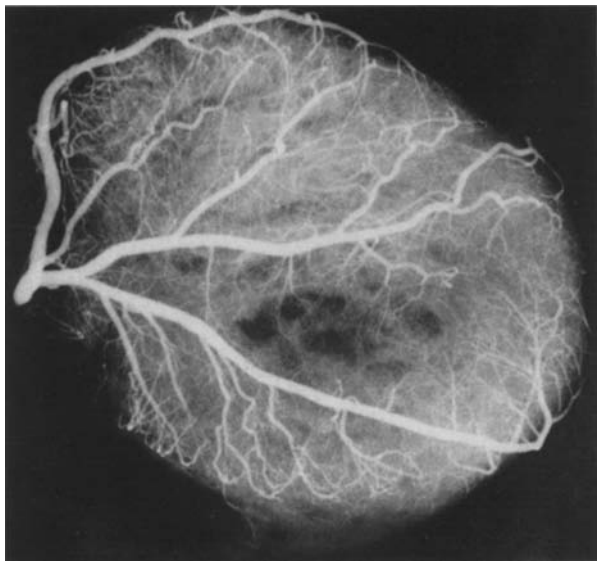

Fig. 5. Post mortem coronary angiography of left coronary branches. Contrast medium has reached distal vessels

vessels, 16.6 in periadventitia, 6 in adventitia, 0.6 in media and 2.8 in intima, values more than four times greater than those of control group.

These data suggest a clear global increase of injected vessels during formation of parietal thickening, most marked in atherosclerotic sections of the vessel but also significant in sections free of atherosclerosis.

In every group or subgroup we noted a decreasing gradient from outside to in, in the number of injected vessels. We also noted the presence of non injected vessels in the wall of arteries, abundant in the periadventitia and decreasing in the adventitia. They were present only sporadically in the media and the intima. An explanation of this fact could be vessels which are not in connection with left coronary artery, but in comunication with the right, or by mediastinal vascularization. We did not expect a lack of filling, because the contrast medium we used had a low enough viscosity to arrive in distal vessels, as resulted from postmortem angiographies (Fig. 5) and histological slides (Fig. 6).

The myocardium in the control group did not show alterations. In cases with coronary atherosclerosis it showed fibrous tissue ranging from minimal to extensive.

We also measured real luminal area and parietal thickening (Fig. 7). Histologically, parietal thickening was seen to be due to intimal thickening.

Discussion

At birth our arteries have almost no intima, the endothelial cells rest immediately on the elastica interna. Intima development begins in the first year and goes on for the rest of our life, a development linked to intraluminal pressure. Atherosclerosis can develop only in arteries having an intima. We investigated the size of anterior descending coronary artery determining the real luminal area and the extent of parietal thickening in diseased vessels. Like Hort et al. (1982) we noted that on the average the diameters of anterior descending coronary arteries were smaller than that of control group.

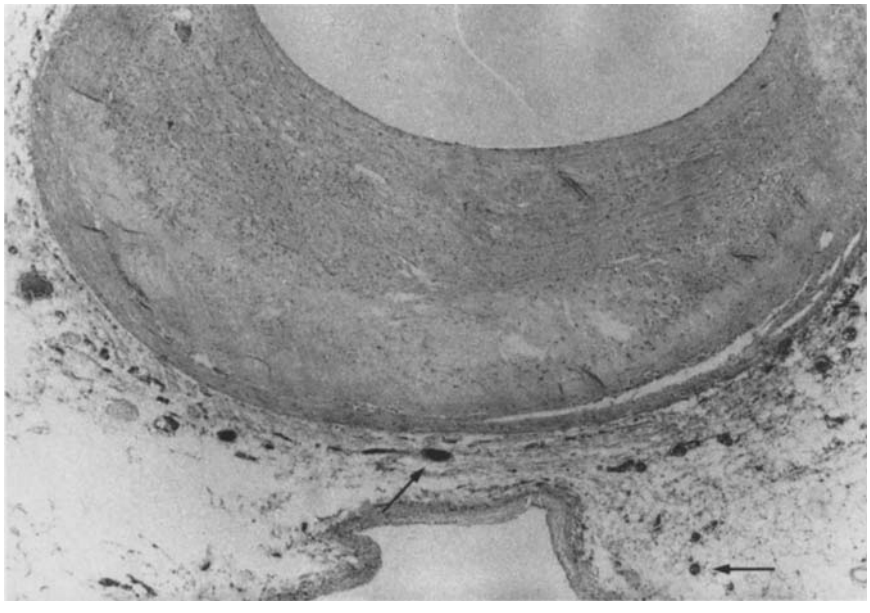

Fig. 6. Transverse section of anterior descending coronary artery. Injected vessels are seen in the adventitia and in periadventitial tissue (*arrows*). [Haematoxylin and eosin (× 200)]

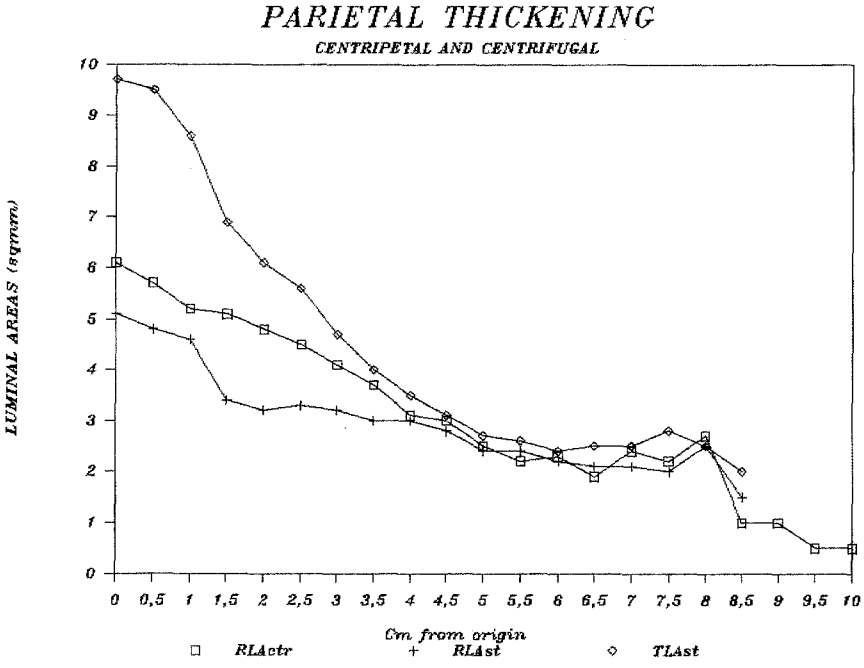

Fig. 7. Misures of real luminal area and parietal thickening along anterior descending coronary artery. RLActr: real luminal areas of control group; RLAst: real luminal area of group at study; TLAst: "theoretical luminal area" of group at study. On x-axis are indicated distances from the beginning of anterior descending coronary artery; luminal areas are expressed on y-axis. The intermediate curve represents the variation of luminal areas along descending anterior coronary artery in control group; we consider it as the criterion of normality (in addition we made the simplification of regarding zero parietal thickening because it was beyond our measurement technique); the lower curve represents atherosclerotic group real luminal areas; the higher curve represents atherosclerotic group parietal thickening. It is evident an overlapping of curves after 4 cm, where parietal thickening is rare

There was a lack of balance between the extent of parietal thickening and the residual lumen: conspicuous parietal thickening was accompanied by small luminal reductions in comparison with the sections free of atherosclerosis, suggesting the presence of compensatory mechanisms.

We therefore divided parietal thickening into centripetal thickening, directed internally, with reduction of the lumen, and centrifugal thickening, directed outwards, without any reduction in the lumen (probably with a compensatory function).

We also used the term "theoretical luminal area" in order to point out the area of the lumen inside the media in atherosclerotic vessels (showing intimal thickening) without regard to the intimal thickening.

Prominent coronary collateral circulation persists during fetal life, regressing after birth and becoming again prominent with aging (Boucek et al. 1984). The collateral communications are markedly increased in pathological conditions and can be interpreted as the result of an hypertrophic evolution of the collateral vessels, existing in every normal heart (Baroldi and Scomazzoni 1956). Tangential wall stress acts as a molding force in the development of collateral vessels (Schaper 1967).

Our study shows that normal hearts have few injected vessels, limited to external layers: as parietal thickening is increasing injected vessels increase first in the periadventitia and adventitia and then also penetrate into the media and intima. We think this fact may denote an active process of neovascularization.

The dynamics of this rearrangement should be interpreted as being directed toward an optimal perfusion of the thickened intima. We believe that penetration of vessels, mentioned above, could reach the lumen. In this way, the possibility of the formation of a new type of collateral vessel is based upon a process of neovascularization: the traditional model contemplates only a structural rearrangement of preexisting vessels.

The opening of these microvessels into the lumen of the main artery might occur in the following ways: one or more outlets could occur beyond the parietal thickening. In this case the blood flowing in microvessels should reach the main artery; or one or more outlets could occur before the parietal thickening. In this case an inversion of blood flow could be directed to other main coronary branches; finally outlets could occur beyond and before the parietal thickening. In this case collateral circulation may bypass parietal thickening.

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