

## STUDIES OF CORONARY ARTERIES IN CHILDREN—THEIR RELEVANCE TO CORONARY HEART DISEASE

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Coronary heart disease has reached enormous proportions, striking more and more young individuals. One had to assume that in looking for etiological factors one must start at very early ages, into the infancy period and even into fetal life.

Our studies of the histology of coronary arteries were developed in two directions: one—with respect to the relevance to coronary heart disease; and two—to learn how the structural changes in the coronary arteries develop in congenital heart disease, especially in those lesions where the coronary arteries are in the area of high blood pressure, again because of its possible implications with regard to relevance to development of atherosclerosis.

We have also placed special emphasis in our studies on the difference in structural changes of coronary arteries in different ethnic groups.

First with your permission, I would like to review our present state of knowledge about the structure of coronary arteries in the normal child.

From the investigations performed up to the present, we have learned to recognize the histological changes which appear in the coronary arteries during the different stages of development in fetal life as well as after birth.

In fetuses the intima is not developed and consists of a very thin layer of endothelial cells. Immediately beneath it lies the internal elastic membrane (*lamina elastica interna*), which separates the intima from the media. The internal elastic membrane is always found as a prominent band of homogeneous material and is essentially a continuous tube with longitudinal corrugations. The media consists of delicate smooth muscle cells with occasional fine elastic fibrils. The adventitia is a defined layer of collagenous connective tissue and some elastic fibers.

The first visible changes are seen a few days after birth and are localized in the internal elastic membrane, in the form of splitting or fragmentation. In the region of the splitting of the elastic membrane, fibroblasts proliferate.

In the first postnatal month the splitting of the elastic membrane becomes more prominent and the adjacent smooth muscle cells of the media lose their shape and position and show degenerative changes.

Between the fibers of the split internal elastic membrane, smooth muscle cells begin to appear, tending to run in a longitudinal direction. In some instances, proliferation and thickening of the intimal layer are present with an increase of mucopolysaccharides under the endothelium.

The number of smooth muscle cells between the elements originating from the splitting of the internal elastic membrane increases and, in addition, fragmented elastic fibrils begin to appear among the ingrowing muscle fibers. As a result of these changes, a new layer, the musculoelastic layer, is formed between the obvious intima and media.

The new layer shows variations in distribution. In some subjects it may have formed a complete circumferential layer at six months of age; in others of the same age, the layer may be found only in localized areas.

We found, as did others, that the intimal changes are of varying intensity, tending to increase with advancing age. In the first month, they consist of intimal cushions composed of fibroblasts and several layers

of fine elastic fibers, occupying not more than half of the arterial circumference. These cushions, when more diffuse, constitute the so-called fibroelastic layer in which droplets of acid mucopolysaccharides are also found.

By the age of six months the intimal thickening is more diffuse. At a more advanced stage, by the end of the first year, marked intimal and medial changes lead to an asymmetrical or diffuse thickening of the arterial wall. Beneath the intima, which is rich in collagen and elastic fibers, there is a thick musculoelastic layer which may in some instances occupy the whole of the media, leaving only two to three rows of stretched muscle cells at the periphery. At this time, the media contains more numerous connective tissue bundles and elastic fibers. In the adventitia, elastic fibers increase in number and density adjacent to the media and form the external elastic membrane.

Are the changes that occur in the coronary arteries during early months of life pathologic or merely normal features of the arterial wall at that period in life?

These morphologic alterations apparently result from many endogenous (sex or inheritance) and exogenous factors. It is assumed that the most important factors affecting the structure are mechanical and/or metabolic in the subject as a whole, as well as localized in the tissues of the coronary arterial wall itself. Some investigators believe that the earliest demonstrable alterations (the splitting of the internal elastic membrane and associated proliferation of cells) represent reaction of the vessel to an injury and should be interpreted as a response to the hemodynamic stresses of the early postnatal state. Others believe that the intimal thickening in infants and children is not to be interpreted as a natural developmental phenomenon, but rather as an abnormal process and a forerunner of the atherosclerotic process. Such authors call the early intimal changes "pre-atheroma."

Nevertheless, the dividing line between the normal and abnormal defies exact definition. In the zone of "abnormality", changes in the coronary arteries that are characterized by plaque-like thickening of the intima are generally classified as atheromas and the process, as atherosclerosis.

As is commonly appreciated, atheromas occur focally along the length of the involved artery. Segments of normal artery may often be present between segments of disease, the latter often severely obstructive. The focal nature of atherosclerosis is also emphasized by the histologic appearance of involved segments. Thus one arc of the artery may very commonly be uninvolved, while the remainder contains an atheroma. The result of focal distribution is that the narrow lumen is eccentric, lying near the uninvolved arc.

Some investigators have found a greater degree of intimal thickening in the male newborn. We could confirm this finding. Others feel, however, that this difference is not significant.

In order to assist in pinpointing the etiology of atherosclerosis, the chief point of reference in many studies has been to determine whether the differences found in the degree of atherosclerotic changes in the coronary arteries were due to ethnic or environmental factors or to the interaction of both.

The predominance of intimal development seen in early life in the male Ashkenazy group in Israel as we have shown in a study with Vlodaver, is similar to that found among American children by Dock and among European children by Schornagel, and is consistent with the well known sex differences in the severity of coronary arteriosclerosis. In the populations

of Oslo, Norway and New Orleans in the United States, advanced atherosclerotic lesions were found to be less extensive in the young female than in the young male. The lack of sex differences in the intimal development in the Yemenite and Bedouin groups in Israel is similar to the findings in other ethnic groups such as Nigerian children who also have a low incidence of coronary heart disease.

Differences in the quantity and intensity of the intimal changes between the sexes and among various ethnic groups are found even in early life. These differences are apparent soon after birth, but are more obvious at the end of the first year of life.

According to our quantitative histological studies, ethnic differences showed up at much earlier ages. Histological examination of 211 consecutive hearts from fetuses and children up to ten years of age was carried out in three different ethnic groups: Ashkenazy Jews, Yemenite Jews and Bedouins. Calculations of the ratio of intimal plus musculoelastic tissue area to total area per individual were based on weighted average of the three arteries measured. The Ashkenazy males were found to have more intima and musculoelastic tissue than the Bedouin or Yemenite males. This was not true of the females. Ashkenazy males also clearly had more intima and musculoelastic tissue than females of this group. No differences were found between the right and left coronary arteries in any of the ethnic groups.

Changes in the internal elastic membrane and the elastic fibers of the intima are less apparent in the Bedouin group than in the Ashkenazy and Yemenite Jews. In the Bedouins, in the one to ten year age group and particularly in the females, an intact internal elastic membrane was a common finding and elastic fiber changes in the intima were moderate. In the Bedouins it appears that the initial elastic changes do not become more pronounced with age, as they do in other ethnic groups. The intima of the Ashkenazy males develops in an eccentric form and has a richer collagenous tissue component than that of the children in the Yemenite and Bedouin groups.

These differences in the findings between sexes and ethnic groups in children up to ten years of age are consistent with the known differences in the prevalence of coronary arteriosclerosis and atherosclerosis, coronary heart disease and myocardial infarction in the corresponding adult populations. Thus there is a significant difference in prevalence and severity of arteriosclerosis in the Ashkenazy compared with the non-Ashkenazy ethnic groups above the age of 40.

A long-term epidemiological study of ischemic heart disease in Israel—an analysis of the adjusted rates for the diagnostic categories of angina pectoris and history of heart attack by areas of birth—shows that the central and east European (Ashkenazy) Jews have the highest rate of the disease, Jews born in the Middle East, including Yemen and North Africa, have the lowest rates, whereas the Jews born in southeast Europe and Israel form an intermediate group.

Other studies in Israel indicate higher rates of myocardial infarction in males of European (Ashke-

nazy) origin compared with those from Asia and Africa. Higher rates in males than in females have also been found in the European born, but not in those born in Asia. Myocardial infarction is particularly rare among the Bedouins.

Groom compared the degree of intimal thickening of the coronary arteries in Haitian and American Negroes of both sexes, up to the age of ten years.

The results showed that the American Negroes have more developed and thickened intima than do the Haitian Negroes. The dissimilarities observed in the coronary vessels of Negro children were predominantly variations in the degree of progression of the basic process. These differences between children of the same ethnic groups living in two different countries parallel apparently the differences in the incidence of coronary atherosclerosis and coronary heart disease found in the corresponding adult Negro groups.

It seems appropriate to assume that an intrinsic factor, probably inherited, determines the maturity stages of the intimal cell component and collagen synthesis. This would explain the sex differences in collagen tissue formation seen in the coronary arteries of male and female children in the European, the Asian and the American groups.

Severe intimal change in the coronary arteries in children and severe coronary atherosclerosis in young adults were found in certain congenital heart anomalies in which hypertension in the coronary vessels had developed. In these cases the media of the coronary arteries was thickened and elastic changes were evident. These changes have been attributed to coronary hypertension, and similar changes have been reported in other anomalies giving rise to coronary hypertension, for example, supra-avalvular aortic stenosis with hypoplasia of the ascending aorta.

We have studied the coronary arteries in fifteen cases of coarctation of the aorta which have been correlated with the hemodynamics of this malformation. Marked intimal changes were present in the form of degenerative and proliferative changes of the elastic fibers and an excess of collagen tissue. In young men with this malformation, atherosclerotic lesions were also conspicuous. The media was remarkably thickened with rich elastic fibers interspersed between muscle bundles. The media often constituted the most prominent of the layers, in contrast to normal subjects of the same age group. The prominent thickening of the media was also present in the intramural coronary arteries and even in the arterioles accompanying the main coronary artery.

These coronary changes are different from those observed in young individuals (adolescents) with systemic hypertension. With longstanding nephrosis and hypertension, the coronary arteries show extensive atheromatous sclerosis as in adult atherosclerosis, with medial disorganization and calcification of the intima. With coarctation of the aorta the coronary capacity is larger than normal and this is confirmed by the measurements of the external diameter, the total area, and the lumen area, all of which are larger than those in the control group.