Virchows Arch [Pathol Anat] (1982) 397:37–59

Virchows Archiv A

The Size of Human Coronary Arteries Depending on the Physiological and Pathological Growth of the Heart the Age, the Size of the Supplying Areas and the Degree of Coronary Sclerosis

A Postmortem Study

W. Hort[1], H. Lichti, H. Kalbfleisch[2], F. Köhler[2], H. Frenzel[1] and U. Milzner-Schwarz[2]

[1] Pathologisches Institut der Universität Düsseldorf, Moorenstraße 5, D-4000 Düsseldorf 1
[2] Pathologisches Institut der Universität Marburg, D-3550 Marburg/Lahn, Federal Republic of Germany

Summary. In 300 human hearts of all age groups (pre-natal to senescence) postmortem angiographs were performed under a pressure of 100 mmHg. The largest diameters of the three coronary arteries (i.e. the right coronary artery, the left descending and the left circumflex branch) were determined.

In our material we did not find ectatic coronary arteries in old age in the absence of atherosclerosis. We suggest that as a rule the larger diameters of the dissected coronary arteries in older hearts may be a postmortem phenomenon, due to the decreased elasticity of the vascular walls, which manifests itself as a progressive loss of retraction.

In female hearts the cross-sectional areas of the coronary arteries were a little smaller than in male hearts of same age groups (statistically not significant). In postmortem hearts of normal weights the diameters of the coronary arteries exceeded intravital measurements of other authors by nearly 15%, but there is good correlation between our postmortem findings and intravital measurements after application of nitroglycerin. It seems that the postmortem diameters of coronary arteries after filling under physiological pressure correspond with the maximal intravital diameters.

In our material we found that even in hearts beyond the critical weight coronary arteries are able to grow. Because of the limited number of hearts with an excessive weight and healthy coronary arteries we cannot decide whether under pathological conditions the growth of the coronary arteries corresponds harmonically with the growth of the myocardium.

There were large variations in coronary artery diameters during the physiological and pathological growth of the heart. If only the sum of the right coronary artery and the common stem of the left main coronary artery were considered the variations were smaller.

Supported by the Deutsche Forschungsgemeinschaft (Ho282/8)

Send offprint requests to: W. Hort at the above address

0340-1227/82/0397/0037/$04.60

On the average the largest diameters of coronary arteries with atherosclerosis were smaller than the diameters of healthy coronary arteries. We found a good correlation between the thickening of the intima of sclerotic vessels and the decrease in their diameters. Therefore we cannot support the view that coronary arteries of hearts with infarctions are smaller before the onset of atherosclerotic lesions.

Furthermore we compared the cross-sectional areas of the coronary arteries with their supplying areas. We found the best correlation for the right coronary artery.

During late fetal development and childhood there was a nearly linear correlation between the increase in the sum of cross-sectional areas of the three coronary arteries and the weight of the heart. During later physiological and pathological growth of the hearts there was a progressively slower increase of the cross-sectional areas. These differences were not present when the diameter of the healthy coronary arteries was compared with the "diameter of the ventricular muscle mass" (calculated as the cube root of the weight of the ventricular part = WVP). The closest correlation of all was found between these two linear parameters.

Key words: Coronary arteries – Coronary sclerosis – Size of coronary arteries – Growth of coronary arteries

Many studies reporting the morphological and histochemical description of normal and pathological coronary arteries exist, but there is little work on the *growth of coronary arteries* in health and disease. Systematic research into the growth of the coronary arteries from birth to early adult life has not been done. Neufeld et al. (1962) limit themselves to describing the progressive increase in the outer diameter of coronaries in the postnatal state and Vogelberg (1957) mentioned in his work only with a single sentence the increase in diameter of the coronary orifices up to the age of 30.

Contrasting views on the diameter of coronary arteries in the elderly exist. Rose et al. (1967); Restrepo et al. (1973); Massmann and Oestreich (1974) and Wilson et al. (1978) described an *age related ectasia* while Sagebiel (1935); Vogelberg (1957) and Wilens et al. (1966) did not find it.

The effect of cardiac hypertrophy on the lumen of the coronary arteries is also debatable; Harrison and Wood (1949) and Arai et al. (1968) found that there was a continuous expansion of the blood vessel with increasing cardiac weight in their extensive studies of postmortem specimens. This was true for concentric hypertrophy but Hutchins et al. (1977) record expansion (of the lumen) of coronary arteries in different types of cardiac hypertrophy. Rodriguez and Robbins (1959) noted an increased capacity of the coronary arterial tree which did not keep pace with the increase in heart weight. Paulsen et al. (1975) found a significant widening of the left coronary ostium in hypertrophic hearts of men but not in women; Rose et al. (1967) could find no significant correlation between coronary artery diameters and cardiac weight and Vogelberg failed to find any enlargement of the coronary lumina beyond the critical cardiac weight of 500 g. Rabe (1973) found no increase following hypertrophy.

In living patients with cardiac hypertrophy Kober et al. (1972) observed in angiograms a dilation of the coronary arteries. In research on lambs and sheep Overy et al. (1966) report a widening of the right coronary artery lumen following induced right hypertrophy. As a result of training, hypoxia or experimental aortic stenosis both Stevenson et al. (1964) and Kerr et al. (1968) found a general increase in the volume capacity of the coronary arteries in prepared coronary artery cast specimens.

Little information exists whether the width of the coronary arteries is dependent on the area supplied. Woods (1961) describes a direct proportional relationship between the cross sectional area of the right coronary artery and the area of myocardium supplied by it but he did not note any increase in hypertrophy of the myocardium. Stelmasiak and Osemlak (1972), following the examination of only two hearts, came to the conclusion that coronary arteries with larger diameters supply a larger area of heart muscle than those of smaller diameters. Milles and Dallessandro (1963); Wilens et al. (1966;) Rose et al. (1967) and Restrepo et al. (1973) maintain that coronary arteries become narrower when atherosclerosis exists than in its absence; on the other hand, Rodriguez and Robbins (1959) state that the whole capacity of the coronary arteries in coronary sclerosis and occlusion is nearly equivalent to those in the normal heart. Perhaps this is due to the collaterals.

From their observations Wilens et al. (1966) came to the conclusion that people with small coronary arteries were prone to a higher degree of coronary occlusion than those with wider coronary lumina and that the presclerotic coronary artery diameter was a significant factor in myocardial infarction.

Because of these unanswered questions measurement of the width of coronary blood vessels from birth to senescence was undertaken in cases of hypertrophy or atherosclerosis, together with a study of the myocardial areas dependent on these arteries for their blood supply.

Materials

Measurements were taken from 300 cadaver hearts of which 188 were male and 112 female. These specimens were obtained from the Institute of Pathology of the University of Marburg (Lahn) during the years 1972–1975. Fifty of these hearts were obtained at random, but the remainder were specifically selected – many had coronary disease, 56 showed myocardial infarcts. Twenty-five were fetal, neonatal or childrens hearts, the remaining 275 came from adults with heart weights ranging between 170 and 1,110 g.

Methods

In undissected hearts showing rigor mortis, firstly the coronary arteries were perfused with saline solution and then injected with a barium sulphate Micropaque and gelatine mixture (5:2) at a pressure of 100 mg of mercury.

Mostly the hearts were perfused through the aorta which below the ostia of the coronary arteries was securely sealed by corks. If it was not possible to achieve a satisfactory filling of the coronary arteries via the aorta, as in cases of aquired valvular deformities, cannulae were inserted in both the right and left coronary arteries.

Following injection the hearts were cooled to a temperature of 4° C for three to four hours and finally x-rayed in the antero-posterior and lateral positions with a film to tube distance of 117 cm, a voltage of 100 KV and a time exposure of 0.3 to 0.6 min.

Following fixation in 4% formalin the ventricular part of the hearts were then cut into 8 mm slices. Inevitably the basal section, which contained the main part of the right coronary and the left circumflex artery, was thicker. All sections were then x-rayed. With the help of x-ray pictures the area of blood supply was determined (see Kalbfleisch and Hort 1977; Kalbfleisch 1975) and the largest diameters of the three main coronary artery stems (i.e. the right coronary artery, the left descending and circumflex branch) and the left main coronary artery were measured. The third branch of the left main coronary artery arising from the bifurcation of the left descending and circumflex branches was also measured when present and added to the measurement of the descending branch.

The diameter of the left main stem and descending branch was measured from the A–P film, the right coronary and left circumflex branch from the film of the basal slice of the heart using a magnification of seven times and a scale graduated to 1/10 mm.

To avoid parallactic mistakes when reading off the vascular diameters, the lens was arranged in such a way that central exposure of the vascular diameter was ensured. Furthermore it was regarded that the investigator should look perpendicularly at the lens.

Accuracy of Measurements

Inevitably there is some inaccuracy due to the difference in distance between the x-ray plate and the coronaries. The following table gives the increase in the diameter of the vessels, as a percentage of the original value (for a tube to film distance of 117 cm).

Coronary to film distance 1 cm increase in diameter 0.86%.
Coronary to film distance 5 cm increase in diameter 4.46%.
Coronary to film distance 8 cm increase in diameter 7.34%.

If the heart was displaced some 20 cm from the tube-film axis there was a further magnification of 1.5%. This is not considered relevant as every effort was made to place the hearts in the centre of the x-ray film.

In the basal slice as a rule the measuring points of the right coronary artery and the left circumflex branch were 1–2 cm distant from the x-ray film. It was therefore practicable to ignore the linear magnification of 0.9–1.8%. It was obvious that at a distance of 6 cm from the x-ray film the diameter of the main left coronary arterial stem and its descending branch were enlarged by about 5.4%. A correction of 11% was found to be necessary for the cross-sectional area of this vessels. In view of the small error with regard to the right coronary and the left circumflex branch no correction was applied. For the left descending branch we corrected the reading only when comparing the vessel diameter with the weight of the heart.

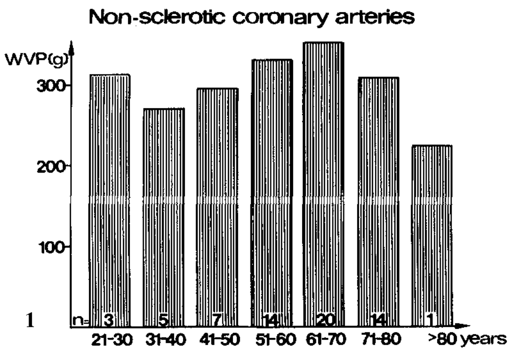
Added to these unavoidable systemic errors there were faults in reading off the diameters but these were confined within narrow limits. In adult hearts 115 double readings of the diameters differed by less than 1%.

Furthermore in 10 neonatal and infant hearts the measurements recorded by x-ray films were compared with those observed by stereomicroscop in transversely sectioned coronary arteries. The average differences in a median diameter of 1.4 mm was ± 0.1 mm. The margin of error necessarily increased in these smaller coronary arteries.

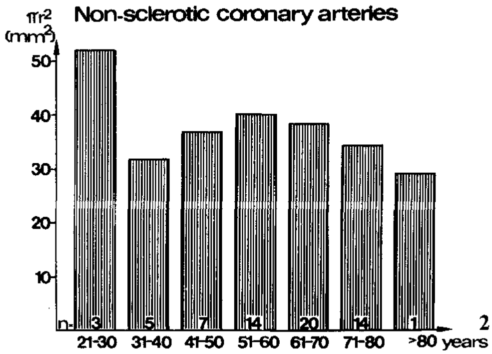
As a rule as a measurement of heart weight, the weight of the formalin fixed ventricular part (= WVP) was chosen. The adipose tissue on the heart was retained, but the atria and great vessels were removed. The average weight of the formalin fixed ventricular part was 81.4% of the whole unfixed heart. In these fresh hearts, however, the aortic stump was somewhat longer than that obtained by conventional sectional techniques. This explains why the weight of the ventricular part after fixation in formalin corresponds to approximately 85% of the fresh whole heart obtained by conventional autopsy technique

Results

The adult hearts were classified into sclerotic and non-sclerotic specimens. The trunks of the coronary arteries were sectioned at 4 mm intervals and the degree of stenosis first assessed macroscopically. The measurements were then fre-



1



2

Fig. 1. Mean weight of ventricular part (WVP) in correlation to age. 64 hearts with non-sclerotic vessels and WVP between 200 and 400 g

Fig. 2. Sum of the cross sectional areas of the three coronary arteries (mean values) in the different age groups. The material is the same as in Fig. 1

quently confirmed by micrometric examination of histological specimens. Vessels were classified as non-sclerotic if they had an intact intima or not more than a trace of atherosclerotic lesions. The limit was stenosis in not more than 2 segments (i.e. in two slices 4 mm thick) and not amounting to a reduction in the diameter to less than 3/4 of the original value (corresponding to a linear stenosis of 25%).

1. Diameter of Vessels and Age, Adults

To examine the effect of ageing all the 64 adult hearts with non-sclerotic vessels and WVP ranging between 200 and 400 g were selected. Thirty-eight were female and 26 male, spanning 22 to 86 years of age.

Firstly the correlation between WVP and age was analysed (Fig. 1) without considering the first group consisting of only three hearts of 21 to 30 years, there was a gradual increase in the WVP from 266 g in the 31 to 40 year old age group up to 338 g in the 61 to 70 year group – and a reduction in weight in the two older age groups. A comparison with the results in Fig. 2 indicated that the sums of the cross-sectional areas of the 3 large coronary arteries at their widest diameter correlate closely with the weight of the heart. If the measurements of the 15 hearts of the younger age group up to 50 years (average age 38 years) and those from 35 hearts of 60 years and older (average 68.2 years) are compared, in the older age group there is an overall diminution in the cross sectional areas from 38.66 $mm^2 \pm 9.82$ mm^2, to 36.87 $mm^2 \pm$ 9.15 mm^2 despite the average increase in WVP (324 g in the older specimens as opposed to 290 g in the younger).

Our findings show that when coronary arteries are filled under pressure no significant change in the lumina could be detected in old age. Therefore a physiological age change under these research conditions could not be demonstrated. The negligible narrowing of the section diameters allied to increasing age was not convincing.

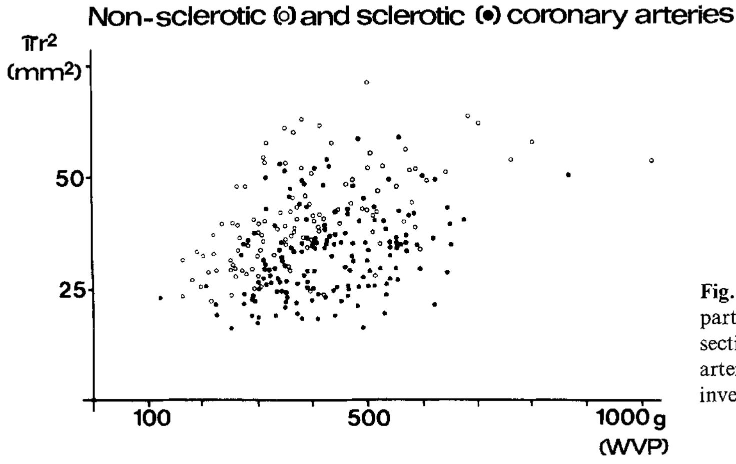


Fig. 3. Weight of the ventricular part (WVP) and sum of the cross sectional areas of the 3 coronary arteries of all 275 adult hearts investigated

Comparing the results in females and males the female age groups showed a more uniform agreement between coronary artery width and heart weight. In male specimens these values were much more variable.

2. The Significance of Cardiac Weight and Coronary Artery Width in Adult Hearts

All measurements obtained from 112 non-sclerotic and 163 hearts with sclerotic coronary arteries are shown in Fig. 3. The degree of scatter of the results is great. For each heart the sum total of largest cross sectional areas of the three coronary arteries was plotted graphically – the values for the narrowest vessels, at the lower border of the graph are exclusively from arteriosclerotic coronary arteries those at the upper border are almost all from normal coronary arteries.

Analysis of the graph shows that a progressive increase in cardiac weight is associated with increased diameter of the blood vessels, it is particularly noticeable in hearts with non-sclerotic vessels. The results for the 112 non-sclerotic hearts (58 men and 54 women) are shown in Fig. 4. The formula of the regression line is $y = 0.045x + 23.51$. The correlation coefficient of $r = 0.61$ showed a statistically significant increase in the cross-sectional area with increase in WVP ($P < 0.001$). Differences in the regressions in men and women were not statistically significant. The cardiac weight in the majority of hearts was greater than normal. A WVP of 300 g is equivalent to 350 g entire heart weight and a WVP of 425 g is equivalent to an entire heart weight of 500 g. A great number of hearts in this category also exceeded Linzbach's critical cardiac weight.

Because of the great discrepancies in the measurements it was decided to test the hypothesis that this might be due to the inclusion of some hearts with minimal atherosclerosis. Therefore 54 hearts with completely normal coronary arteries were examined separately (Fig. 5). These hearts, however, yielded almost the same findings as the group of 112 hearts with "non-slcerotic" coro-

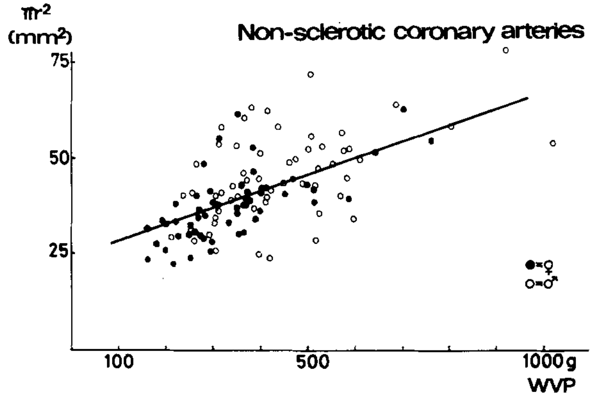


Fig. 4. WVP and cross sectional areas of the 3 coronary arteries of the 112 hearts with non-sclerotic coronary arteries

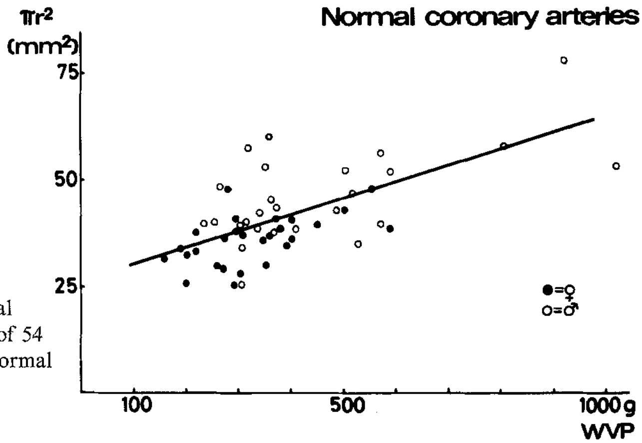


Fig. 5. WVP and cross sectional areas of the coronary arteries of 54 adult hearts with completely normal coronary arteries

nary arteries. The formula of the regression line was $y=0.039\,x+26.47$ and the correlation coefficient was taken as $r=0.625$. There is only a slight increase in comparison with the entire group ($r=0.61$). Therefore the inclusion of hearts with minimal coronary atherosclerosis in the "non-sclerotic" group had no specific influence on the calculations.

In the following histogram (Fig. 6a) the cross sectional areas of the 3 coronary arteries in the 112 hearts with non-sclerotic arteries are compared with the WVP. It is evident that even in case of excessive cardiac weight (beyond a WVP of 600 g) growth with increase of the coronary artery diameter can occur, as seen in the last 2 pairs of column of Fig. 6a. In the 8 hearts of these two groups coming from patients averaging 54 years the following factors were responsible for marked hypertrophy: Aquired deformity of aortic valves (3), chronic cor pulmonale (2), systemic hypertension (1), patent ductus arteriosus (1) and congestive cardiomyopathy (1). The measurements of the areas of cross-sections of the coronaries of these 8 hearts gave values that are distrib-

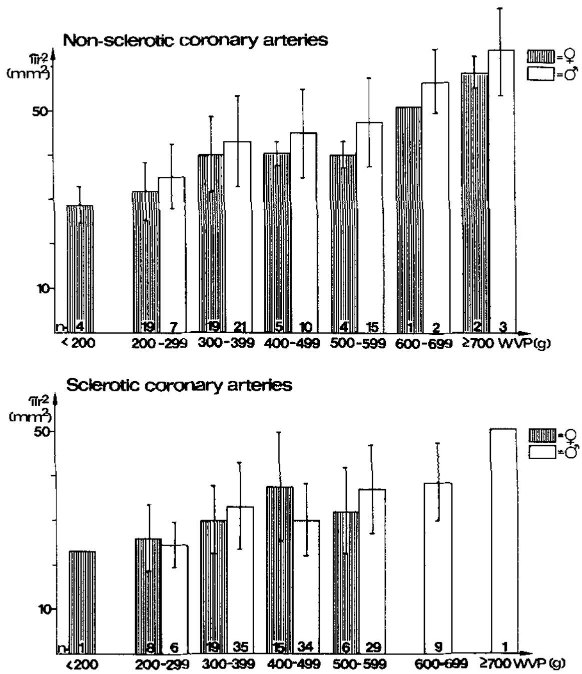


Fig. 6a, b. WVP and mean values of cross sectional areas of the 3 coronary arteries in women and men.
(a) 112 hearts with non-sclerotic coronary arteries.
(b) 163 hearts with sclerotic coronary arteries

Table 1. Sum of the cross sectional areas of the coronary arteries (mean values) in the different weight groups of hearts with nonsclerotic coronary arteries

Weight groups (WVP)	Cross sectional areas of Coronary arteries (mean values in mm²)				Statistic significance of the differences of mean values. Comparison of the different groups with the lowest and highest weight group		
	n	men	*n*	woman	WVP 200–229 g		WVP ≥600 g
					men	woman	men
200–299 g	7	35.04± 7.76	19	32.12±6.40			<0.001
300–399 g	21	42.84±10.54	19	39.73±8.55		<0.01	<0.01
400–499 g	10	44.67±10.71	5	40.53±3.14		<0.01	<0.02
500–599 g	15	47.51±10.72	4	39.96±2.45	<0.02	<0.05	<0.05
≥600 g	5	60.66±11.16	3	55.82			
	58		50				

uted in a regular manner close to the regression line as shown in Fig. 4. Coronary artery areas even in these heavy weight groups were shown to have dilated approximately in proportion to the cardiac weight.

Table 1 includes the group of hearts with nearly normal weight (WVP 200 to 299 g, mean 252 g; corresponding to an average entire heart weight of roughly

300 g) and the group of hypertrophied hearts (those with a WVP above 300 g), together with the cross-sectional areas of the coronary arteries in men and women. Only hearts without sclerotic coronary arteries were used. From Table 1 and Figs. 4 and 6 the following results can be seen. There is a statistically significant increase in the diameter of the coronaries in women with slight to moderate cardiac hypertrophy compared with hearts of nearly normal weight (WVP 200 to 299 g), in men on the other hand this is apparent only for the group with a WVP 500 to 599 g ($P<0.02$). The average increase in width in the group with little or moderate hypertrophy was small in men. Even in women with the weight group of 400–599 g there was no marked widening of the coronary arteries compared with the group with a WVP ranging between 300 to 399 g. However because of the small size of this group the significance of these findings is doubtful.

In contrast to the paucity or absence of a rise in the mean value in the groups with small or moderate hypertrophy a steep increase in the areas of the cross-sections in hearts with marked hypertrophy (WVP > 600 g) was seen. In men the cross sectional area increase compared with the WVP group between 500 and 599 g is probably significant and compared with the group of WVP 400 to 499 and those of 300 to 399 the difference is certainly significant ($P<0.02$ or <0.01). In women however the group showing the most severe hypertrophy is too small for valid statistical evaluation.

If however the ventricular weight groups 500 to 599 g of both men and women are assessed together then the difference in the coronary diameters between this group and that with a WVP over 600 g is statistically significant ($P<0.02$).

These observations showed growth of the coronary arteries in connection with a severe hypertrophy. Whether the widening of the coronary arteries from minor to major hypertrophy is a continuous process has not been established.

The inclusion of the subepicardial adipose tissue and the large coronary arteries in the WVP in our investigations should be critically viewed. It is of course conceivable that this very variable mass of subepicardial adipose tissue might influence the research results. Therefore in a preliminary study we examined 31 hearts with an average WVP of about 350 g. Those with little adipose tissue and well developed musculature had wider coronary arteries than those with a lot of adipose tissue. It was possible to conclude that the discrepancy in the coronary artery measurements was minimally corrected by this change.

Further our studies show that results in hearts with sclerotic coronary arteries differ noticeably from those with non-sclerotic vessels. The individual values were for the 49 women and the 114 men recorded separately in Fig. 7. The formula of the regression line is $y=0.031\ x+20.16$ and the correlation coefficient was $r=0.343$. The level and the increase of the regression line was markedly less than in non-scerotic hearts (see Fig. 4). An increase of arterial width in relation to increasing cardiac weight is indicated by the correlation coefficient. The statistical significance was however lower than in the group with non-sclerotic vessels.

Figure 6b shows that as a rule the cross sectional areas of the sclerotic

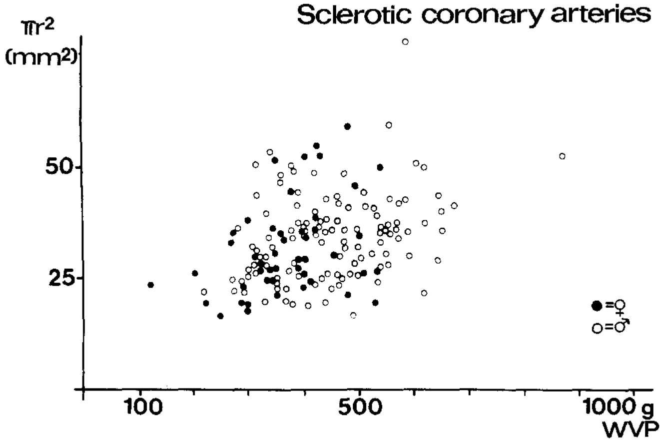


Fig. 7. WVP and sum of the cross sectional areas of the 163 hearts with sclerotic coronary arteries in men and women

Table 2. *Comparison of the measurements of the* cross-sectional areas of right and main left coronary arteries (R+L) and of the right and left descending and left circumflex artery (R+Ld+Lc) (area of cross-section in mm^2)

Group	*n*	WVP	R+L	R+Ld+Lc
Non-sclerotic	53	393	30.71	41.23
Sclerotic	90	427	25.96	33.23

Abbreviations: WVP: Weight of the ventricular part (g)

R=Right coronary artery; L=Main left coronary artery; Ld=Left descending coronary artery; Lc=Left circumflex coronary artery

coronary arteries are smaller than from hearts with non-sclerotic arteries (Fig. 6a). The histograms of Fig. 6b show that within the range group WVP 400 to 699 g no marked or further increase in the arterial width had occured. The majority of these hearts surpassed the critical cardiac weight of 500 g (Linzbach 1947).

The studies reported so far concern measurements of the three main coronary arteries. In a further study we measured the combined maximum cross-sectional area of the right coronary artery and the main left coronary artery in 53 hearts without atherosclerosis and 90 with atherosclerosis. The numbers are small because hearts with a very short left main coronary artery were excluded.

The sum of these two cross-sections is mostly distincly less than that of the three arteries (right coronary artery and left descending and left circumflex branches). In both instances measurements were the same for the right coronary. It therefore follows that the cross-section of the main left coronary artery was usually smaller than the sum of the largest cross-section of the left descending and the left circumflex branches. Only two times in the 53 heart with non-sclerotic coronary arteries and seven times in the 90 hearts with sclerotic coronary arteries the width of the stem of the left coronary artery was greater than the sum of the diameters of the left descending and left circumflex coronary artery. For individual groups, the mean values were as follows (Table 2).

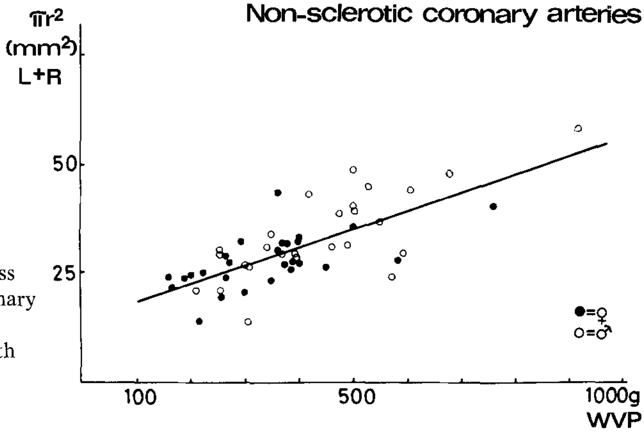


Fig. 8. WVP and sum of the cross sectional areas of the right coronary artery (*R*) and the left main coronary artery (*L*) of hearts with non-sclerotic coronary arteries

Table 3. Intimal thickness in the widest part of the coronary artery in hearts with and without arteriosclerosis

Group	Examined		Male	Female	Mean values		
	hearts	coronary arteries			age (years)	WVP g	thickness of the intima (mm)
Without sclerosis	25	74	11	14	56	395	0.16 ± 0.12
With sclerosis	22	60	13	9	66	439	0.43 ± 0.23

This also demonstrated that the average width of the coronary arteries is smaller in sclerotic vessels despite the greater average heart weight. For hearts with nonsclerotic blood vessels the individual measurement values were noted in Fig. 8. These indicate a continuous general relationship between the width of the coronary arteries and the increase in heart weight, this applies also to hearts weighing more than 500 g. For both men and women the formula was $y=0.041\ x+14.29$ for the regression line, the correlation coefficient was $r=0.731$. This high value indicates that the deviation of measurements here was less than in the hearts of Fig. 4 where the sum of measurements of the three coronary arteries is noted ($r=0.61$). Hearts with sclerotic coronary arteries showed a much greater deviation in measurements and there was no significant increase of the regression line ($y=0.01\ x+21.55$; $r=0.155$).

3. The Thickness of the Intima at the Widest Diameter of the Coronary Arteries in Adults

In hearts with no coronary sclerosis the mean diameter at the widest part of the vessel was obviously larger than those in hearts with coronary sclerosis. The average intima thickness was measured at the previously measured widest areas in 25 hearts with no sclerosis and in 22 hearts with arteriosclerosis. The measurement results are tabulated in Table 3.

From this it is clear that the intima in the widest parts of sclerotic coronary arteries was markedly thickened in comparison to that in hearts with normal blood vessels. The difference in thickness averaged 0.27 mm and was statistically highly significant ($P<0.001$). This value is almost identical with the mean difference of the lumen diameters of the sclerotic and non-sclerotic vessels (taken from the x-rays). These measurements indicate that the diameters of the sclerotic coronary arteries before the onset of the sclerotic lesions were in the same range as in the non-sclerotic group.

Mostly intimal thickening at the widest diameters of sclerotic coronary arteries was slightly eccentric, only in some cases concentric or distinctly eccentric. In cross sections the lumen usually appeared circular but in the presence of thicker sclerotic lesions it was slightly oval.

4. Coronary Arterial Width and the Size of the Myocardial Area Supplied in Adults

The areas of blood supply in 61 hearts with non sclerotic blood vessels were investigated by x-ray. The myocardial area (measured in arbitrary units) represents the sum total of the areas measured in the single slices of the heart. The findings are recorded in Figs. 9–11. All 3 blood vessels increase their diameter with an increasing myocardial area. This increase is continuous up to mean sized supplying areas. If this continuous increase is valid for large supplying areas too, has to be investigated in a larger material.

Results for the 3 arteries are different. As a rule the supplying area of the left circumflex artery is the smallest and that of the left descending coronary artery the largest one (Hort et al. 1973; Kalbfleisch and Hort 1977). These results are influenced by the coronary arterial pattern (Kalbfleisch and Hort (1977). The regression lines for the individual arteries are calculated as following:

Right coronary artery $y=0.0077\,x+4.76$; $r=0.71$.
Left circumflex artery $y=0.082\,x+5.64$; $r=0.562$.
Left descending artery $y=0.0014\,x+12.56$; $r=0.151$.

For the right coronary artery and the left circumflex artery a clear rise in the area supplied by it is certain ($P<0.001$). However no such claim is made for the left descending coronary artery. It appears that in this vessel no further increase occurs in larger supplying areas (between 1000 and 2000 myocardial areas, Fig. 11). These results are obtained from men and women. For females only the formula of the regression line is given as $y=0.0082\,x+5.73$; $r=0.61$. Here again a clear increase is found to exist ($P<0.001$).

The marked scatter of measurements for the left descending coronary artery may be due to the fact that often immediately adjoining its origin a diagonal branch arises. We added the cross-sectional area of this diagonal branch to the cross-sectional area of the left descending artery. Taking the sum of the measurements of two vessels into consideration the values show less uniformity than when only a single vessel is measured. Similarly we have shown (see above) that the sum of the measurements of the left descending and the left circumflex coronary artery gives less uniform results than the measurements of the left main coronary arteries only.

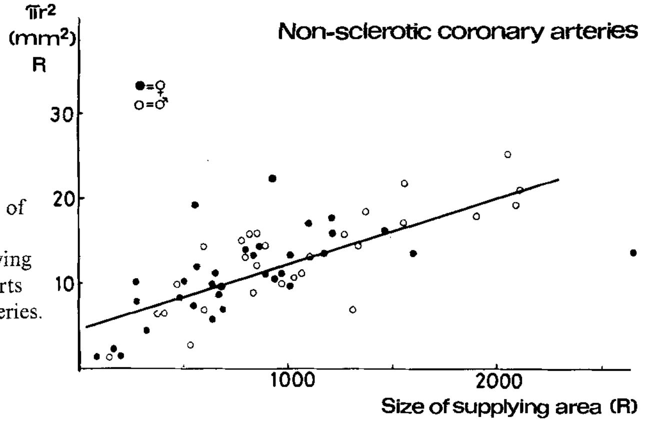
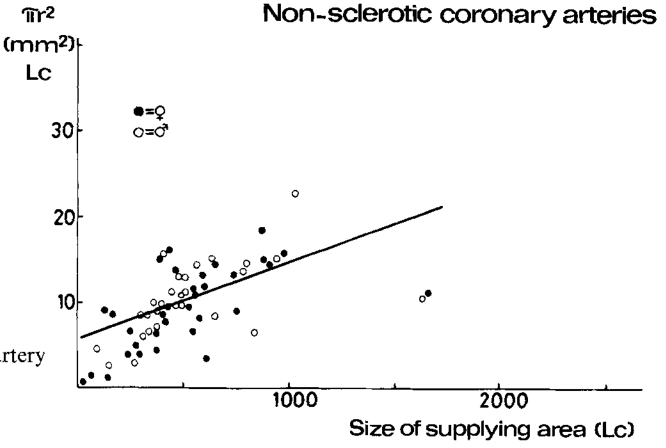
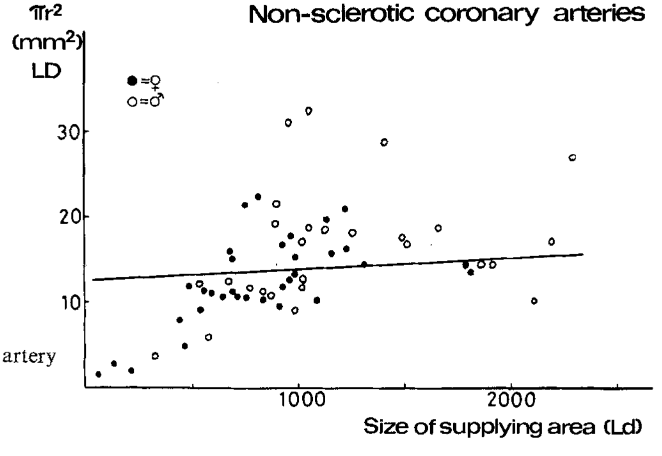


Fig. 9–11. Cross-sectional areas of the 3 coronary arteries in correlation to the size of supplying areas (in arbitrary units) in hearts with non-sclerotic coronary arteries.

(**9**) Right coronary artery (*R*).



(**10**) Left circumflex coronary artery (*Lc*).



(**11**) Left descending coronary artery (*Ld*)

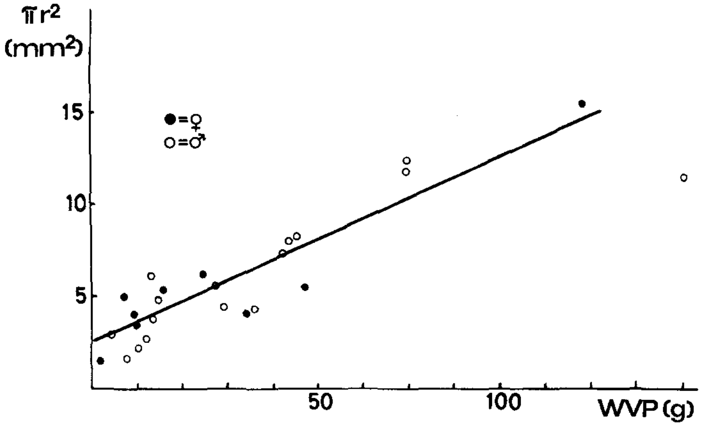


Fig. 12. Sum of the cross sectional areas of the 3 coronary arteries from fetals to adolescents in correlation to WVP

In comparing sclerotic vessels and non-sclerotic ones, a general decrease in the diameter per unit of supplied myocardial area was found in the sclerotic vessels. Moreover the scattering of measurements was substantially increased with the exception of the left descending coronary artery.

In the left circumflex artery however, an increase in the regression line was not obviously.

5. Fetal and Neonatal Growth in Coronary Arteries up to Adolescence

This group comprised 25 hearts including some fetal and some childhood cases with a WVP between 2.2 g and 130 g. Fig. 12 shows a nearly constant increase in the sum of the cross-sectional areas of the 3 coronary arteries in relation to heart weight. The regression line is described by the formula $y = 0.0986\,x + 2.66$. The correlation coefficient ($r = 0.88$) was very high and significant at the 0.001 level.

6. Relative Widths of Coronary Arteries

a) Cross-Sectional Area and Heart Weight in Adults. The relationship between the lumen of the coronary arteries and the weight of the heart is important to blood supply of the myocardium (vide Restrepo et al. 1973). The relative width of the vessels was calculated from the formula

$$W = \frac{\text{Sum total of the cross-sectional areas (mm}^2\text{)}}{\text{Weight of the ventricular part (g)}}.$$

This indicates how many mm^2 of the entire cross-sectional area are adequate to 1 g of myocardium. Figure 13 shows all measurements for adult hearts. These establish that the relative width of the vessel diminishes continuously with rising heart weight – only in the heaviest hearts there was an almost constant relationship. The number of cases we examined is too small to give a final record for the tail of the graph.

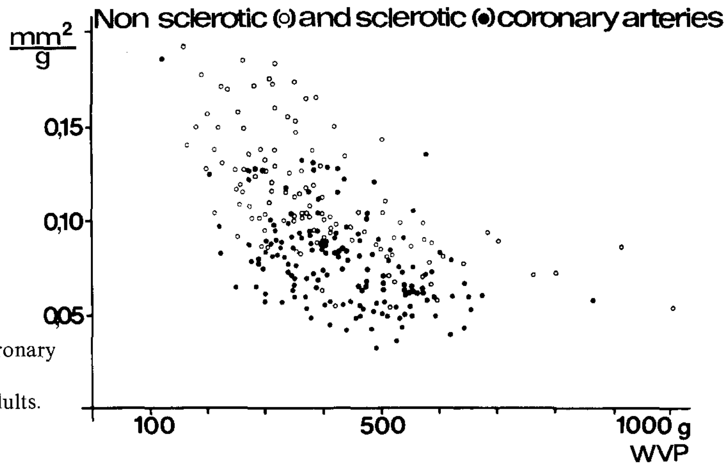


Fig. 13. Relative width of coronary arteries (formula see text) in correlation to the WVP in adults.

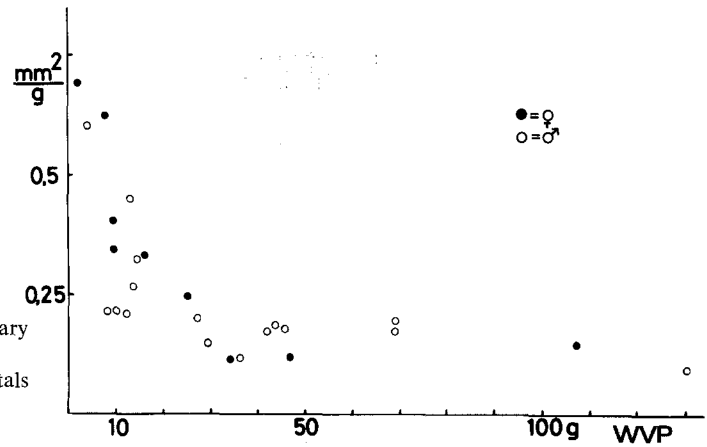


Fig. 14. Relative width of coronary arteries (formula see text) in correlation to the WVP from fetals to adolescents

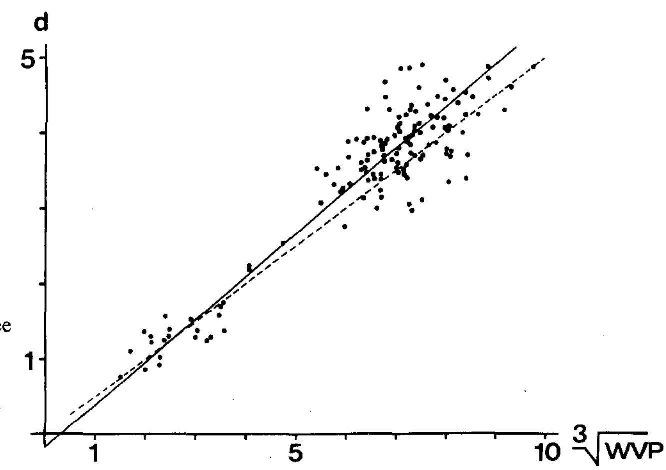


Fig. 15. Correlation between the diameter (d) of the hypothetical single coronary artery (definition see text) and the diameter of the mass of ventricular part ($\sqrt[3]{WVP}$) in hearts without atherosclerosis in all age groups

The measurements for hearts with sclerotic vessels (average value (0.08 mm^2/g average WVP 427 g) were considerably smaller than those for non-sclerotic vessel material (0.112 mm^2/g averaging a WVP of 393 g).

In non-sclerotic coronary arteries the formula of the regression line is $y = 0.00013\,x + 0.165$ and the correlation coefficient $r = 0.63$ which is significant at a level of 0.001%. This correlation coefficient should be still greater employing an exponential function instead of the linear one. In our material the relative coronary artery widths are smaller in women than in men.

It must also be noted that in hearts with sclerotic coronary arteries there is a marked decrease of the relative lumen width with increasing heart weight too. In this case the function of the regression line is $y = 0.00010\,x + 0.126$; $r = 0.46$.

b) Coronary Artery Cross-Section Areas and Heart Weight up to Adolescence. The relative vessel widths of the 25 hearts (the same ones as in chapter A.5) show a rapid decrease during the early neonatal years. This can be demonstrated with a clear exponential curve, see Fig. 14.

c) Coronary Artery Diameters and Heart "Diameter" During Physiological and Pathological Cardiac Growth. If the relationship between the cross-sectional areas of coronary arteries and cardiac weight are compared two different dimensions are used, the surface area (second power) on the one hand and the volume (third power) on the other. Therefore in a further calculation we compared the same dimension of coronary arteries and hearts using the linear dimension. The x-ray measurements of coronary diameters of 25 fetal neonatal and childrens hearts and of the 112 hearts with non-sclerotic coronary arteries were compared with the cube root of the ventricular weight. This cube root approximates to the radius (or the diameter) of the cardiac muscle mass. The three coronary arteries were replaced by a hypothetical single coronary artery, its cross sectional area was calculated from the sums of the cross-sectional areas of the three coronary arteries. The measurements of the left descending coronary artery are affected by the enlargement of its distance from the x-ray plate with increasing heart weight. An appropriate correction was made (see methods).

The results are noted in Fig. 15. The equation for the regression line is $y = 0.52\,x + 0.12$. The correlation coefficient of 0.89 is exceptionally high. From this can be followed that the closest correlation exists between the increase in width of the coronary arteries and the linear growth of the cardiac muscle mass.

There is also clear evidence of a continuous growth in the diameter of coronary arteries in relation to the "diameter" of the muscle mass even with very high WVP.

In Fig. 15 the broken line shows the regression for perfect agreement between increase in muscle mass and diameter of coronary arteries. By comparing this line with the continuous line which gives the regression calculated from our results, it will be seen that there is almost complete agreement. The diameter of the vessels increases a little faster than the diameter of the heart, but this small difference is not statistically significant.

Discussion

For this investigation the widest part of each coronary artery was chosen. This was usually about 2 cm from the orifice. In hearts with non-sclerotic coronary arteries there were only little differences between the calibre of the lumen at the ostium and at the widest part. The diameter of the right coronary artery showed a relatively small decrease in diameter (due to the smaller blood demand of the right ventricular wall) in contrast to the left descending and circumflex coronary arteries.

The results of measurements of the width of coronary arteries depend on the method used. The ordinary postmortem technique gives a narrower lumen (due to retraction of the dissected arteries) than fixation under pressure, so a control experiment (Nauth et al. 1979) was carried out, using 100 unselected hearts with an average weight of 430 g and an average age of 65. The circumference of the coronary arteries opened with the usual post-mortem technique were measured at their origins giving the following results

Right coronary artery	9.8 mm
Left descending coronary artery	9.0 mm
Left circumflex coronary artery	7.6 mm

These findings were about 1/5 to 1/4 lower than the comparable measurements in this investigation, where the arteries had been filled under pressure of 100 mm Hg, approximating to the normal mean arterial pressure.

How may these postmortem findings be equated with the findings in life since postmortem blood vessels might be affected not only by rigor mortis but also by a lack of muscle tone and autonomic innervation? In general, in vivo measurements of coronary artery diameters have been compared with the whole heart weight. In view of this, the calculations in Table 4 were made with regard to the whole heart weight, not the WVP.

In Table 5 in vivo measurements in men and women with normal heart weights are compared with our postmortem findings in hearts with non-sclerotic coronary arteries. It is seen that, measurements in vivo, despite wide individual variations (compare also Kober et al. 1972) conform with one another. Our postmortem findings are roughly 15% above this.

Following treatment with nitroglycerine probably maximum dilation of the coronary arteries occurs and the diameter of living coronaries increases by approximately 10–20% (Rafflenbeul et al. 1975 and Conti et al. 1979). The resultant vessel diameters equate overall favourably with our postmortem specimen findings. Our postmortem diameter measurements should therefore be a close approximation to the maximum in vivo width. The heart weights of our control specimens (nearly 350 g) appear to be a little high. A 4% decrease of the coronary diameters was expected for an average cardiac weight of 300 g. Such a difference would in no way modify established conclusions.

Our findings on the widths of coronary arteries in relation to age and in hearts of approximately the same weight, in the absence of coronary atherosclerosis, failed to establish a physiological age related dilatation.

This topic has brought about a great deal of controversy in the literature. In the International Atherosclerosis Project, when a large number of hearts (12,680 hearts) from various countries was

Table 4. Mean coronary artery diameters at the widest lumen in nonsclerotic coronary arteries in correlation to the entire heart weight

Heart weight	*n*	L[a]	Ld[a]	Lc[a]	R[a]
<300 g	13	3.60	3.68	3.13	3.63
300–399 g	26	3.68	3.72	3.57	3.79
400–499 g	26	4.27	3.83	3.40	4.05
500–599 g	15	4.31	4.09	3.62	4.53
600–699 g	18	4.40	3.98	3.76	4.38
>700 g	13	5.58	4.20	3.95	4.78
	111				

[a] Abbreviations: See Table 2

Table 5. Intravital coronary artery diameters in mm (values obtained from literature) in comparison with our postmortem findings in hearts with normal weight and without coronary sclerosis

Authors	Ld[a]	Lc[a]	R[a]
McAlpin et al. (1973)	3.4	3.0	3.2
Lewis and Gotsman (1973)			3.3 (calculated)
Rafflenbeul et al. (1975)	3.3	3.0	3.3
Our postmortem findings (Heart weight) 300–399 g)	3.7	3.6	3.8

[a] Abbreviations: See Table 2

examined, the fact was apparently established that average coronary diameters were greater in older than in younger people (Restrepo et al. (1973). Hieronymi (1956) as well as Massmann and Oestreich (1974), in less extensive investigations, came to the same conclusion.

In injected control hearts, Rose et al. (1967) described dilatation of the right coronary artery with age. This proportion is, however, of no great scientific value because the heart weight was not noticed in this paper.

Wilson et al. (1978) worked on coronary arteries, fixed with formalin under pressure and they described an age related dilatation. Because of the paucity of their research material (12 male hearts and 14 female) it is necessary to treat their findings with caution. Nevertheless, other researchers have failed to demonstrate dilatation with age. Rössle and Roulet (1932) in their research on dissected coronary arteries and Wilens et al. (1966) by planimeter measurements of opened coronary arteries fixed on cork found no distinct circumferential increase of the coronary arteries of the aged. Vogelberg (1957), investigating fomalin fixed heart speciments beyond the third decade failed to demonstrate any widening of the coronary orifices.

In autopsy coronary angiograms performed under almost physiological pressure circumstances in a collection of 37 hearts investigated by Sagebiel (1935), no ageing arterial dilatation was found. Rodriguez and Robbins 1959 in the examination of 100 old male hearts found no increase in the capacity of the coronary arteries.

To summarize: As a rule measurements on dissected coronary arteries revealed ectatic vessels in old age in contrast to measurements on coronary arteries filled under physiological pressure. Probably these differences are due to changes in the elastic properties. In our research program this was systematically investigated by Köhler and Köhler (1975). They found that the distensibility of coronary arteries when tested with gradually increasing moderate pressures, was higher in children and young people than in older persons. It followed, therefore, that the diameter of ageing coronary arteries is less reduced in size when pressure diminished. In contrast to younger arteries the final dimensions of ageing blood vessels not subjected to pressure were found to be only minimally smaller than in arteries subjected to physiological pressure.

In the muscular arteries of the extremities Klingelhöfer and Meyer (1962) noted the loss of retraction with age and its significance in the postmortem diagnosis of an age related ectasia. These findings speak for the fact that as a rule the dilatation of the dissected coronary arteries with age is due to a decreased elasticity.

Differences in diameter of male and female vessels are often discussed. In our material not affected by atherosclerosis it was found that for the same heart weight female coronary arteries were generally a little smaller than the male ones. The differences were not statistically significant. Can any significance be attributed to them in the light of the lower incidence of female coronary heart disease? It has been shown (see Nauth et al. (1979) that the incidence of coronary sclerosis increases with increasing vessel diameter. Restrepo et al. (1973) also showed that women coronary arteries are narrower than men's. But Orlandini (1968) in his postmortem research found that only the circumference of the left coronary artery was smaller and Paulsen et al. (1975) stated that only the ostium of the right coronary artery was narrower. The findings of Rose et al. (1967) on the smaller coronary lumina in women cannot be considered because age and weight had not been taken into account. The same applies to the work of Milles and Dalessandro (1963) who stand alone in recording wider coronary arteries in women. Rodriguez and Robbins (1959) missed significant differences in the coronary arterial diameters in both sexes.

Physiological growth in coronary arteries has been considered only in a perfunctory manner (see Introduction). Progressive thickening of the intima during physiological post-natal growth is the main result of the work of Neufeld et al. (1962) while Vogelberg (1957) has focussed his investigations on the the coronary ostia.

In order to relate growth of coronary arteries to cardiac growth the coronary artery cross-sectional areas were assessed in relation to the myocardial weight. This quotient was taken as a crude measurement of the adequacy of the blood flow. The value obtained decreased progressively during postnatal growth. The heart weight increased substantially more rapidly than the cross-sectional area of the coronary vessels. However, linear size comparisons gave the best agreement between growth of arteries and myocardium. The diameter of the coronary arteries almost uniformly increases in step with the "diameter" of cardiac muscle mass.

From these calculations it was concluded that the volume surrounded by the coronary artery lumen also increased with heart weight. In case of a constant blood demand of the unit of myocardial mass the coronary volume should increase proportionally with increasing blood demand. To date Ehrich et al. (1931) and Hutchins et al. (1977) were the only groups to emphasize that the same dimensions of coronary arteries and hearts should be compared. Ehrich et al. (1931) noted that in heart studies from birth to the 70th year there was a 15 fold increase in heart size; but the cross-sectional area of the coronaries increased only 6–7 times. They stressed that keeping in mind the various dimensions (second and third power) there existed a surprising correspondence between the growth of the coronary arteries and the heart muscle. Furthermore our measurements suggest the possibility of a somewhat faster growth of the coronary arteries.

The same conclusions were reached as the result of a comparative study of 32 animal species blood vessels and was carried out together with Thüroff on animals including guinea pigs, giraffes and horses (see Hort 1977). Perhaps the somewhat faster growth of the coronary artery diameters as well as the fall in the pulse rate with increasing heart weight prevent a dangerous increase of the velocity of blood flow according to an increase in the coronary artery bed.

During the pathological growth of the heart we have seen a nearly corresponding growth of the coronary arteries too. But whichever way one looks at it, research has not clearly resolved all the questions on the growth of coronary arteries under pathological circumstances. The problem is multifaceted and depends on what is used as comparison. When the width of all three coronary arteries is considered then, in women, there is a statistically significant widening with slight to moderate cardiac hypertrophy. Male hearts comprised the larger quota of our material and showed that in marked hypertrophy the coronary arteries were wider than those in hearts with slight to moderate hypertrophy.

The measurements carried out on the right coronary artery and the left main coronary artery, indicated a continual increase in coronary artery diameter even beyond the critical heart weight. When considering the supplying areas the width of the relevant coronary vessels were closely and continuously related to the heart weight up to moderate hypertrophy. With extreme hypertrophy the widening of the lumen was often less than anticipated. In our material the best correlation of these factors occured in the right coronary artery. In contrary Woods did not establish an increase of the cross-sectional area in the case of right sided hypertrophy of the heart.

The summary of these findings is that the coronary arteries are able to enlarge even beyond the critical heart weight, but it has not been established if growth in pathological circumstances is completely continuous and harmonious.

Another matter which our measurements demonstrated was a wide variation in coronary artery diameters which for instance, exceeded the variations in heart weight found in normotensive hearts. The small resistance to blood flow in the large coronary arteries suggests that under physiological conditions the widths of the lumen is not critical, so that widely differing values are acceptable. Probably the pure myocardial weight (i.e. without subepicardial adipose tissue) would offer a more valid parameter then the whole ventricular part weight.

The present literature on coronary artery growth as a result of pathological increase in heart size has already been quoted in the Introduction, but the view that there is little or no growth of coronary arteries if the heart is increased beyond the critical weight will have to be revised.

The much quoted work of Vogelberg 1957, stating that the ostia of the coronary arteries (in formalin fixed hearts) do not widen beyond the critical heart weight certainly cannot be applied to the diameter of the coronary arteries.

Investigations by Schoenmackers (1948) indicate that the functional mass of the coronary arteries either shows only a slight increase or decline in severe hypertrophy cannot be applied to the lumen of the coronary vessels. Our findings are in agreement with those of Hutchins et al. (1977) who investigated 145 hearts without significant coronary arteriosclerosis. Comparing hearts with normal weight and hypertrophic hearts they found a linear correlation between the cube root of the cardiac weight and the coronary diameters too. Their formula for calculating the hypothetical single common coronary differed somewhat from ours.

Obviously the blood supply to the hypertrophied heart is threatened primarily by the development of atherosclerosis and not by failure of growth of the coronary vessels. Our investigations show that in sclerotic arteries even the widest diameter is, on average, less than that of healthy coronary arteries. There are two possible explanations – either the widest part of the diseased vessel was already subject to atherosclerosis, or that the diseased vessel had a narrower lumen even before atherosclerosis set in.

Wilens et al. (1966) were the first to suggest this possibility, namely that arteries of hearts with infarcts had always been narrower than normal even before the onset of atherosclerosis. No proof was produced for this view. They have only carried planimetry of opened, fixed coronary arteries and found lower values than in normal hearts. Milles and Delessandro (1963) also found smaller coronary circumferences in hearts with infarctions and Rose et al. (1967) described similar results.

Our morphometric investigations of the thickness of the intima at the widest part of the atherosclerotic and non-atherosclerotic arteries speak for the fact that the diameters of the vessels were the same in both groups before atheroma developed and that patients with myocardial infarction did not have pre-existing abnormally narrow coronary arteries.

References

Arai S, Machida A, Nakamura T (1968) Myocardial structures and vascularization of hypertrophied hearts. Tohoku J Exp Med 95:35–54

Conti CR, Pipine CJ, Feldman RL, Curry RC, Christie LG, Nichols WW (1979) Angiographic definition of critical coronary artery stenosis. In: Adv Cardiol 26:100–109

Ehrich W, De la Chapelle C, Cohn AE (1931) A study of the coronary arteries. Am J Anat 49:241–282

Harrison CV, Wood P (1949) Hypertensive and ischaemic heart disease: a comparative clinical and pathological study. Br Heart J 11:205–229

Hieronymi G (1956) Über den altersbedingten Formwandel elastischer und muskulärer Arterien. Sitzungsbericht Heidelberger Akad Wiss Math-nat Klasse, 3. Abhandlung. Heidelberg 1956

Hort W (1977) Myocardial hypertrophy – Light microscopic findings on the myocardium – Blood supply – Ventricular dilatation and heart failure. Basic Res Cardiol 72:203–208

Hort W, Kalbfleisch H, Köhler F, Milzner-Schwarz U, Frenzel H (1973) Kombinierte coronarangiographische, makroskopische und mikroskopische Untersuchungen an menschlichen Herzen. Verh Dtsch Ges Pathol 57:384–385

Hutchins GM, Bulkley BH, Miner MM, Boitnott JK (1977) Correlation of age and heart weight with tortuosity and caliber of normal human coronary arteries. Am Heart J 94:196–202

Kalbfleisch H (1975) Eine Methode zur postmortalen Größenbestimmung der Versorgungsgebiete einzelner Herzkranzarterien. Z Kardiol 64:987–994

Kalbfleisch H, Hort W (1977) Quantitative study on the size of coronary artery supplying areas postmortem. Am Heart J 94:183–188

Kerr A, Bommer WJ, Pilato S (1968) Coronary artery enlargement in experimental cardiac hypertrophy. Am Heart J 75:144

Klingelhöfer D, Meyer WW (1962) Vergleichende mikrometrische Untersuchungen an den entfalteten und retrahierten muskulären Arterien der oberen und unteren Extremität. Virchows Arch [Pathol Anat] 335:529–43

Kober G, Spahn G, Spitz P, Becker HJ, Kaltenbach M (1972) Weite der großen Koronararterien im selektiven Arteriogramm bei Myokardhypertrophie. Verh Dtsch Ges Kreislf 38:191–194

Köhler F, Köhler H (1975) Über Altersveränderungen der elastischen Wandeigenschaften menschlicher Coronararterien. Verh Dtsch Ges Pathol 59:344–348

Lewis BS, Gotsman MS (1973) Relation between coronary artery size and left ventricular wall mass. Br Heart J 35:1150–1153

Linzbach AJ (1947) Mikrometrische und histologische Analyse hypertropher menschlicher Herzen. Virchows Arch [Pathol Anat] 314:534–594

Massmann J, Oestreich S (1974) Angiometric studies of human coronary artery sclerosis. Atherosclerosis 20:287–294

MacAlpin RN, Abbasi AS, Grollmann JH, Eber L (1973) Human coronary artery size during life. Diagn Radiol 108:567–576

Milles G, Dalessandro W (1963) The relation of the circumference of the coronary arteries to the weight of the heart and to myocardial infarction and myocardial failure. Rev Can Biol 22:325–327

Nauth HF, Hort W, Hubinger R (1979) Untersuchungen über die Lokalisation sklerotischer Veränderungen in den Koronararterien und ihren großen epikardialen Ästen. Z Kardiol 68:832–838

Neufeld HN, Wagenvoort CA, Edwards JE (1962) Coronary arteries in fetuses, infants, juvenils and young adults. Lab Invest 11:837–844

Orlandini GE (1968) La circonferenza rettificata delle arterie coronarie. Mal Cardiovasc 9:331–361

Overy HR, Vogel JHK, Grover RF, Blount SG (1966) Coronary vascular development in response to increased right ventricular pressure loads. Circ Res 18:634–640

Paulsen S, Vetner M, Hagerup LM (1975) Relationship between heart weight and the cross sectional area of the coronary ostia. Acta Pathol Microbiol Scand (Sect A) 83:429–432

Rabe D (1973) Kalibermessungen an den Herzkranzarterien und dem Sinus coronarius. Bas Res Card 68:356–379

Rafflenbeul W, Heim R, Dzuiba M, Henkel B, Lichtlen P (1975) Morphometrische Untersuchungen bei Koronarangiographie. Verh Dtsch Ges Kreislf 41:116–120

Restrepo C, Eggen DA, Guzman MA, Tejada C (1973) Postmortem dimensions of the coronary arteries in different geographic locations. Lab Invest 28:244–251

Rodriguez F, Robbins SL (1959) Capacity of human coronary arteries. A postmortem study. Circulation 19:570–578

Rössle R, Roulet F (1932) Maß und Zahl in der Pathologie. Berlin und Wien

Rose G, Prineas RJ, Mitchell JRA (1967) Myocardial infarction and the intrinsic calibre of the coronary arteries. Br. Heart J 29:548–552

Sagebiel H (1935) Über die Blutversorgung des alternden Herzens. Virchows Arch [Pathol Anat] 294:147–158

Schoenmackers J (1948) Zur quantitativen Morphologie der Herzkranzschlagadern. Z Kreislf 37:617–623
Stelmasiak KM, Osemlak J (1972) Relations of the coronary arteries and areas of the heart supplied by them in man. Folia Morphol (Warsz) 31:515–526
Stevenson JAF, Feleki V, Rechnitzer P, Beaton JR (1964) Effect of exercise on coronary tree size in the rat. Circ Res 15:265–269
Vogelberg K (1957) Die Lichtungsweite der Koronarostien an normalen und hypertrophen Herzen. Z Kreislauff 46:101–115
Wilens SL, Plair CM, Henderson D (1966) Size of the major epicardial coronary arteries at necropsy. JAMA 198:1325–1329
Wilsons J, Adams CWM, Brander WL (1978) The antiocclusive effect of coronary dilatation with age. Atherosclerosis 29:503–507
Woods JD (1961) Relative ischaemia in the hypertrophied heart. Lancet, 696–698

Accepted September 1, 1981