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Hypoplastic Aortic Arch Morphology Pertinent to Growth After Surgical Correction of Aortic Coarctation

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Background. Whether a hypoplastic transverse arch will grow after successful coarctectomy remains controversial.

Methods. We studied 15 coarctation specimens with hypoplastic transverse arch. Eight patients were less than 1 month old and 7 were between 1 and 3 months. The diameter and length of the various segments of the aortic arch were measured. The number of elastin lamellae was determined histologically. Collagen density was quantified with a microdensitophotometer. Using immunohistochemistry, we determined α -actin-positive smooth muscle cells in the media of the ascending aorta and the hypoplastic transverse arch.

Results. Despite a hypoplastic transverse arch, the ascending and descending aorta grew. The absolute num-

ber of elastin lamellae in the hypoplastic transverse arch was low, but when expressed as a ratio versus its diameter, this number was high ($p < 0.05$). Collagen density showed high absolute values in the descending aorta. In the older group, 4 of 7 showed no staining for α -actin in the hypoplastic transverse arch, whereas under 1 month of age, only 2 of 8 cases were negative.

Conclusions. The hypoplastic transverse arch is characterized by a relatively high number of elastin lamellae. Fewer α -actin-positive cells in the hypoplastic transverse arch occur in older specimens, which could indicate a diminished potential growth.

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The question of whether the hypoplastic transverse arch will grow after successful relief of an associated coarctation remains controversial. It appears that in some patients adequate growth can be obtained, but in others this is not the case [1]. In recent years, extended end-to-end anastomosis has been promoted as a surgical option for hypoplastic transverse arch, with or without coarctation of the aorta [2, 3]. The indication for this procedure, however, remains controversial [4, 5]. It is clear that growth of the hypoplastic segment depends on an adequate coarctectomy and on coexisting cardiac anomalies, if present. In addition, the morphology of the hypoplastic segment at the time of operation may play a role. It has been reported that the hypoplastic segment contains fewer elastin lamellae than the comparable normal aortic arch segment [6]. The functional importance of this observation remains as yet hypothetical, in particular because it has not been put in the perspective of other potential indices of growth, such as the presence or absence of smooth muscle cells, the collagen density, and the relation of these items compared with other segments of the aorta.

We have examined the morphologic characteristics of the thoracic aorta, taking into account dimensions as well

as histologic features, in specimens with tubular hypoplasia of the aortic arch.

Material and Methods

Definitions

The aortic arch is divided into three parts: the proximal transverse arch, the distal transverse arch, and the aortic isthmus (Fig 1). We have applied the definitions of hypoplasia set by Moulaert and colleagues [7], which are based on measurements from autopsy specimens. The proximal transverse arch was thus considered hypoplastic when the external diameter was 60% or less of that of the ascending aorta. For the distal transverse arch and the aortic isthmus, these figures were 50% or less and 40% or less, respectively. A hypoplastic segment was defined as tubular hypoplasia when its length was 5 mm or more.

Heart Specimens

Fifteen specimens with some type of tubular hypoplasia of the transverse arch were obtained from mature neonates and infants. They ranged from 1 day to 3 months of age at the time of death. A division was made into cases less than 1 month of age ($n = 8$) and cases between 1 and 3 months of age ($n = 7$). All specimens had associated coarctation of the aorta. Other associated intracardiac abnormalities are shown in Table 1.

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Fig 1. Diagram of the thoracic aorta with hypoplastic arch segments and the sites of measurements (dotted lines between arrowheads). (Dist. TA = distal transverse arch; ist = aortic isthmus; prox. TA = proximal transverse arch.)

All specimens were obtained from the Cardiovascular Registry, and all had been fixed in 4% formalin for a considerable length of time.

Gross Morphology

The external diameter of the different segments was measured in the middle, as indicated in Figure 1. The diameter of the descending thoracic aorta was measured 2.5 cm distal to the insertion of the arterial duct, and the aortic arch branches were measured 5 mm distal from their origin (see Fig 1).

To compensate for age and other developmental effects, we divided the diameter of each segment by that of the descending thoracic aorta and expressed it as a ratio. The length (to the nearest 0.5 mm) was measured for the proximal transverse arch, the distal transverse arch, and the aortic isthmus (see Fig 1).

Histology

Cross sections were taken from the ascending aorta, the distal transverse arch, both the right and left subclavian arteries, and the descending aorta at the sites where the measurements had been taken. The site of coarctation was not included (see Fig 1). The rings of tissue were routinely processed, embedded in paraffin, and cut at 5 μ m thickness. They were stained with hematoxylin and eosin, an elastin tissue stain, and the picrosirius red F3BA stain.

The number of medial elastin lamellae was counted at two opposing sites. The average of the two counts was calculated and considered to represent the number of elastin lamellae. To compensate for age and other developmental effects, the calculated number of elastin lamellae for each segment was divided by that of the descend-

Table 1. Relevant Data Regarding the Heart Specimens and the Distal Transverse Arch for Group 1 (Less Than 1 Month of Age) and Group 2 (More Than 1 to 3 Months)

Case No.	Age	Sex	Major Cardiac Anomalies	LVOTO	Size of Distal Transverse Arch (mm)		No. of Elastin Lamellae	Collagen Density	Smooth Muscle Cell α -Actin
					Diameter	Length			
Group 1									
1	1 day	M	LV hypoplasia	...	2.5	5.5	26	36.8	-
2	5 day	M	LV hypoplasia	BAV	3.0	5.0	34	31.5	+
3	8 day	F	DILV	...	2.5	7.0	17	28.8	+
4	11 day	M	DILV	...	3.0	5.5	26	26.3	-
5	8 day	M	LV hypoplasia	BAV	4.0	8.0	44	29.1	++
6	1 day	F	LV hypoplasia	...	2.5	9.5	24	27.0	+
7	5 day	M	DILV	...	3.0	5.5	27	25.7	$\pm$
8	7 day	M	TGA, VSD	...	4.0	5.5	35	33.2	++
Group 2									
9	1 mo	F	...	SAS, BAV	5.0	8.0	33	25.7	+
10	2 mo	M	VSD	...	3.5	14.5	27	45.3	-
11	1 mo	M	DILV	...	3.5	11.5	22	27.6	-
12	1 mo	M	DILV	...	3.0	6.0	31	35.6	+
13	3 mo	M	DILV	...	3.0	6.5	23	23.1	+
14	1 mo	M	VSD	SAS	3.5	11.0	27	35.3	-
15	3 mo	F	DORV	...	3.5	12.0	29	22.1	-

BAV = bicuspid aortic valve; DILV = double-inlet left ventricle; DORV = double-outlet right ventricle; LV hypoplasia = small left ventricle with the ascending aorta more than 5.5 mm in diameter; LVOTO = left ventricular outflow tract obstruction; SAS = subaortic stenosis; TGA = transposition of the great arteries; VSD = ventricular septal defect; ++ = almost all cells positive; + = approximately half of cells positive; $\pm$ = a few cells positive; - = negative.

Table 2. Morphometry of the Aorta and Main Branches in the Two Age Groups^a

Measurement	Group 1 (< 1 mo)	Group 2 (1 mo to ≤ 3 mo)	<i>p</i> Values
External diameter			
Ascending aorta	6.8 ± 0.9 (1.01 ± 0.13)	8.4 ± 1.1 (1.10 ± 0.11)	0.005 (0.161)
Brachiocephalic artery	5.5 ± 0.8 (0.82 ± 0.12)	5.4 ± 0.4 (0.71 ± 0.08)	0.659 (0.049)
Right subclavian artery	3.1 ± 0.7 (0.61 ± 0.10)	4.1 ± 0.5 (0.53 ± 0.06)	0.977 (0.123)
Right common carotid artery	4.0 ± 0.8 (0.60 ± 0.13)	4.3 ± 0.3 (0.54 ± 0.08)	0.458 (0.312)
Proximal transverse arch	5.1 ± 1.5 (0.74 ± 0.17)	5.9 ± 0.9 (0.78 ± 0.10)	0.205 (0.670)
Left common carotid artery	3.8 ± 0.6 (0.57 ± 0.11)	4.1 ± 0.5 (0.54 ± 0.06)	0.260 (0.555)
Distal transverse arch	3.1 ± 0.6 (0.46 ± 0.10)	3.6 ± 0.7 (0.47 ± 0.08)	0.152 (0.790)
Left subclavian artery	3.5 ± 0.6 (0.50 ± 0.09)	3.9 ± 0.4 (0.50 ± 0.06)	0.259 (0.978)
Aortic isthmus	3.8 ± 0.7 (0.55 ± 0.09)	3.4 ± 0.9 (0.44 ± 0.12)	0.385 (0.099)
Descending aorta	6.8 ± 0.8	7.6 ± 0.5	0.023
Length			
Proximal transverse arch	1.9 ± 0.8	1.9 ± 1.3	0.926
Distal transverse arch	6.4 ± 1.6	9.9 ± 3.2	0.016
Aortic isthmus	2.6 ± 0.9	2.7 ± 1.5	0.874

^a Results are expressed as mean value ± standard deviation, together with *p* values. The figures in parentheses refer to the mean value ± standard deviation of the external diameter divided by that of the descending aorta.

ing aorta and expressed as a ratio. In addition, the calculated number of elastin lamellae was divided by the diameter for each segment and also expressed as a ratio.

Collagen Density

The amount of collagen was quantified using a microdensitophotometric method after staining the sections with picosirius red F3BA [8]. A reference section with a known value was taken as a control for each batch. The measurements were performed at 20 frames in each section, covering the middle part of the aortic media. The average obtained was considered the collagen density. The values were then expressed as a percentage of total protein in the media.

Immunocytochemistry

Sections from the ascending aorta and the hypoplastic segment were stained immunocytochemically with a monoclonal antibody for human smooth muscle α -actin (DAKO-smooth muscle actin, 1A4; DAKO Corporation, Carpinteria, CA).

Statistical Analysis

Statistical analysis was performed using Student's *t* test or analysis of variance which was suitable for analysis. The

results were expressed as mean ± standard deviation. A *p* value of less than 0.05 was considered significant.

Results

Morphologic Features

All cases showed tubular hypoplasia of the distal transverse arch. Associated hypoplasia of the proximal transverse arch was present in 2 specimens, and in 3 other cases the aortic isthmus was hypoplastic also.

The morphometric data are summarized in Table 2. The diameters of the ascending and descending aorta in specimens of 1 month of age or older were significantly larger than those in the ones less than 1 month of age (*p* < 0.01 and *p* < 0.05, respectively). There were no significant changes in other segments. The hypoplastic distal transverse arch was significantly longer in the older group than in cases of less than 1 month (*p* < 0.05). The ratio of the diameter of the various segments, divided by that of the descending aorta, changed only in the brachiocephalic artery (*p* < 0.05), where it was decreased (see Table 2).

Histologic Features

Between the age groups, there were no changes in either the absolute number of elastin lamellae or the ratios obtained by dividing the number of elastin lamellae by that of the descending aorta (Table 3). The ratios obtained by dividing the number of elastin lamellae by the diameter of the corresponding segments decreased significantly in the distal transverse arch (Table 4); none of the other segments had a significant change. The distal transverse arch had a significantly larger value of this ratio than any other segment in the younger group or any other segment but the right subclavian artery in the older group. The left subclavian artery otherwise had a significantly smaller value than any other segment throughout the observed period.

Collagen Density

The collagen density showed no significant changes between the age groups. The descending aorta had a greater

Table 3. Absolute Number of Elastin Lamellae^a

Vessel	Group 1 (< 1 mo)	Group 2 (1 mo to ≤ 3 mo)	<i>p</i> Values
Ascending aorta	48.3 ± 7.7 (1.08 ± 0.25)	51.9 ± 6.5 (1.13 ± 0.17)	0.348 (0.663)
Right subclavian artery	25.0 ± 5.3 (0.55 ± 0.10)	27.6 ± 7.8 (0.60 ± 0.14)	0.465 (0.479)
Distal transverse arch	29.1 ± 8.3 (0.65 ± 0.20)	27.4 ± 4.0 (0.60 ± 0.11)	0.630 (0.590)
Left subclavian artery	17.8 ± 5.5 (0.39 ± 0.12)	15.8 ± 1.6 (0.35 ± 0.04)	0.446 (0.479)
Descending aorta	45.3 ± 5.8	46.0 ± 4.7	0.789

^a Results are expressed as mean ± standard deviation and *p* values for both age groups. The figures in parentheses refer to the mean ± standard deviation of the ratio of the number of elastin lamellae divided by that of the descending aorta.

Table 4. Ratios Obtained by Dividing the Number of Elastin Lamellae by the Diameter of the Corresponding Segment^a

Vessel	Group 1 (< 1 mo)	Group 2 (1 mo to ≤ 3 mo)	<i>p</i> Values
Ascending aorta	7.17 ± 0.83	6.22 ± 0.97	0.061
Right subclavian artery	6.54 ± 1.38	6.87 ± 2.20	0.731
Distal transverse arch	9.44 ± 1.47^b	7.80 ± 1.31^c	0.040
Left subclavian artery	5.06 ± 1.05^d	4.19 ± 0.57^d	0.134
Descending aorta	6.82 ± 1.39	6.02 ± 0.47	0.172

^a Results are expressed as mean $\pm$ standard deviation and *p* values. ^b Significant differences ($p < 0.05$) with ascending aorta, right and left subclavian artery, and descending aorta. ^c Significant differences ($p < 0.05$) with ascending aorta, left subclavian artery, and descending aorta. ^d Significant differences ($p < 0.05$) with ascending aorta, right subclavian artery, distal transverse arch, and descending aorta.

density of collagen than both the ascending aorta and the distal transverse arch in younger specimens, compared with the ascending aorta in older specimens (Table 5).

Immunocytochemical Features

Immunocytochemical staining revealed positive smooth muscle α -actin cells in the ascending aorta in all cases but 1 (case 11). In the distal transverse arch, α -actin was absent in 2 of 8 cases under 1 month of age and in 4 of 7 cases in the older group (Fig 2). The latter cases all had a significantly longer distal transverse arch than the cases from the same age group but with positive staining for α -actin ($p < 0.05$) (see Table 1).

Comment

This study reveals that the hypoplastic transverse arch is not simply a miniature of the corresponding segment of the normal aortic arch. It has been reported that the hypoplastic segment has a lesser number of elastin lamellae than normal [6] and that the collagen density in the media proximal and distal to a coarctation also differs

Table 5. Collagen Density^a

Vessel	Group 1 (< 1 mo)	Group 2 (1 mo to ≤ 3 mo)	<i>p</i> Values
Ascending aorta	30.7 ± 5.8	29.8 ± 4.7	0.656
Distal transverse arch	29.8 ± 3.83	30.7 ± 8.4	0.798
Descending aorta	40.7 ± 3.0^b	37.5 ± 4.4^c	0.121

^a Results are expressed as mean $\pm$ standard deviation, as a percentage of total protein, and *p* values. ^b Significant differences ($p < 0.05$) with ascending aorta and distal transverse arch. ^c Significant differences ($p < 0.05$) with ascending aorta.

[9]. However, we are not aware of any study correlating morphometric data of the hypoplastic segment with its histologic features. The results of this study are interpreted in light of the results obtained in our previous study of growth characteristics of normal aortas [10].

The present study confirms that the hypoplastic segment has a significantly lower number of elastin lamellae than normal ($p < 0.02$) [10]. However, the ratio obtained by dividing the number of elastin lamellae by the diameter is significantly higher than normal ($p < 0.02$). In other words, this segment has only a few elastin lamellae, but in relation to the diameter, it has a high number of lamellae. This in our opinion is characteristic of tubular hypoplasia of the aortic arch. The possibility exists that the hypoplastic segment received a relatively large volume of blood during early gestation, which may have diminished gradually because of progression of the coarctation lesion. This possibility is based on the observation of Allan and co-workers [11], using fetal echocardiography from 18 weeks' gestation onward, that the coarctation gradually progressed and eventually also produced aortic arch hypoplasia.

It is important to know whether the hypoplastic segment has the potential to grow. In some surgical procedures, the hypoplastic segment is not taken into further consideration, and simple resection of the coarctation

Fig 2. Immunocytochemical staining for smooth muscle α -actin in the distal transverse aortic arch. (A) Positive staining in the media between elastin lamellae (case 8; 7 days). (B) Negative staining of cells in the media, while the vasa vasorum stains positive (case 11; 1 month). (1A4 stain; A, $\times 115$; B, $\times 87$; both before 38% reduction.)

with end-to-end anastomosis is performed [4]. Other procedures are tailored in such a way that the impact of the hypoplastic segment is minimized, eg, by performing an extended end-to-end anastomosis. In this operation, the hypoplastic segment is incised and reconstructed to form the roof of the new aortic arch [3]. The indication for the latter procedure, however, varies among centers, but usually relates to the ratio obtained by dividing the diameter of the hypoplastic transverse arch by that of either the ascending aorta or the descending aorta. Some would consider a ratio of 0.5 as an indication to perform an extended operation, whereas others take a ratio of less than 0.25 [5]. However, it is of interest that neither one of these approaches considers the length of the hypoplastic segment [12]. This is surprising because length has an effect on the pressure gradient, even after coarctectomy [13]. Hence, one may speculate that adequate growth after "simple" end-to-end anastomosis is achieved only in cases with a short hypoplastic segment. Recently, a 6-month follow-up with good results has been reported after end-to-end anastomosis, but no mention was made of the length of the hypoplastic segment [4].

We included length in our study and have revealed some findings that may bear on the problem. First, the hypoplastic segment was longer in specimens of patients over 1 month of age than in those less than 1 month. Second, the older group contained a relatively large number (4 of 7) without α -actin-positive cells in the media, which indicates either absence of smooth muscle cells or a change in phenotype. In these cases, moreover, the hypoplastic segment was significantly ($p < 0.05$) longer than in the remaining cases with positive staining. At the same time, we also found that in the young age group, 2 cases (cases 1 and 4) were negative for α -actin. Nevertheless, this observation is potentially important because in the fetal aorta, smooth muscle α -actin increases and smooth muscle β -actin decreases with gestational age [14]. This change is interpreted as a differentiation phenomenon in which smooth muscle cells gradually transform from the synthetic state (smooth muscle β -actin positive) to the contractile state (smooth muscle α -actin positive). This could indicate, therefore, that the absence of staining with the monoclonal marker for smooth muscle α -actin relates to the state of differentiation of the cells, rather than to an absence of cells. In fact, routine staining with hematoxylin and eosin suggests the presence of smooth muscle cells within the media in all instances. The phenotypic characteristics of these smooth muscle cells are important because the synthetic cells are the ones that are capable of proliferation and production of extracellular matrix components. In other words, this is the type of cell one may anticipate to be actively involved in a process of growth.

An additional feature, albeit unrelated to length, is the fact that once we compared collagen density of the media of the hypoplastic segment with previously obtained data from normal aortas [10], the hypoplastic segment had significantly more collagen than normal. This feature is already evident at the time of birth. The ascending aorta

also presents a significantly higher collagen density than normal, although this becomes clear only after 1 month of age. Nevertheless, an indication that morphologic changes occur rapidly, affecting other parts of the thoracic aorta than only the hypoplastic segment. These morphologic changes, moreover, have potential functional significance in having a negative effect on the distensibility of the aorta.

The present study thus documents that growth abnormalities in the thoracic aorta with a hypoplastic arch segment are not restricted to the area with tubular hypoplasia. It seems likely that these differences also relate to the hemodynamic abnormalities created by the obstructed arch. From a morphologic point of view, this study supports the concept of early coarctectomy soon after birth, even in neonates without overt heart failure.

During this study, Dr Machii was a Research Fellow from the Kitasato University, Faculty of Medicine, Kanagawa, Japan.

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