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Quantitative morphology of the left subclavian artery in human fetuses

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ABSTRACT

Purpose: The present study was performed to compile normative data for dimensions of the left subclavian artery at varying gestational age.

Material and Methods: Using anatomical dissection, digital image analysis (Leica Q Win Pro 16 system) and statistical analysis (ANOVA, regression analysis) a range of measurements (length, original external diameter, volume) for the left subclavian artery in 128 spontaneously aborted human fetuses aged 15–34 weeks was examined.

Results: No significant gender differences were found ($P>0.05$). The length ranged from 4.62 ± 0.49 to 12.28 ± 1.25 mm, according to the linear function $y = -2.1482 + 0.4302 x \pm 0.9972$ ($r = 0.93$; $P<0.001$). The original external diameter increased from 0.68 ± 0.16 to 2.89 ± 0.29 mm, according to the linear model $y = -1.2169 + 0.1233 x \pm 0.2389$ ($r = 0.95$; $P<0.001$). The left subclavian artery-to-aortic root diameter ratio increased from 0.337 ± 0.064 to 0.423 ± 0.103. Distance between the left common carotid and left subclavian arteries increased from 0.57 ± 0.17 to 3.92 ± 0.91 mm. Aortic arch diameter to distance between the left common carotid and left subclavian arteries decreased with advanced fetal age, from 2.82 ± 0.51 to 1.56 ± 0.27. The volume ranged from 1.77 ± 0.89 to 80.60 ± 22.18 mm^3, in accordance with the quadratic function $y = 76.0 - 8.956 x + 0.031 x^2 \pm 10.945$ ($R^2 = 0.85$).

Conclusions: The developmental dynamic of the length and diameter of the left subclavian artery follows a linear regression, whereas its volumetric dynamic follows a quadratic regression. The ratio of the aortic arch diameter to the distance between the left common carotid and left subclavian arteries has clinical application in the early recognition of aortic coarctation.

Key words: left subclavian artery, measurements, length, original external diameter, volume, regression analysis

INTRODUCTION

The left subclavian artery is the most stable branch of the aortic arch. According to Anson [1], in 98.4% of individuals it constitutes the last branch of the left aortic arch. Occasionally, it arises from the left brachiocephalic trunk of the left (1.2%) or right (0.1%) aortic arch, and from the single arterial trunk (0.3%). Kozielec [2] and Yeh et al. [3] described isolation of the left subclavian artery, in which it does not communicate with the aortic arch but instead is connected to the pulmonary trunk by the ductus arteriosus. In these cases the subclavian steal syndrome from the vertebrobasilar system into the pulmonary trunk and left subclavian artery is usually persistent. The left subclavian artery ascends into the neck, arches laterally to the medial border of the scalenus anterior muscle (first part), courses behind the scalenus anterior muscle (second part), and finally it descends laterally from the lateral margin of the scalenus anterior muscle to the outer border of the first rib (third part), where it becomes the axillary artery.

Measurements of the left subclavian artery, concerning its diameter only, have been conducted previously on limited human material [4,5]. To date, the length and volume of the left subclavian artery have not been reported, either prenatally or postnatally.

Our objectives were to investigate:

- the normal values for the length, original external diameter, and volume of the left subclavian artery at varying gestational ages,

- the growth curves for normal development of the parameters studied,
- the relative growth of the original external diameter of the left subclavian artery in relation to the aortic root diameter,
- the distance between the left common carotid and left subclavian arteries,
- aortic arch diameter to distance between the left common carotid and left subclavian arteries,
- possible gender differences.

MATERIAL AND METHODS

The examinations were carried out on 128 human fetuses of both sexes (63 male, 65 female) from spontaneous abortions or stillbirths, cardiovascular abnormalities having been excluded at necropsy. The fetal age ranged from 15 to 34 weeks of gestation. The present study was approved by the University Research Ethics Committee (KB/217/2006). Developmental age was determined on the basis of the following criteria: 1) gestational age based on crown-to-rump length [6], 2) known date of the beginning of the last normal menstrual period, and 3) in some cases corrections regarding fetal age were established by measurement of the humeral and femoral bones using USG equipment [7]. Fetuses were grouped into six monthly cohorts, corresponding to the 4^{th} to 9^{th} months of gestation. The arterial bed was filled with white latex LBS 3060, without over-distention of perfused vessels, through a Stericath catheter (diameter 0.5–1.0 mm), which was introduced by lumbar access into the abdominal aorta. The fetal arteries were filled under a controlled pressure of 50–60 mm Hg, using a syringe infusion pump SEP 11S. All specimens were immersed in 10% neutral formalin solution for 4–24 months for preservation. Dissection of the aortic arch and its branches was performed according to standard autopsy techniques, under 10-fold magnification using a stereoscope with Huygens ocular. In each fetus, the left subclavian artery *in situ* with the millimeter scale was placed perpendicular to the optical lens axis, then recorded using a Nikon Coolpix 8400 camera, and digitalized to JPEG images. Next, digital pictures of the left subclavian artery underwent quantitative analysis using Leica QWin Pro 16 (Cambridge) digital image analysis system, which automatically estimated length, original external diameter and volume of the marked artery. Automatic measurements of the parameters examined were derived by assuming that the filled arteries were circular in cross section and therefore constituted a flexible cylinder.

For each fetus the eight following measurements and calculations were performed:

1. largest original external diameter of the aortic root (mm), at the level of the aortic valve annulus,
2. external diameter of the aortic arch (mm), distal to the left common carotid origin (i.e. transverse aortic diameter),

3–5. length, original external diameter and volume of the left subclavian artery,

6. relative diameter of the left subclavian artery, expressed as the diameter ratio of the left subclavian artery to the aortic root,
7. distance between the left common carotid and left subclavian arteries,
8. aortic arch diameter to distance between the left common carotid and left subclavian arteries.

The length, original external diameter and volume of the left subclavian artery were correlated to fetal age so as to establish their growth. Finally, the results obtained were evaluated by the one-way ANOVA test for unpaired data and post-hoc RIR Tukey test. Regression analysis was used to derive the line of best fit for the length, original external diameter and volume against gestational age. Correlation coefficients (r) between length or original external diameter and fetal age, and coefficient of determination (R^2) between volume and fetal age, were estimated. Because of the different size of specimens, we calculated the ratio between the original external diameter of the left subclavian artery and that of the aortic root (the left subclavian artery-to-aortic root diameter ratio). Moreover, we calculated the aortic arch diameter to distance between the left common carotid and left subclavian arteries.

RESULTS

The native pictures of the left subclavian artery in human fetuses are presented in *Fig. 1–3*. The statistical analysis of the examined features of the left subclavian artery did not show gender differences ($P>0.05$). Hence the morphometric values obtained, without regard to sex, are presented in *Tab. 2*. Both the length and original external diameter of the left subclavian artery revealed a proportional increase in values with advanced fetal age. The values of the length of the left subclavian artery ranged from 4.62 ± 0.49 mm for the 4-month group to 12.28 ± 1.25 mm for the 9^{th} month of gestation. The length of the left subclavian artery in relation to fetal age in weeks increased according to the linear function $y = -2.1482 + 0.4302x \pm 0.9972$ ($r = 0.93$; $P<0.001$) (*Fig. 4*). The values of the original external diameter of the left subclavian artery ranged from 0.68 ± 0.16 to 2.89 ± 0.29 mm for the 4-month and 9-month groups respectively. The original external diameter of the left subclavian artery was dependent on fetal age in weeks according to the linear function $y = -1.2169 + 0.1233x \pm 0.2389$ ($r = 0.95$; $P<0.001$) (*Fig. 5*).

Parallel to the absolute increase in the values of the original external diameter of the left subclavian artery, its relative diameter increased with advanced fetal age (*Tab. 3*). In the examined age range the left subclavian artery-to-aortic root diameter ratio increased from 0.337 ± 0.064 to 0.423 ± 0.103. The significant increase in the ratio was observed between the 5- and 6-month groups, only ($P<0.05$). During the study period, the distance between the left common carotid and left subclavian arteries ranged from 0.57 ± 0.17

Figure 1. **Aortic arch branching in a male fetus aged 22 weeks: 1-ascending aorta, 2-aortic arch, 3-left subclavian artery 4-brachiocephalic trunk, 5-left common carotid artery, 6-left vertebral artery, 7-thyrocervical trunk, 8-internal thoracic artery.**

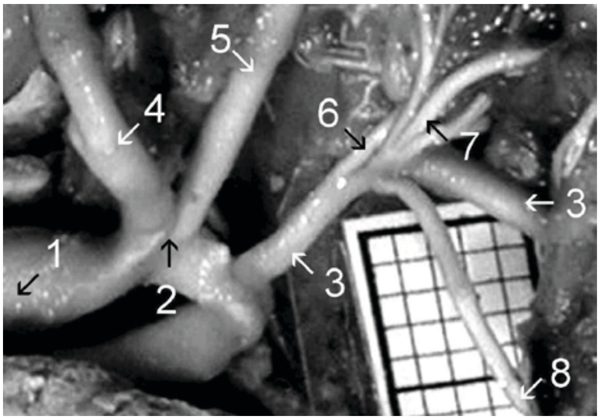
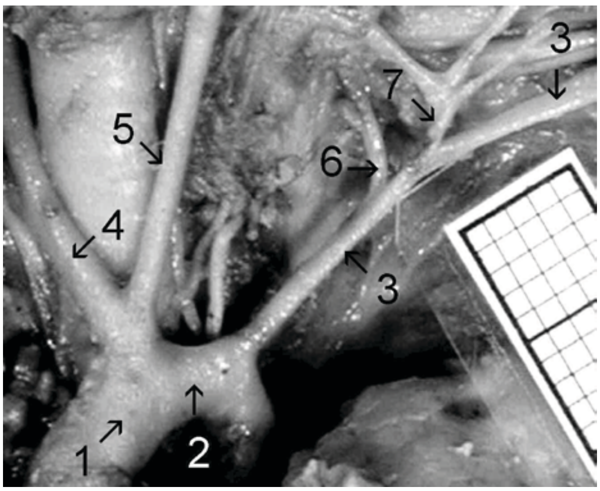


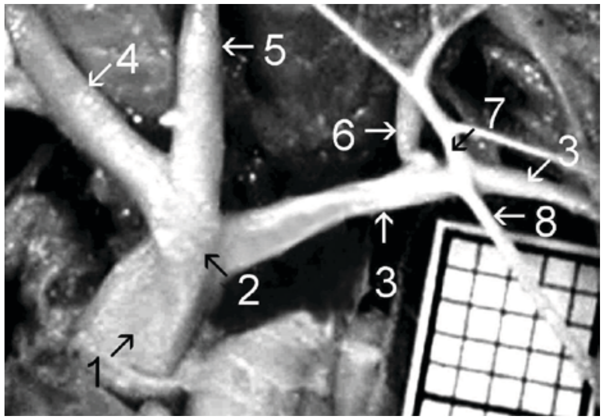
Figure 3. **Aortic arch branching in a female fetus aged 30 weeks: 1-ascending aorta, 2-aortic arch, 3-left subclavian artery 4-brachiocephalic trunk, 5-left common carotid artery, 6-left vertebral artery, 7-thyrocervical trunk.**



to 3.92 ± 0.91 mm (P<0.001). In turn, aortic arch diameter to distance between the left common carotid and left subclavian arteries decreased with advanced fetal age, from 2.82 ± 0.51 to 1.56 ± 0.27. However, a significant increase was observed only between the 4 and 5 (P<0.001), 6 and 7 (P<0.05), and 8 and 9 (P<0.05) month groups.

The values of the volume of the left subclavian artery ranged from 1.77 ± 0.89 mm^3 for the 4th month to 80.60 ± 22.18 mm^3 for the 9th month of gestation. The volumetric growth of the left subclavian artery generated the quadratic function $y = 76.0 - 8.956\,x + 0.031\,x^2 \pm 10.945$ (*Fig. 6*). The coefficient of determination between volume and fetal age was statistically significant (P<0.001) and attained the value $R^2 = 0.85$.

Figure 2. **Aortic arch branching in a female fetus aged 23 weeks: 1-ascending aorta, 2-aortic arch, 3-left subclavian artery 4-brachiocephalic trunk, 5-left common carotid artery, 6-left vertebral artery, 7-thyrocervical trunk, 8-internal thoracic artery.**



DISCUSSION

Reference data for dimensions of the left subclavian artery, as determined using both autopsy study and echocardiographic imaging, are scarce on human material. In this anatomical study, a Leica Q Win 16 Pro digital image analysis system was used to provide normal morphometric values for the left subclavian artery at gestational ages ranging from 15 to 34 weeks. A particular strength of this study is the large number of normal specimens used to generate the growth curves. The growth curves for the normal development of the left subclavian artery dimensions have not been previously reported in the professional literature. From the present data, growth of the length and original external diameter of the left subclavian artery appears to be linearly related to gestational age. Plots showing both the length and original external diameter of the left subclavian artery were modeled by the linear functions $y = -2.1482 + 0.4302\,x \pm 0.9972$ (r = 0.93; P<0.001) and $y = -1.2169 + 0.1233\,x \pm 0.2389$ (r = 0.95; P<0.001) respectively. Machii and Becker [5] showed an increase in external diameter of the left subclavian artery from 3.4±0.3 to 6.2±0.6 mm in 19 specimens aged 0–4 years. Morrow et al. [8] performed echocardiographic measurements of the internal diameter of the left subclavian artery in 14 neonates with isolated coarctation and in 14 normal control neonates. All neonates with coarctation demonstrated larger diameters (3.4 ± 0.4 mm) than in the control subjects (2.8 ± 0.5 mm) (P<0.001).

In the present study, the ratio of the left subclavian artery diameter to aortic root diameter showed an increasing trend throughout gestation. The left subclavian artery to aortic root diameter ratio increased from 0.337 ± 0.064 to 0.423 ± 0.103. However, it should be noted that a statistically significant increase in the ratio was found only between the 5-month and 6-month groups

Table 1. **Age, number and sex of fetuses studied.**

Fetal age		Crown-rump length (mm)				Number	Sex	
Months	Weeks(Hbd-life)	Mean	SD	Min.	Max.		male	female
4	15	89.4	6.1	85.0	92.0	10	5	5
	16	103.7	6.1	95.0	106.0	7	3	4
5	17	114.9	8.2	111.0	121.0	6	4	2
	18	129.3	6.6	124.0	134.0	8	3	5
	19	142.7	7.7	139.0	148.0	6	3	3
	20	155.3	5.8	153.0	161.0	4	1	3
6	21	167.1	4.7	165.0	173.0	3	2	1
	22	178.1	6.9	176.0	186.0	7	4	3
	23	192.3	6.3	187.0	196.0	9	4	5
	24	202.9	5.7	199.0	207.0	11	6	5
7	25	215.2	4.8	211.0	218.0	7	5	2
	26	224.7	5.2	220.0	227.0	7	4	3
	27	234.1	4.3	231.0	237.0	4	0	4
	28	244.2	5.1	240.0	246.0	5	2	3
8	29	253.8	4.5	249.0	255.0	6	1	5
	30	262.7	3.1	260.0	264.0	6	5	1
	31	270.7	5.2	268.0	275.0	4	1	3
	32	281.4	3.7	279.0	284.0	5	4	1
9	33	290.3	6.1	286.0	293.0	9	4	5
	34	301.4	3.2	296.0	302.0	4	2	2
Total	128	63	65					

Table 2. **Block scheme of the statistical analysis of the absolute values of the left subclavian artery parameters.**

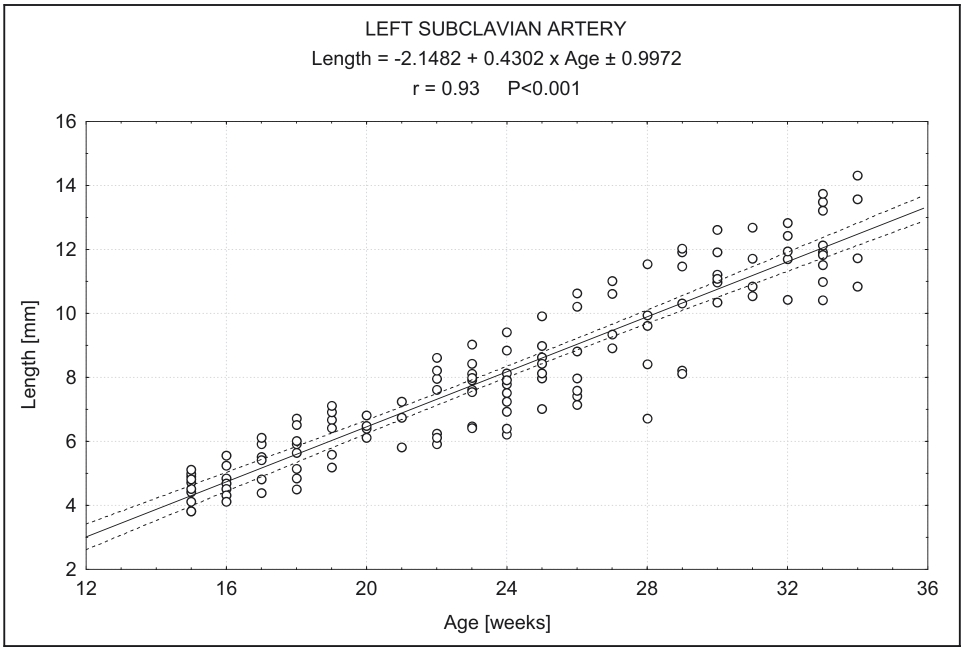
Fetal age [month]	n	Length [mm] (mean ± SD)	Original external diameter [mm] (mean ± SD)	Volume [mm^3] (mean ± SD)
4	7	4.62 ± 0.49 ↓ (P<0.01)	0.68 ± 0.16 ↓ (P<0.01)	1.77 ± 0.89 ↓ (P>0.05)
5	24	5.88 ± 0.78 ↓ (P<0.001)	1.07 ± 0.18 ↓ (P<0.001)	5.46 ± 2.28 ↓(P<0.05)
6	30	7.48 ± 0.97 ↓ (P<0.001)	1.60 ± 0.30 ↓ (P<0.001)	15.40 ± 6.20 ↓(P<0.01)
7	23	8.91 ± 1.35 ↓ (P<0.001)	2.01 ± 0.31 ↓ (P<0.001)	28.93 ± 12.28 ↓(P<0.001)
8	21	11.20 ± 1.27 ↓ (P<0.001)	2.52 ± 0.40 ↓ (P<0.05)	57.12 ± 21.39 ↓(P<0.001)
9	13	12.28 ± 1.25	2.89 ± 0.29	80.60 ± 22.18

(P<0.05). Therefore, our findings confirmed an increase in the relative diameter of the left subclavian artery with advanced fetal age. These results correspond to the observations of Machii and Becker [5], where the external diameter of the left subclavian artery divided by that of the descending aorta increased from 0.52 ± 0.06 to 0.64 ± 0.03 in specimens aged 0–4 years. As reported by Morrow et al. [8], the ratio of the left subclavian artery diameter to that of the descending aorta was 0.86 ± 0.13 for coarctation neonates versus 0.52 ± 0.10 for the control group. In our view, the increase of the relative diameter of the left subclavian artery resulted from the increased proportion of blood received by the brain stem and upper limbs with advanced fetal age. Rudolph and Heymann [9] held that on animal model (lambs) the growth of the arterial diameter is proportional to the amount of blood carried by them. Thus similar flow produces vessels of similar diameter. According to Morrow et al. [8], the diameters of the left subclavian artery, the left common carotid artery and the aortic arch were essentially equal in coarctation patients. In contrast, in the normal neonate the diameters of the left common carotid

Table 3. **Block scheme of the statistical analysis of the relative diameters of the left subclavian artery.**

Fetal age[month]	n	Aortic root diameter (mm) (mean ± SD)	Aortic arch diameter (mm) (mean ± SD)	Distance between the left common carotid and left subclavian arteries (mm)	Aortic arch diameter-to-the distance between the left common carotid and left subclavian arteries
4	17	2.02 ± 0.26 ↓ (P<0.001)	1.61 ± 0.24 ↓ (P<0.001)	0.337±0.064 ↓ (P>0.05)	2.82±0.51 ↓ (P<0.001)
5	24	2.94 ± 0.49 ↓ (P<0.001)	2.32 ± 0.45 ↓ (P<0.001)	0.364±0.075 ↓ (P<0.05)	2.10±0.43 ↓ (P>0.05)
6	30	3.96 ± 0.57 ↓ (P<0.001)	3.23 ± 0.45 ↓ (P<0.001)	0.404±0.087 ↓ (P>0.05)	2.08±0.46 ↓ (P<0.05)
7	23	4.91 ± 0.47 ↓ (P<0.001)	4.10 ± 0.42 ↓ (P<0.001)	0.409±0.095 ↓ (P>0.05)	1.81±0.37 ↓ (P>0.05)
8	21	6.11 ± 0.50 ↓ (P<0.01)	5.41 ± 0.47 ↓ (P<0.001)	0.412±0.098 ↓ (P>0.05)	1.78±0.32 ↓ (P>0.05)
9	13	6.84 ± 0.63	6.13 ± 0.49	0.423±0.103	1.56±0.27

Figure 4. **Regression line for the length (y) of the left subclavian artery versus fetal age (x); y = - 2.1482 + 0.4302 x ± 0.9972 (r = 0.93; P<0.001).**



and left subclavian arteries were approximately 50% of the aortic arch diameter.

Our findings demonstrated that the distance between the left common carotid and left subclavian arteries increased from 0.57 ± 0.17 mm for the 4-month group to 3.92 ± 0.91 mm for the 9-month group. According to some authors [8,10], this distance was longer in neonates with coarctation than in control neonates. The distance took the value 8.8 ± 2.3 mm in neonates with coarctation versus 3.9 ± 1.8 mm for control subjects (P<0.001) [8].

Our results showed that the ratio of the aortic arch diameter to the distance between the left common carotid and left subclavian arteries decreased with advanced fetal age from 2.82 ±0.51 to 1.56 ± 0.27. Dodge-Khatami et al. [11] proved that this parameter was significantly smaller in patients with coarctation. This ratio, which they propose as the carotid-subclavian artery index, is a simply noninvasive screening parameter which may be useful in unstable patients or in those with a patent ductus arteriosus, in which coarctaction may be overlooked.

In the material under examination the left subclavian artery volume increased from 1.77 ± 0.89 to 80.60 ± 22.18 mm^3. The regression equation for the volume of the left subclavian artery in mm^3 modeled as a function of gestational age in weeks was $y = 76.0 – 8.956 x + 0.031 x^2 ± 10.945$. This quadratic function was the best model for the volumetric growth of the left

Figure 5. **Regression line for the original external diameter (y) of the left subclavian artery versus fetal age (x); y = -1.2169 + 0.1233 x ± 0.2389 (r = 0.95; P<0.001).**

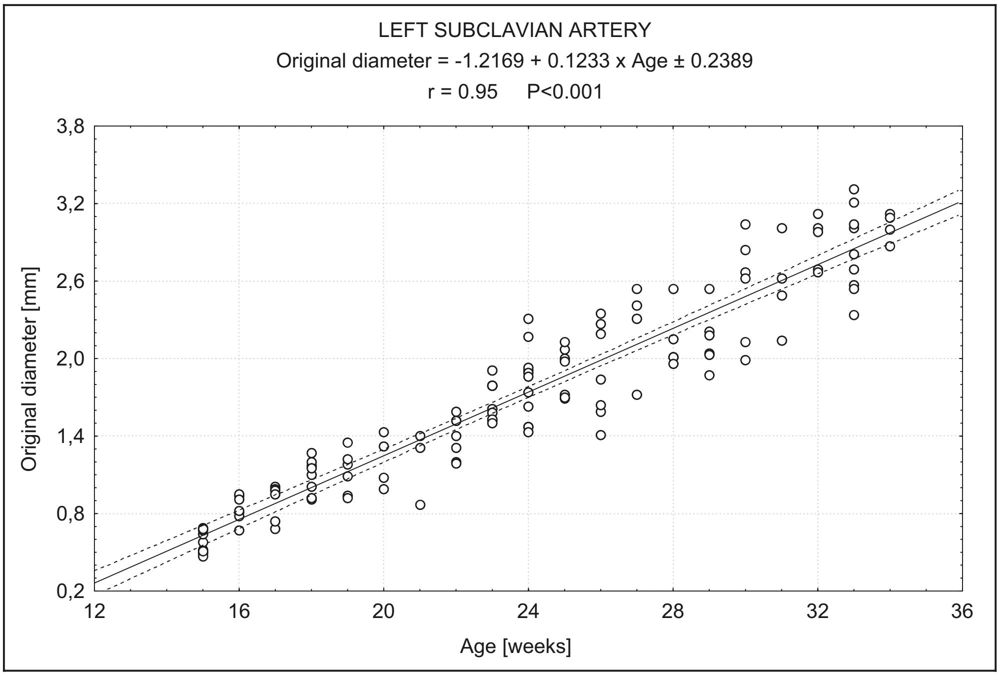
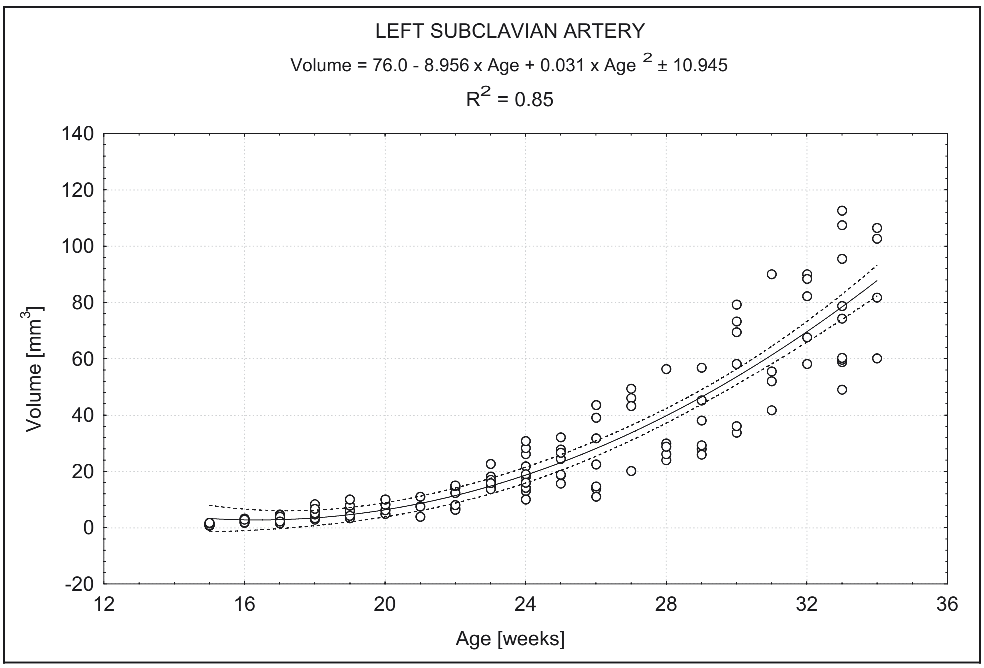


Figure 6. **Regression line for the volume (y) of the left subclavian artery versus fetal age (x); y = 76.0 – 8.956 x + 0.031 x^2 ± 10.945 (R^2 = 0.85)**



subclavian artery, because the coefficient of determination between volume and fetal age attained the value R^2 = 0.85.

A lack of statistically significant gender differences for the dimensions of the left subclavian artery was observed in this study. In this respect the present results are in close accordance with the author's previous studies concerning measurements of the dimensions of the aortic and great pulmonary arterial pathways in human fetuses [12–14]. Poutanen et al. [15] found slight differences in aortic measurements between the genders in children and young adults, they being greater in males than females. Nevertheless, the values were similar in both genders when indexed to BSA. In children, growth of the aortic root diameter has been found to be independent of gender [16,17]. Macchi et al. [4] stated that among the typical branches of the aortic arch, only the left subclavian artery showed gender differences, being larger in men. There was no statistically significant correlation between arterial caliber and either height or body weight.

CONCLUSIONS

1. The developmental dynamic of the length and diameter of the left subclavian artery follows a linear regression, whereas its volumetric dynamic follows a quadratic regression.
2. The relative diameter of the left subclavian artery increases with advanced gestational age.
3. The parameters examined provide morphometric reference information for future studies on this subject.
4. The ratio of the aortic arch diameter to the distance between the left common carotid and left subclavian arteries has clinical application in the early identification of aortic coarctation.

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