

Development of the cardiac venous system in prenatal human life

Research Article

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Received 2 November 2010; Accepted 16 November 2010

Abstract: The human coronary sinus is an evolutionary modification of the terminal part of the left sinus horn. Anatomically, the coronary sinus is a short, broad vessel that runs along the coronary groove situated on the diaphragmatic surface of the heart. This structure, which opens into the right atrium, collects blood from the great cardiac vein and from other veins of the heart as well. In this study, we assessed the growth and dimensions of the coronary sinus at the fourth and eighth months of fetal development from whole material received from the Nicolaus Copernicus University, Collegium Medicum, Department of Histology and Embryology in Bydgoszcz. A group of 219 specimens, 105 male and 114 female fetuses, presented no visible malformations or developmental abnormalities. The results of this study determined that the dimension of the coronary sinus during prenatal development is not sexually dimorphic. Furthermore, following a monthly period of rapid growth in length of this structure, there are no further increases in length after the six months gestation. Finally, we concluded that the dimensions of the coronary sinus obtained during autopsy are similar to those determined through intravital ultrasound examination. The diameter of the coronary sinus is the best parameter to monitoring the fetal age and the growing of the fetus. Accordingly, we suggest that the best way of estimate for proper blood drainage from heart veins is study of coronary sinus volume.

Keywords: Coronary sinus • Human development • Heart • Fetus

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1. Introduction

The epicardial venous network of the human body consists of two independent systems. The coronary sinus, a short, broad vein situated within the coronary groove, is the anatomical structure that collects almost 60% of the blood flowing from the heart. The remainder of this blood volume drains into the anterior cardiac veins and the minimal cardiac veins of the body. The coronary sinus opens into the right atrium and collects blood from the great cardiac vein, the posterior cardiac vein, the left atrial oblique vein (known also as the vein of Marshall), the middle cardiac vein, and the small cardiac vein of the heart [1-4]. Its importance is emphasised by

the description that coronary sinus “begins in the ostium of the right atrium and ends as the great cardiac vein” [5].

The coronary sinus, as a remnant of the embryonic left sinus horn, plays a crucial role in the development of the entire venous system of the heart [6-8]. Previous research initially indicated that the entire venous system originated from the coronary sinus. However, more recent work has demonstrated that the coronary sinus is merely the place where precursor endothelial cells initially undergo migration. Subsequently, these cells migrate into the myocardium where they become the actual precursor cells of the cardiac venous system. These cells essentially form venous canals, which then become connected to the coronary sinus [7,9].

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This developmental process has been shown to take place between days 33 and 41 of gestation [10,11]. Interestingly, in male embryos the process of cardiac vein formation occurs four to five days earlier than that in female embryos.

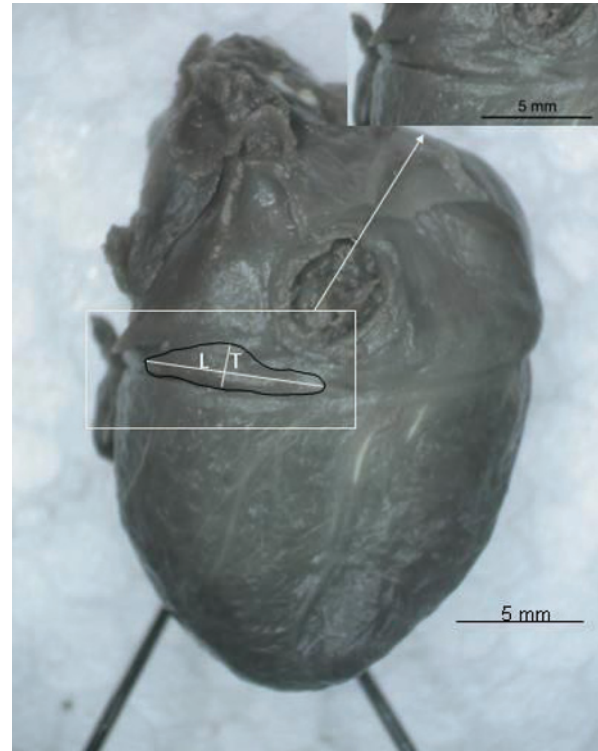
Coronary arteries are often studied in much more detail than the veins of the heart [11]. Recently, however, much research has been devoted to acquiring added information on the coronary sinus, in particular because the tissues that form the coronary sinus are the substrate for many types of supraventricular arrhythmias. The coronary sinus itself is the main target vessel for cardiac resynchronization therapy with pacing lead implantation. Current studies focus mostly on its microscopic structure and its specific electrical function [5,12,13]. The anatomy of this component is seldom given as much importance, and if so, usually only in the context of congenital malformations acquired during early embryogenesis [4,13]. To date, no studies have been published on the growth or sexual dimorphism of the coronary sinus during prenatal life, even though these factors could have an impact on its microscopic structure and its electrophysiological properties [14].

2. Material and Methods

We analyzed 219 human fetal specimens, 105 male and 114 female subjects from the fourth to eighth month of gestation. Whole material for this project was received from the Collegium Medicum, Nicolaus Copernicus University, Department of Histology and Embryology in Bydgoszcz. All fetal specimens had been conserved in a 9% formaldehyde solution for a period of over three months; only spontaneous abortuses of normal karyotype were collected for this work. None of the analyzed specimens demonstrated any visible malformations or developmental abnormalities upon close inspection. The fetal age was established by measurements of the length of the humeral and femoral bones. All specimens were categorized into monthly subgroups according to the determined morphological age. Random numbers were assigned to each fetus of each age group in the project.

The vessel bed was filled with latex LBS 3060 without distortion of the dimensions of the vessels, at an amount of approximately 15–30 mL, through a catheter that was introduced by dorsal access into the thoracic aorta. All measurements of parameters related to the coronary sinus were performed by two investigators who, with the aid of a binocular magnifying glass (magnify $\times 0.6$ – $\times 14$, MBS-9, Russia), used an electronic compass (definitude 0.01 mm, INCO, Poland) to collect all

Figure 1. Diaphragmatic surface of the prenatal human heart from 19 weeks old fetus. Measured parameters: the length of the coronary sinus at its greatest longitudinal dimension (L), the diameter at its greatest transverse dimension (T).



dimensions required to an accuracy of one hundredth of a millimeter. All measurements were done twice by each investigator for consistency and verification. The mean value of the two obtained values was included for further quantitative analysis. The following parameters were measured: the length of the coronary sinus at its greatest longitudinal dimension (L) (between the point of connection the great cardiac vein with the left atrial oblique vein (vein of Marshall) and the ostium to the right atrium); the diameter at its greatest transverse dimension (T); and the sum of the diameters of all the veins draining into the coronary sinus (Figure 1).

Statistical analysis was performed using the STATISTICA 8.0 software (StatSoft Polska). The developmental growth of morphometric parameters (length, diameter – transverse dimension) of the coronary sinus and diameters of the cardiac veins were statistically analyzed by regression analysis. The gender differences and differences between dimensions were analyzed using the Student's t-test for two mean independent variables. Differences were considered significant at $p \leq 0.05$.

Absolute increase (in mm) is the result of the subtraction of the dimension in the fixed month (A) and in the month before (A-1).

Table 1. Length of coronary sinus between IV-VIII months of prenatal human life. N - number, X – average, SD – standard deviation, test t-Student show gender differences.

fetal age (month)	N			X ± SD (mm)			test t (p value)
	all	male	female	all	male	female	
IV	14	5	9	5.07±1.34	4.87±1.25	5.13±1.35	0.48
V	70	32	38	5.62±1.37	5.33±1.32	5.88±1.42	0.268
VI	105	50	55	7.49±1.69	7.07±1.65	7.81±1.72	0.38
VII	18	12	6	8.41±1.54	8.01±1.47	9.21±1.68	0.187
VIII	12	6	6	10.02±1.85	9.65±1.62	10.34±1.92	0.252
all	219	105	114	6.85±1.52	6.54±1.49	7.16±1.59	0.21

Table 2. Diameter of coronary sinus between IV-VIII months of prenatal human life. N - number, X – average, SD – standard deviation, test t-Student show gender differences.

fetal age (month)	N			X + SD (mm)			test t (p value)
	all	male	female	all	male	female	
IV	14	5	9	1.67±0.34	1.75±0.32	1.65±0.35	0.424
V	70	32	38	1.93±0.49	1.87±0.48	1.98±0.5	0.353
VI	105	50	55	2.20±0.55	2.13±0.55	2.26±0.56	0.392
VII	18	12	6	2.51±0.47	2.45±0.46	2.63±0.49	0.470
VIII	12	6	6	2.92±0.6	2.82±0.58	2.98±0.61	0.327
all	219	105	114	2.12±0.51	2.07±0.50	2.17±0.52	0.258

Table 3. Proportions of diameter and the length of coronary sinus between IV-VIII months of prenatal human life (D/L). Test t-Student show gender differences.

fetal age (month)	D/L (%)			test t (p value)
	all	male	female	
IV	32.9	35.9	32.2	0.38
V	34.5	35.1	33.7	0.238
VI	29.4	30.1	28.9	0.123
VII	29.9	30.6	28.6	0.091
VIII	29.1	30.0	28.8	0.348
all	30.9	31.7	30.3	0.656

Relative (proportional) increase (RI) (in %) was calculated by:

$$RI_{[A - (A-1)]} = [A - (A-1)/A] \times 100\%$$

A - the dimension in the fixed month

A - 1 - the dimension in the month before

3. Results

Based on the measurements collected, it was noted that differences in the length of the coronary sinus within the study population were not statistically significant ($p=0.21$) (Table 1). The diameter of the coronary sinus showed no significant sexual dimorphism within our study population ($p=0.258$) or in the sub-analysis of particular age subgroups ($p>0.05$). However, a trend toward greater length and diameter of the coronary

sinus in female fetuses was noted in the measurements in all age subgroups (Table 2). The diameter to length ratio was $30.9\% \pm 4\%$ for the whole group; it did not differ significantly according to gender ($p>0.05$). This ratio was found to be greatest among the younger subjects and smallest among the older subjects (Table 3). The sum of the diameters of the veins draining into the coronary sinus showed no sexual dimorphism when assessed for the whole population or in any of the designated age subgroups (Table 4). The growth of the coronary sinus was analyzed in the consecutive monthly time periods between the fourth and the eighth months. We found that growth of the length of coronary sinus was most rapid between the fifth and sixth month (33.3% relative increase; Table 5), whereas in the following month the growth slowed significantly. The diameter of the coronary sinus increased at a fairly constant rate during the entire time period analyzed (Table 5). The diameter of the coronary sinus correlated well with the gestational age and increased slowly throughout gestation (diameter= 0.3 ± 0.09 month, $p=0.0001$). Similarly, the sum of the diameters of the veins draining into coronary sinus tended to grow much faster between the fifth and sixth months than in the seventh month, as did the length of the coronary sinus (Table 6). The length of the coronary sinus increased during pregnancy at an uneven rate, as did the total sum of the diameters of the cardiac veins that drain into the coronary sinus (Tables 5, 6). However, the length of the coronary sinus and the total sum of the diameters of the cardiac veins

Table 4. The total sum of the diameters of the cardiac veins that drain into the coronary sinus (the great cardiac vein, the posterior cardiac vein, the left atrial oblique vein, the middle cardiac vein and the small cardiac vein) shown in relation to the age of the subjects in the particular subgroups. N - number, X – average, SD – standard deviation, test t-Student show gender differences.

fetal age (month)	N			X ± SD (mm)			test t (p value)
	all	male	female	all	male	female	
IV	14	5	9	2.25±0.41	2.23±0.43	2.26±0.4	0.732
V	70	32	38	2.45±0.41	2.41±0.50	2.48±0.33	0.681
VI	105	50	55	3.16±0.81	3.12±0.83	3.19±0.79	0.744
VII	18	12	6	3.44±0.47	3.37±0.43	3.57±0.56	0.456
VIII	12	6	6	3.85±0.54	3.74±0.58	3.89±0.53	0.743
all	219	105	114	2.91±0.6	2.88±0.63	2.92±0.58	0.992

Table 5. The increases (absolute and proportional-relative) of the investigated linear features in fetal subjects of both sexes and the growth index determined based on the differences between consecutive age groups. X – average, N – number.

parameters	age(month)	N	X (mm)	absolute increase (mm)	relative (proportional) increase (%)
length of coronary sinus	IV	14	5.07	-	-
	V	70	5.62	0.55	9.8
	VI	105	7.49	1.87	33.3
	VII	18	8.41	0.92	10.9
	VIII	12	10.02	1.61	16.0
diameter of coronary sinus	IV	14	1.67	-	-
	V	70	1.93	0.26	13.5
	VI	105	2.20	0.27	13.9
	VII	18	2.51	0.31	14.0
	VIII	12	2.92	0.41	14.0

Table 6. The increases (absolute and proportional-relative) of the investigated linear features in fetal subjects of both sexes and the growth index determined based on the differences between consecutive age groups. X – average, N- number.

parameter	fetal age (month)	N	X (mm)	absolute increase (mm)	relative (proportional) increase (%)
total sum of the diameters of the cardiac veins	IV	14	2.25		
	V	70	2.45	0.20	8.2
	VI	105	3.16	0.71	28.9
	VII	18	3.44	0.28	08.9
	VIII	12	3.85	0.41	10.6

correlated well ($r=0.95$, $p<0.05$) (Table 7). The coronary sinus diameter was about 3 times smaller than its length, and the diameter-to-length ratio ($31\%\pm 5\%$) did not vary significantly through pregnancy ($p=0.15$).

4. Discussion

The coronary sinus is of great importance in modern diagnostic and therapeutic procedures. Its dimensions play important role not only in morphometric study but also in catheterization and implantation of electrode [4,5,12].

Studies in the literature have found a range of values for the dimensions of the coronary sinus. According to Bochenek and Reicher [15], the length of the coronary

sinus is in the range 30 to 50 mm and its diameter is approximately 10 mm. D'Cruz et al. [16,17] found a similar diameter, 8.27 ± 2.5 mm, while Maros et al. [18] stated that the length of the coronary sinus is 36 mm and its width is 9 mm. Ortale [19] stated that the diameter of the coronary sinus in adults ranges from 6 to 12 mm. El-Maasarany found that "the coronary sinus was 48.4 ± 5.2 mm long and 9.3 ± 5.3 mm in diameter [20]. Mahmud [21] engaged in scientific intravital research by ultrasonography and defined the diameter as between 4 and 16 mm (mean, 8 mm), similar to the value found by Gunez [22], 8.1 ± 2.4 mm. Kronzon et al. [14] (measuring 10 mm from the right atrium entrance) reported a mean coronary sinus-diameter of 9 ± 2 mm (range 6 to 14 mm). Andrade et al. [23] studied 400 patients from 5 to 80 years of age and found coronary sinus diameter as 4–8

Table 7. The correlation matrix (r) between fetal age (x_1), the diameter (x_2) and length (x_3) of coronary sinus and total sum of the diameters of the cardiac veins (x_4), $p < 0.05$.

	fetal age	diameter of coronary sinus	length of coronary sinus	total sum of the diameters of the cardiac veins
fetal age	1	0.96	0.93	0.91
diameter of coronary sinus	0.96	1	0.93	0.68
length of coronary sinus	0.93	0.93	1	0.95
total sum of the diameters of the cardiac veins	0.91	0.68	0.95	1

mm. In addition, dimensions change during heart cycle, with the dimensions greatest during heart systole [24].

Clearly, discrepancies exist in the measurements cited for this anatomical structure. As mentioned earlier, anatomical research in the field of prenatal development of the coronary sinus is scarce. The diameter of the coronary sinus according to contemporary papers ranges between 1.2 and 2.7 mm [25]. These values were obtained by ultrasonography, a method in which the risk of receiving inaccurate measurements is quite large [25]. Nevertheless, measurements obtained with this method are quite congruent with those found in our study using the method described previously. These data are supported by another paper that sets the value of this parameter between 1 and 3.2 mm, with an average value of 2 ± 0.13 mm in the fetal subject [26]. That same paper analyzed the diameter (D) to length (L) ratio in the coronary sinus and found it to be $24\% \pm 6\%$ [26], which is similar to that found in the present study. Therefore, large differences were not caused by ultrasonographic measurements of the internal dimension. In our research, we measured the external dimension. The D/L ratio is a parameter that assists the determination of coronary sinus pathology or congenital fetal defects. Many congenital fetal pathologies are accompanied by an increased diameter of the coronary sinus [25–28].

The diameters of the coronary sinus in our examination correlated well with fetal development found in other studies [25,26]. According our data, the length of the coronary sinus is parameter that is better correlated with fetal age, and provides the best correlation with the diameters of the veins draining into the coronary sinus. Differences between our data and other publications (that also used ultrasonography) are probably caused by the measurement method. Determining the dimensions (especially the length of coronary sinus) by ultrasonographic methods is more difficult than in the method traditionally used in morphometry (or in morphometric study). The results of the measurements of the diameters of the veins draining into the coronary sinus are of great interest, because they can help explain the inconsistent growth in its length. These veins do not grow at a constant rate, as is seen in the progressive

growth of the length of the coronary sinus: this suggests a relationship between the two processes. The constant speed of increase of the diameter of the coronary sinus may indicate parallels between the lengthening of the coronary sinus and the increase in diameter of the veins draining into it. To date, no data have been published on this subject. Accordingly, we suggest that dependence necessarily exists between increasing of coronary sinus volume and increasing diameter of the veins for proper blood drainage from veins.

5. Conclusion

In this study, the length and the diameter of the coronary sinus during prenatal development was found to be greater in female fetal subjects, although not to a statistically significant level ($p > 0.05$). The growth of the diameter during the investigated time period (i.e. in consecutive monthly periods between the fourth and eighth months of development) was constant. In the other parameter like the length of the coronary sinus, the rate of the growth is changeable. We observed a decrease in the growth in the seventh, eight months of gestation, following the period from the fifth to sixth month which displayed rapid increase. Therefore, it could be concluded that the growth of this parameter (the length of the coronary) was not constant.

The diameter of the coronary sinus is the best parameter to monitoring the fetal age and the growing of the fetus.

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