

Morphological Basis for the Study of the Interatrial Septum in the Human Fetus

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Summary

Objective: To describe morphological features of the interatrial septum in normal fetuses, especially foramen ovale (FO) and septum primum (SP), in order to compare septum primum excursion with foramen ovale diameter.

Methods: Septum primum excursion (SPE) toward the left atrium (LA) and foramen ovale diameter (FOD) were measured in the hearts of ten formaldehyde-fixed human fetuses ranging from 28 to 36 weeks of gestation. Histological sections were obtained from the foramen ovale (FO), septum primum (SP), septum secundum (SS), left atrium (LA), and right atrium (RA).

Results: FOD and SPE measurements were the following: FOD 3.1-3.5 mm and SPE 2.8-3.1 mm in three fetuses with presumed gestational age (GA) of 28 weeks; FOD 3.3-3.5 mm, and SP excursion 4.0-5.0 mm in four fetuses with presumed GA of 34 weeks, plus FOD 3.3-4.5 mm and SPE 6.0-9.0 in three fetuses with presumed GA of 36 weeks. Cardiac muscular fibers were identified in both the septum primum and secundum.

Conclusion: Based on its muscular components, it may be suggested that SP is active in character, influencing blood flow through the FO, SP mobility, and its excursion into the LA.

Key words: Fetal heart, heart septum/anatomy & histology, heart septal defects, atrial.

Introduction

Embryonic development of the human heart depends on cell-cell interaction, particularly myocardial and mesenchymal cells¹⁻⁶. This interaction accounts for the differentiation and morphogenesis of specific areas in the heart, among them cardiac septa⁷⁻¹⁰. The endocardial cushion, a clustering of endocardial and mesenchymal cells, plays a direct role in cardiac septa and atrioventricular valve formation^{7,11}.

Partitioning of the primitive atrium begins at the end of the fourth gestational week through formation, modification, and subsequent fusion of the septum primum and septum secundum¹². The primitive atrium division process is complex not only because the septum primum fuses with endocardial cushions, but also because permanent communication must exist to allow blood flow from the right to the left atrium^{12,13}. The septum primum edge is attached to endocardial cushions, delimiting an interatrial communication called ostium or foramen primum, which disappears after fusion of the septum primum to the endocardial cushions^{12,13}.

Before the ostium primum disappears, numerous

perforations caused by programmed cell death develop at the center of septum primum, forming the ostium or foramen secundum, which serves as a shunt for oxygenated blood from the ductus venosus to pass from the right to the left atrium¹². The septum secundum develops more slowly, to the right of the septum primum, migrating as the ostium primum closes and gradually overlapping the ostium secundum. Septum secundum separates the atria incompletely, thereby forming the foramen ovale¹³.

During intrauterine life, the foramen ovale allows most oxygenated blood entering the right atrium from the inferior vena cava and ductus venosus to pass into the left atrium. It also prevents blood from flowing in the opposite direction, because the septum primum closes against a relatively rigid septum secundum. After birth, the foramen ovale usually closes, and the interatrial septum completely separates atrial chambers¹².

Cell analysis has demonstrated that, during the first developmental stages, septum primum has a muscular central portion in which myocytes are in close contact¹⁴. In addition to myocytes, there is also the aforementioned presence of mesenchymal tissue in the septum primum¹⁴⁻¹⁶. The septum primum is covered by the endocardium, which is made up of elongated and flattened cells¹⁷.

Color Doppler echocardiography has led to major advances in the field of fetal heart and circulatory physiology; therefore, understanding the functional mechanism of foramen ovale is of prime importance.

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Manuscript received June 18, 2006; revised manuscript received October 18, 2006; accepted November 10, 2006.

In earlier studies, our team analyzed septum primum mobility, its development during intrauterine life¹⁸, and its relationship with the presence of atrial extrasystoles^{19,20} and left ventricular diastolic function²¹. To evaluate septum primum excursion quantitatively at every cardiac cycle, its maximal excursion toward the left atrium is measured in a four-chamber view. An “excursion index” of septum primum was created to correlate its maximal excursion to left atrial diameter^{20,21}.

This study aimed at describing morphological features of the interatrial septum in normal fetuses, especially foramen ovale and septum primum, to compare septum primum excursion with foramen ovale diameter.

Methods

For anatomical evaluation, both septum primum maximal excursion toward the left atrium and foramen ovale diameter were measured in the hearts of ten formaldehyde-preserved human fetuses (gestational ages between 28 and 36 weeks) from the *Laboratório de Anatomia do Feto e do Recém-nascido do Departamento de Morfologia do Centro de Ciências da Saúde da Universidade* (Fetal and New-born Anatomy Laboratory of the Morphology Department of the University’s Health Sciences Center).

Anatomical dissection was performed according to standard technique, with *en bloc* resection of the heart and lungs. The lungs were then resected at the level of the pulmonary hila, and the heart was cut transversely to the interventricular septum from the apex to the base, allowing ventricular cavities to be visualized by opening the atrial wall and exposing the septum primum, septum secundum, and foramen ovale. Septum primum maximal excursion and foramen ovale diameter were measured under a colposcope with 13x magnification using an adapted measurement device (a caliper with two sharp metal ends).

Septum primum excursion was measured by fixing one of the ends of the measurement device in the septum secundum and the other in the middle of the free edge of the septum primum, which was pushed toward the left atrium as far as its maximal excursion, without deforming neighboring structures.

Foramen ovale diameter was measured at a 90° angle in relation to the septum primum excursion measurement, corresponding to a line between septum primum implantation sites.

Histological sections were obtained from the foramen ovale, septum primum, septum secundum, left atrium, and right atrium. Subendocardial and subepicardial tissue slides were stained using the hematoxylin-eosin method and Goldner’s technique, in light green solution.

Results

The anatomical measurements of the formaldehyde-preserved fetal hearts are presented in Table 1.

Histological examination of septum primum and septum secundum from the base to the apex (longitudinal section)

Table 1 – Foramen ovale diameter and septum primum excursion measured in millimeters (mm)

Presumed gestational age in weeks	FOD (mm)	SPE (mm)
28	3.5	2.8
28	3.1	2.9
28	3.5	3.1
34	3.5	4.0
34	3.3	4.5
34	3.5	4.9
34	3.5	5.0
36	3.3	6.0
36	3.5	8.0
36	4.5	9.0

FOD - foramen ovale diameter; SPE – septum primum excursion.

allowed identification of cardiac muscular fibers in both structures and, hence, the presence of contractility. It also enabled visualization of blood vessels supplying these sites, in addition to intramural nerves and neurons of the neurovegetative system. Figures 1 through 7 show the macroscopic and microscopic sections and their descriptions.

Discussion

During fetal life, septum primum acts as a valve that closes the foramen ovale when atrial contractions occur. During diastole, septum primum bulges into the left atrium, allowing maximal opening and right-to-left flow^{22,23}.

In previous studies, our team evaluated septum primum echocardiographic behavior during fetal life. The relationship between septum primum mobility and the presence of atrial extrasystoles was assessed in a study comparing a group of fetuses with atrial extrasystoles and a control group of normal fetuses. The redundancy index (RI), defined as the ratio between septum primum maximal excursion and left atrial maximal diameter on fetal echocardiogram (four-chamber view), showed that septum primum is more redundant in fetuses with atrial extrasystoles during intrauterine life¹⁶.

Septum primum mobility has proved to be an indicator of left diastolic function. Taking into account that septum primum mobility may reflect changes related to left atrial pressure, alterations in left ventricular relaxation and/or compliance may affect the behavior of the former. With the use of groups of fetuses of diabetic mothers with septal myocardial hypertrophy as a model for decreased left ventricular compliance and relaxation it was noted that, in this situation, septum primum excursion is reduced. Septum primum may also develop hypertrophy. Therefore, the greater the myocardial hypertrophy in the interventricular septum, the more restricted the left ventricular filling and the shorter the septum primum excursion into the left atrium during the cardiac cycle^{20,21}. In this same study, it has been

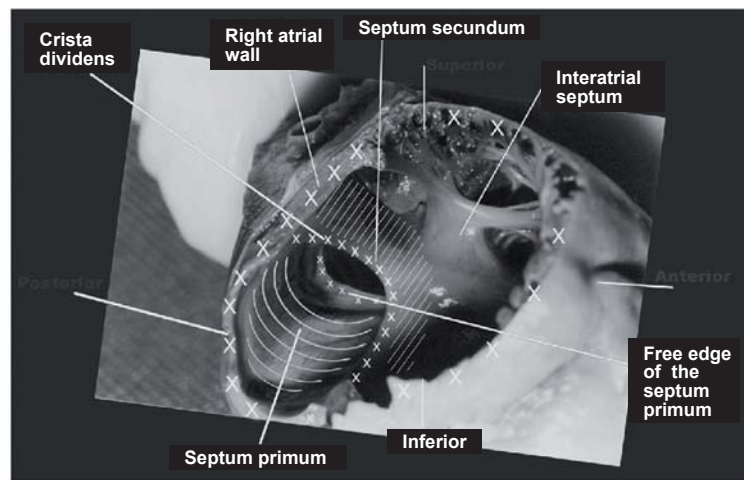


Fig. 1 - Foramen ovale seen from the right atrium to the left atrium.

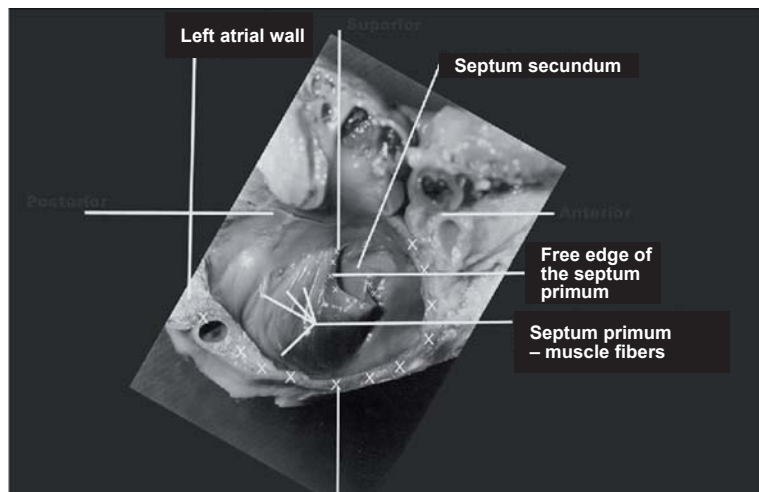


Fig. 2 - Foramen ovale seen from the left atrium. Septum primum excursion into the left atrium.

suggested that septum primum excursion may be a more suitable index for ventricular diastolic function than those traditionally accepted, since it shows an inverse relationship with interventricular septal hypertrophy and is easier to perform than the atrioventricular valve flow analysis.

In an earlier study, it was also found that septum primum maximal excursion is increased during fetal breathing, a finding that was related to an increase in left ventricular distensibility due to respiratory movements²⁴.

The most recent hypothesis raised by our team attempts to explore the notion that the morphological composition of septum primum would directly influence its echocardiographic

behavior, most notably its mobility, thereby reflecting its excursion index.

Each stage during septum primum formation is directly related to its role in fetal heart circulation. Its histological structure directly affects its behavior on blood flow that cross the foramen ovale^{25,26}.

Thus, it may be suggested that septum primum is active in character, and this behavior may influence the blood flow through the foramen ovale. Moreover, septum primum mobility itself, as well as its excursion into the left atrium, depends not only on left atrial pressure, but also on its muscle fibers.

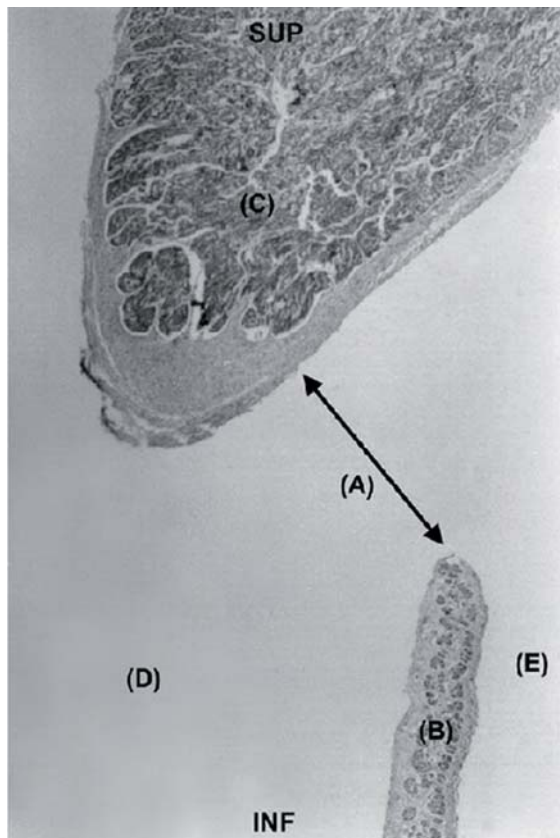


Fig. 3 - Foramen ovale (A). Septum primum (B). Septum secundum (C). Right atrium (D). Left atrium (E). 400x magnification. Goldner staining.

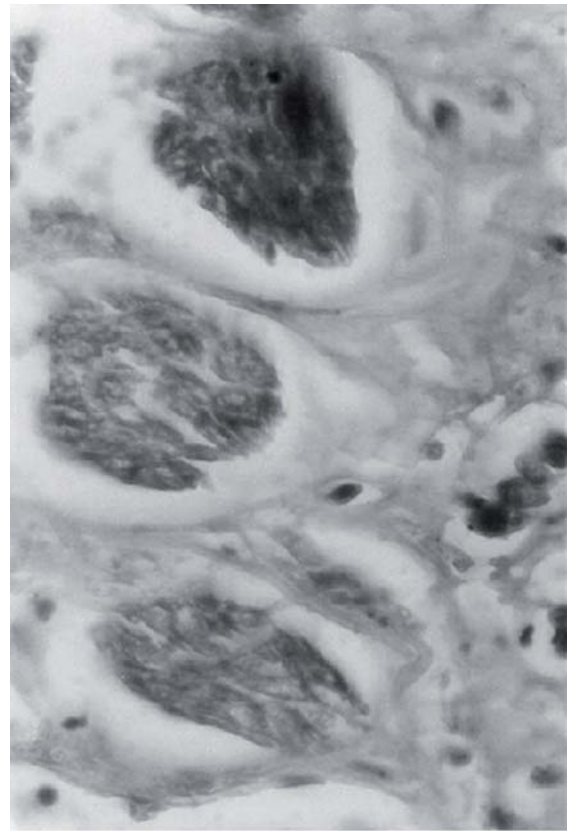


Fig. 4 - Septum primum origin on the left atrium wall (A). Septum primum (B). Right atrium (C). Left atrium (D). 400x magnification. Goldner staining.

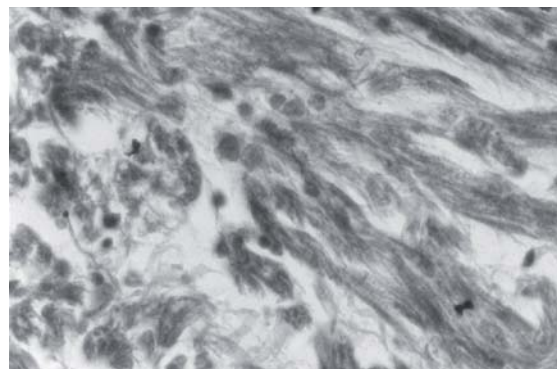


Fig. 5 - Cross-section of the free edge of the septum primum (A). 400x magnification. Goldner staining.

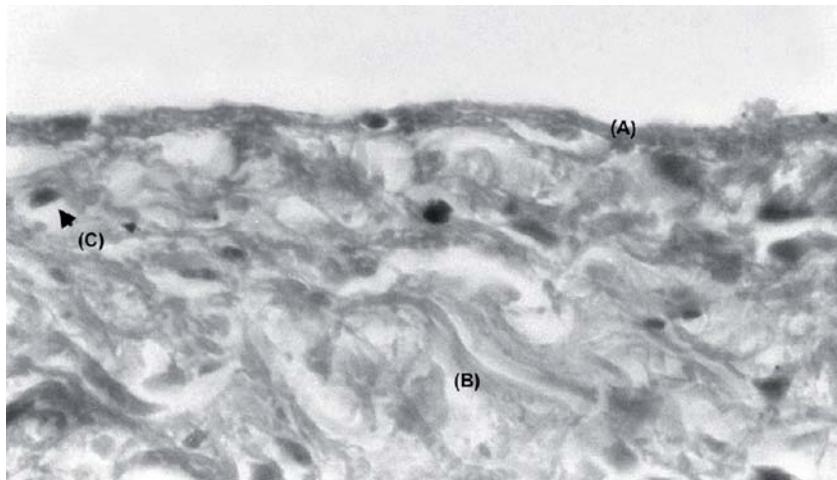


Fig. 6 - Septum primum endocardium showing the endothelium (A) and subendothelium with collagenous fibers (B) and fibroblasts (C). 400x magnification. Goldner staining.



Fig. 7 - Base of the septum secundum showing vascularization (A) and a neural ganglion. Vegetative neuron (B). 400x magnification. Goldner staining.

Acknowledgements

We would like to thank Sérgio Oliveira Silveira, laboratory technician, Department of Morphology, CCS, UFSM.

Supported by: FAPERGS – Fundação de Amparo à Pesquisa

do Estado do RS, CAPES and CNPq.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

References

1. De Haan RL. Morphogenesis. *Annu Rev Physiol.* 1964; 26: 15-46.
2. De Haan RL. Morphogenesis of the vertebrate heart. In: Haan RL, Ursprung H, ed. *Organogenesis.* New York: Holt, Rinehart and Winston; 1965. p. 377-419.
3. De Haan RL, Fujii S, Satin J. Cell interactions in cardiac development. *Dev Growth Differ.* 1990; 32: 233-41.
4. Manasek FJ. The extracellular matrix: a dynamic component of the developing embryo. In: Moscona A, Monroy A, eds. *Current topics in developmental biology.* New York: Academic Press; 1975. p. 35-102.
5. Icardo JM. Cardiac morphogenesis and development. *Experientia.* 1988; 44: 11-2.
6. Icardo JM. Development biology of the vertebrate heart. *J Exp Zool.* 1996; 275: 144-61.
7. Markwald R, Fitzharris T, Manasek F. Structural development of endocardial cushions. *Am J Anat.* 1977; 148: 85-120.
8. Hay DA. Development and fusion of the endocardial cushion. In: Rosenquist GC, Bergfima D, eds. *Birth defects, original articles.* New York: Allan R Liss Inc.; 1978. p. 69-90. (Series XIV, nº 7).
9. Bolender DL, Markwald RR. Epithelial-mesenchymal transformation in atrioventricular cushion tissue morphogenesis. *Scanning Electron Microsc.* 1979; 3: 313-22.
10. Steding G, Seidl W. Contribution to the development of the heart. Part I: normal development. *Thorac Cardiovasc Surg.* 1980; 28: 386-409.
11. Argüelo C, De La Cruz M, Sanchez M. Ultrastructural and experimental evidence of myocardial cell differentiation into connective tissue cell in embryonic chick heart. *J Mol Cell Cardiol.* 1978; 10: 307-15.
12. Moore K, Persaud TVN. Sistema cardiovascular. In: Moore KL, Persaud TVN. *Embriologia clínica.* 6ª ed. Rio de Janeiro: Guanabara Koogan; 2000. p. 332-82.
13. Anderson RH, Webb S, Brown NA. Clinical anatomy of the atrial septum with reference to its developmental components. *Clin Anat.* 1999; 12: 362-74.
14. Patten BM. The formation of the cardiac loop in the chick. *Am J Anat.* 1922; 30: 373-97.
15. Patten BM, Kramer TC, Barry A. Valvular action in the embryonic chick heart by localized apposition of endocardial masses. *Anat Rec.* 1948; 102: 299-312.
16. Arrechdera H, Alvarez M, Strauss M, Ayesta C. Origin of mesenchymal tissue in the septum primum: a structural and ultrastructural study. *J Mol Cell Cardiol.* 1987; 19: 641-51.
17. Wessels A, Anderson RH, Markwald RR, Webb S, Brown NA, Viragh S, et al. Atrial development in the human heart: an immunohistochemical study with emphasis on the role of mesenchymal tissues. *Anat Rec.* 2000; 259 (3): 288-300.
18. Zielinsky P, Firpo C, Martha VF, Silva ES. Estudo ecocardiográfico pré-natal da redundância do septum primum e sua relação com a gênese de extra-sístoles atriais no feto. *Arq Bras Cardiol.* 1995; 65: 153-7.
19. Zielinsky P, Firpo C, Martha VF, Silva ES. Papel da membrana da fossa oval no desencadeamento de arritmias cardíacas fetais. *Rev Bras Ginec Obstet.* 1995; 17: 711-9.
20. Firpo C, Zielinsky P. Mobility of the flap valve of the primary atrial septum in the developing human fetus. *Cardiol Young.* 1998; 8 (1): 67-70.
21. Firpo C, Zielinsky P. Behavior of septum primum mobility in third-trimester fetuses with myocardial hypertrophy. *Ultrasound Obstet Gynecol.* 2003; 21: 445-50.
22. Puerta Fonolla AJ, Orts Llorca F. Origin and development of the septo primo. *Acta Anat (Basel).* 1978; 100 (2): 250-7.
23. Morse DE, Rogers CS, McCann PS. Atrial septation in the chick and rat: a review. *J Submicrosc Cytol.* 1984; 16: 259-72.
24. Miyague NI, Ghidini A, Miyague LLT. Fetal breathing movements are associated with changes in compliance of the left ventricle. *Fetal Diagn Ther.* 1997; 12: 72-5.
25. Anderson RH, Webb S, Brown NA. Clinical anatomy of the septum primum with reference to its developmental components. *Clin Anat.* 1999; 12: 362-74.
26. Anderson RH, Webb S, Brown NA. Development of the heart: septation of the atriums and ventricles. *Heart.* 2003; 89: 949-58.