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RESEARCH ARTICLE

Flap valve of the heart foramen ovale revisited: macroscopic and histologic observations of human near-term fetuses

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A B S T R A C T

We assessed the flap valve of the foramen ovale (FO valve) by examining 30 hearts from human fetuses of gestational age 30–40 weeks. We dissected the hearts, examined their macroscopic morphology, and then prepared semiserial sagittal sections across the valve. Although the primary septum is expected to extend along the left atrial face, eight hearts had a superior rim of the fossa ovalis on the left atrial face that was too thick and high, so there was no smooth continuation with the valve. Moreover, three of these eight hearts each had a flap valve that was fused with a long and narrow plate arising from the caval orifice. Histological analysis indicated that 21 specimens each had a candidate primary septum that contained myocardium, although the left sinuatrial valve (LSAV) contained fibrous tissue, but little or no myocardium. In each of 17 hearts, a candidate primary septum was attached to the left atrial face of the fossa, and parts of the LSAV extended to and approached the right atrial face. However, seven of these 17 hearts each had a folded small primary septum. Another four of these 17 hearts each had an LSAV that extended widely to the fossa, and a candidate primary septum (which might be a remnant) attached to the left atrial side of the LSAV. These variations suggest that the LSAV makes a major contribution to the FO valve in some fetal hearts. Consequently, the fetal FO valve appears to have heterogeneous morphology and origin.

1. Introduction

Cardiologists who study fetal heart development have traditionally believed that the foramen ovale of the heart is a slit in the secondary septum, and that the flap valve is derived from the primary septum of the atria. However, recent research by Anderson et al. (Anderson et al., 2014; Anderson et al., 2015; Jensen et al., 2017) have led to a reconsideration of this view. First, the vestibular spine, a mesenchymal bulge at an inferior joining of the left and right sinusoidal valves (SA valves), provides an inferior buttress or a dull inferior margin of the fossa at Carnegie stages 14–16. Second, a fold of the atrial roof, due to migration or absorption of the pulmonary vein, provides a superior rim or an acute margin after the embryonic period. The infolded atrial roof, a deep groove when viewed from the outside, also has rich epicardiac innervation, and has been called the left atrial nerve fold (Gardner and O'Rahilly, 1976; Pauza et al., 2000). Our recent immunohistochemical studies of near-term fetuses demonstrated that the nerves were from a cardiac nerve between the ascending aorta and the pulmonary arterial trunk (Cho et al., 2019). The significant contribution of the infolded atrial roof to septation was first described by Rőse in *Morphologishes Jahrbuch* (Rőse, 1890).

The secondary septum does not contribute to fossa ovalis morphology. Thus, we decided to re-examine the flap valve of the fossa ovalis (FO valve) because classical studies hypothesized the presence of a secondary septum. In particular, Christie (1963) considered the major part was derived from the septum, and the left SA valve constituted the inferoposterior marginal part of the FO valve. Large SA valves at the orifice of the systemic venous sinus

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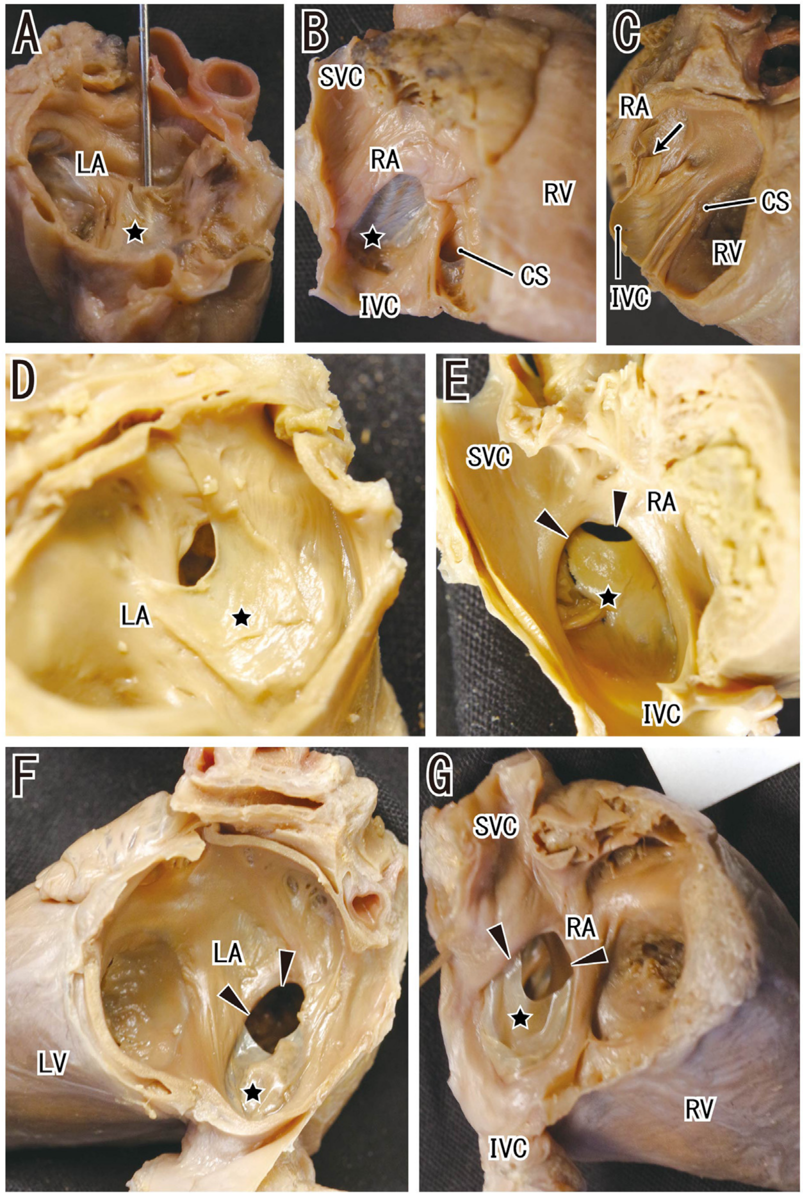

Fig. 1. Macroscopic observations of foramen ovale (FO) valves in four representative specimens.
Fetuses with CRLs of 256 mm (panels A and B), 250 mm (panel C), 276 mm (panels D and E), and 328 mm (panels F and G). The foramen is probe-patent at the left atrial face (LA) in panel A, and the FO valve (star) appears membranous at the right atrial face (RA) in panel B. The tricuspid valve or ventricular lumen is not evident because the right ventricular wall was not yet dissected in panel B. A plate-like structure (arrow) that is continuous with an orifice of the inferior vena cava (IVC) attaches to the FO valve at the right atrial face and an arrow indicates the fossa in panel C. A macroscopically open foramen is evident in panels D and G. A myocardial ridge, or superior rim of the fossa ovalis (arrowheads), is thick and evident at the right atrial face (arrowheads) in panels E and G, but the rim is absent at the left atrial face in panel D. Thus, the FO valve appears to be continuous with the left atrial endocardium in panel D, but it appears deep in panel F. CS, coronary sinus; LV, left ventricle; RV, right ventricle; SVC, superior vena cava.

develop earlier than the primary septum and, during early stages of septation, valve-like projections in the atrial cavity are limited to the septum spurium, which is formed by joining of these valves above the opening (Williams, 1995). When a human embryo has a crown-rump length (CRL) of 28.5 mm, the primary and secondary atrial septa, in combination with the left SA valve, form a complete circular diaphragm-like structure (Odgers, 1934). However, Anderson and colleagues concluded that the SA valve did not contribute to the FO valve because it is distant from the fossa (Sizarov et al., 2010; Anderson et al., 2014; Anderson et al., 2015). Nevertheless, as Patten (1931) originally reported and all subsequent researchers agree, the primary septum (or SA valve-derived tissue) should be located in the left (or right) atrial face of the subsequent FO.

We recently demonstrated significant variations in the size and shape of SA valves among human fetuses that had CRLs of 24–31 mm (Kim et al., 2014; Naito et al., 2015). These studies showed that fetal SA valves contain fibrous tissue continuous with subendocardial tissue, whereas the primary septum contains myocardium. This observation is consistent with those of Patten (1931). Therefore, macroscopic examination of the FO valve, followed by histological examination of these specimens, is required to distinguish an SA valve from the primary septum when they are attached or fused. This study assessed whether the left SA valve contributes to the closure of the foramen as a flap valve in near-term fetuses.

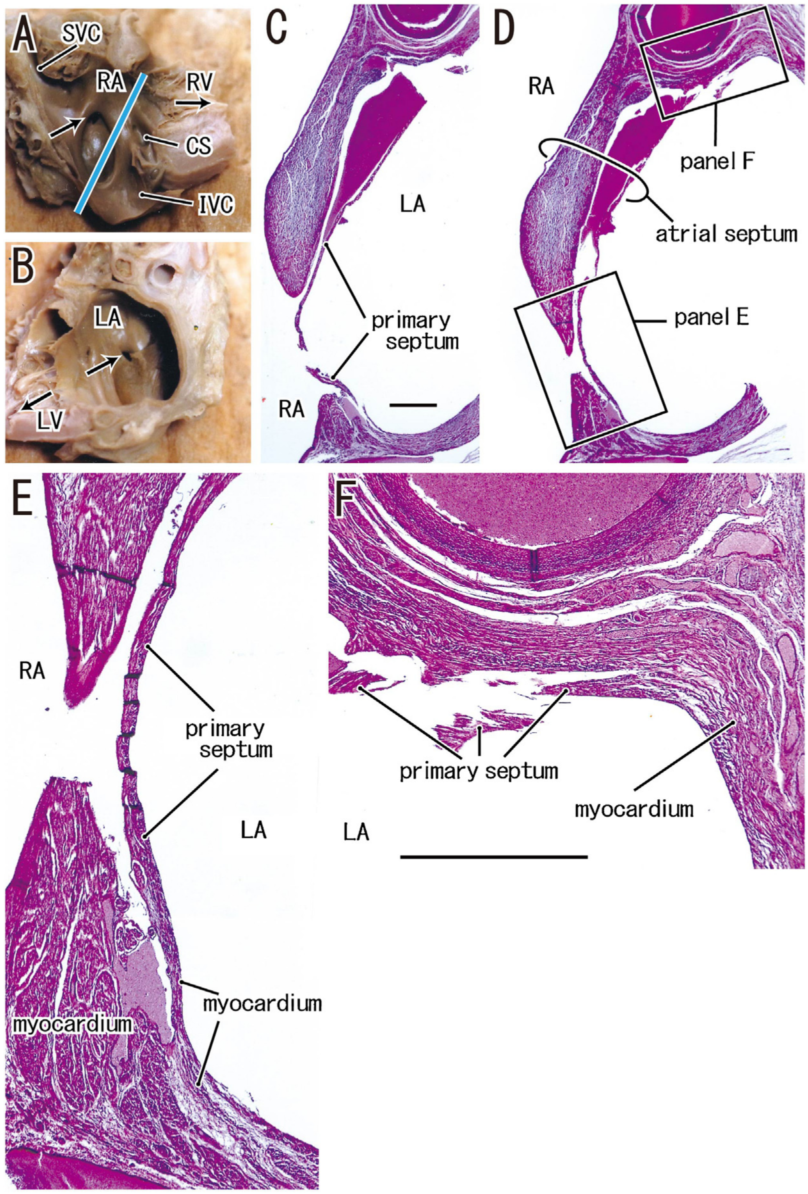

Fig. 2. Macroscopic observations and histology of a primary septum-derived strong valve in a specimen with a CRL of 243 mm.
Macroscopic views of the right and left atria (RA, LA; panels A and B) before preparation for histology (panels C–F); arrows indicate an opening of the foramen ovale and the blue line indicates the sectional plane (almost sagittal). Panels C and D are at low magnification and panels E and F show views of the squares in panel D at high magnification (scale bars in C and F: 1 mm). The candidate primary septum is long and wide and extends along the left atrial aspect of the muscular septum (panels C and D). The myocardium continues to the candidate primary septum (panels E and F). The sinoatrial valve is not evident in these sections. CS, coronary sinus; IVC inferior vena cava; LV, left ventricle; RV, right ventricle; SVC, superior vena cava. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2. Materials and methods

This study was performed in accordance with the provisions of the Declaration of Helsinki 1995 (as revised in 2013). Hearts were obtained from 30 human near-term fetuses, with gestational age of 30 to 40 weeks and CRL of 250 to 350 mm. These fetuses were part of the collection at the Department of Anatomy of Akita University (Japan), and were donated by their families between 1975 and 1985, and were preserved in 10% w/w neutral formalin solution for more than 30 years. Data on these specimens included the date of donation, legally induced or spontaneous abortion, and the number of gestational weeks. The names of the families and obstetrician or hospital, and the reason for abortion were unavailable. The use of these specimens for research was approved by the Akita University Ethics Committee (No. 1428).

The left and right atria were dissected, followed by macroscopic examination of the atrial septum, including the FO valve. Care was taken to preserve the orifices of the inferior vena cava, the coronary sinus, and the atrioventricular valves to allow better interpretation of the photographs. Photographs were taken with a Pentax K-1 camera using a 50–100 mm zoom lens. Large paraffin blocks of the specimens were subsequently prepared; these blocks contained the whole septum and the surrounding structures, including the inferior caval vein and coronary sinus. From each block, 50–100 semiserial sections across the FO valve (5 μm thickness; 50 μm intervals) were prepared. The sectional plane was sagittal or oblique sagittal, and included the FO valve and the left SA valve. All sections were stained with hematoxylin and eosin (H&E) for previous studies (Kim et al., 2018; Cho et al., 2019). Samples were observed, and most photographs were taken with

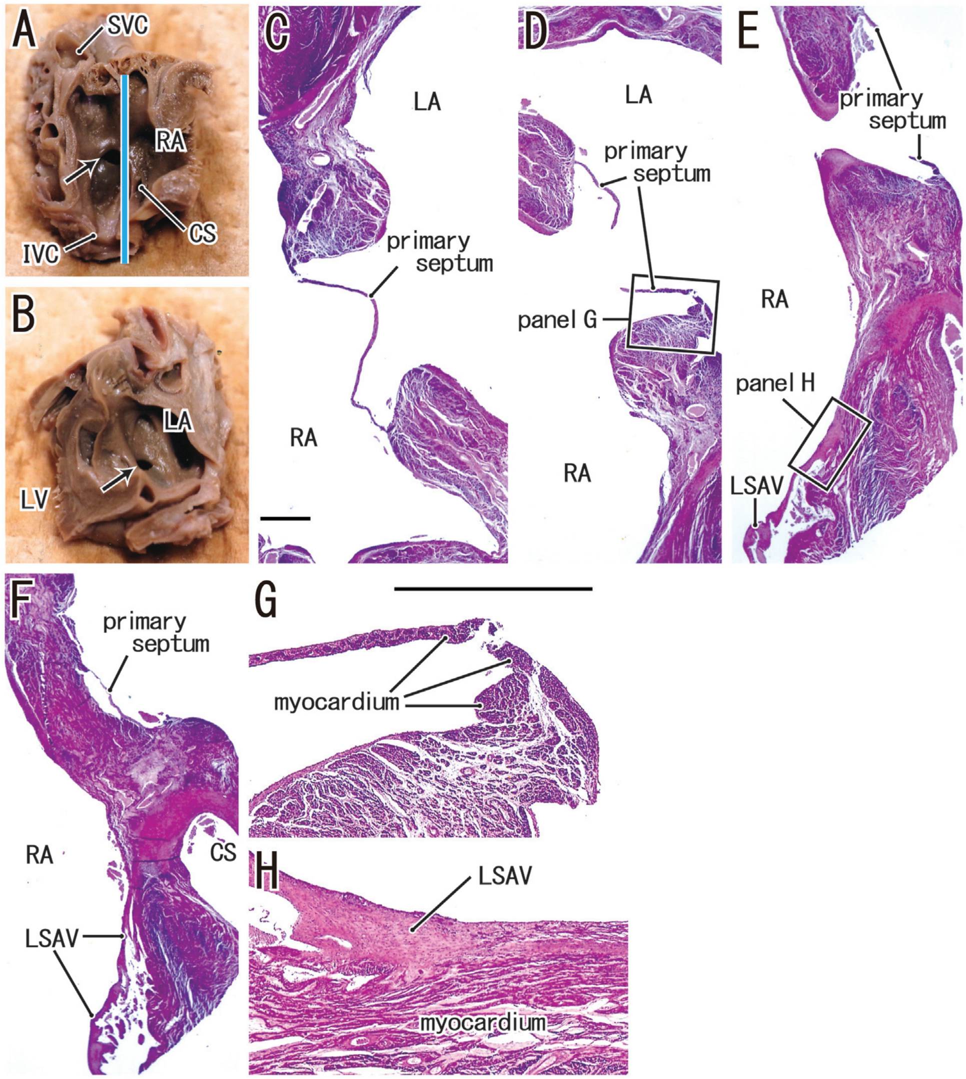

Fig. 3. Macroscopic observations and histology of a primary septum-derived short valve in a specimen with a CRL of 322 mm.
Macroscopic views of the right and left atria (RA, LA; panels A and B) before preparation for histology (panels C to H); arrows indicate an opening of the foramen ovale and the blue line indicates the sectional plane (almost sagittal). Panels C to F are at low magnification and panels G and H show views of the squares in panels D and E at high magnification (scale bars in C and G: 1 mm). Panel F shows the most anterior site. The upper and lower attachments of the candidate primary septum shifted from the left atrial aspect (panel C) to the right atrial aspect (panel E) of the muscular septum. The left sinoatrial valve (LSAV) is evident in the RA of panels E and F. The candidate primary septum contains myocardium (panel G), but the sinoatrial valve consists of fibrous tissue that is continuous with the subendocardial tissue (panel H).CS, coronary sinus; IVC, inferior vena cava; LV, left ventricle; SVC, superior vena cava. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

a Nikon Eclipse 80. Photographs at ultra-low magnification (objective lens less than 2×) were taken with a high-grade flat scanner using translucent illumination (Epson scanner GTX970).

Before beginning this study, it was necessary to establish typical changes of the FO from gestational age 30–40 weeks. A classical study by Patten (1931) examined 4 fetuses in this age range and reported this opening was 7.1 mm, 0 mm, 0 mm, and 0.2 mm, from the smallest to largest specimen. In addition, Christie (1930) examined 590 fetuses and reported the size of this opening varied by less than 2 mm. Therefore, we believe that inter-individual differences in the size of the FO of our specimens probably masked any age-related differences.

3. Results

3.1. Macroscopic observations

The foramen ovale appeared to be closed by the FO valve in only eight of 30 specimens (Figs. 1A–C and 5 A and B), and was easily identified by insertion of a pin (probe-patent). However, in the left and right atrial faces, an opening of the foramen was present in 22 of 30 specimens (Figs. 1D–G, 2 A and B, 3 A and B, 4 A and B, 5 A and B, and 6 A and B). In all cases, the macroscopically open foramen was just below the thick superior rim of the fossa when viewed from the right atrial side (Fig. 1E and G). At the right atrial face, the superior rim of the fossa was also evident in all eight hearts with probe-patent foramens (Fig. 1B); however, in each case the rim was not evident at the left-atrial face (Fig. 1A) and the left atrial endocardium appeared to smoothly continue to the FO valve. Notably, for each of these eight hearts with a macroscopically open foramen, the superior rim of the fossa ovalis was thick and high in the right and left atrial faces, and there was a deep fossa at the left and right atrial faces. Thus, the left atrial face of each of these eight hearts (Fig. 1D and F) had a rim that was too thick and high, so there was no smooth continuation with the valve. Moreover, three of the eight hearts each had a flap valve that was fused with a long and narrow plate arising from the inferior caval orifice (Fig. 1C). This long and narrow plate appeared to correspond to parts of the

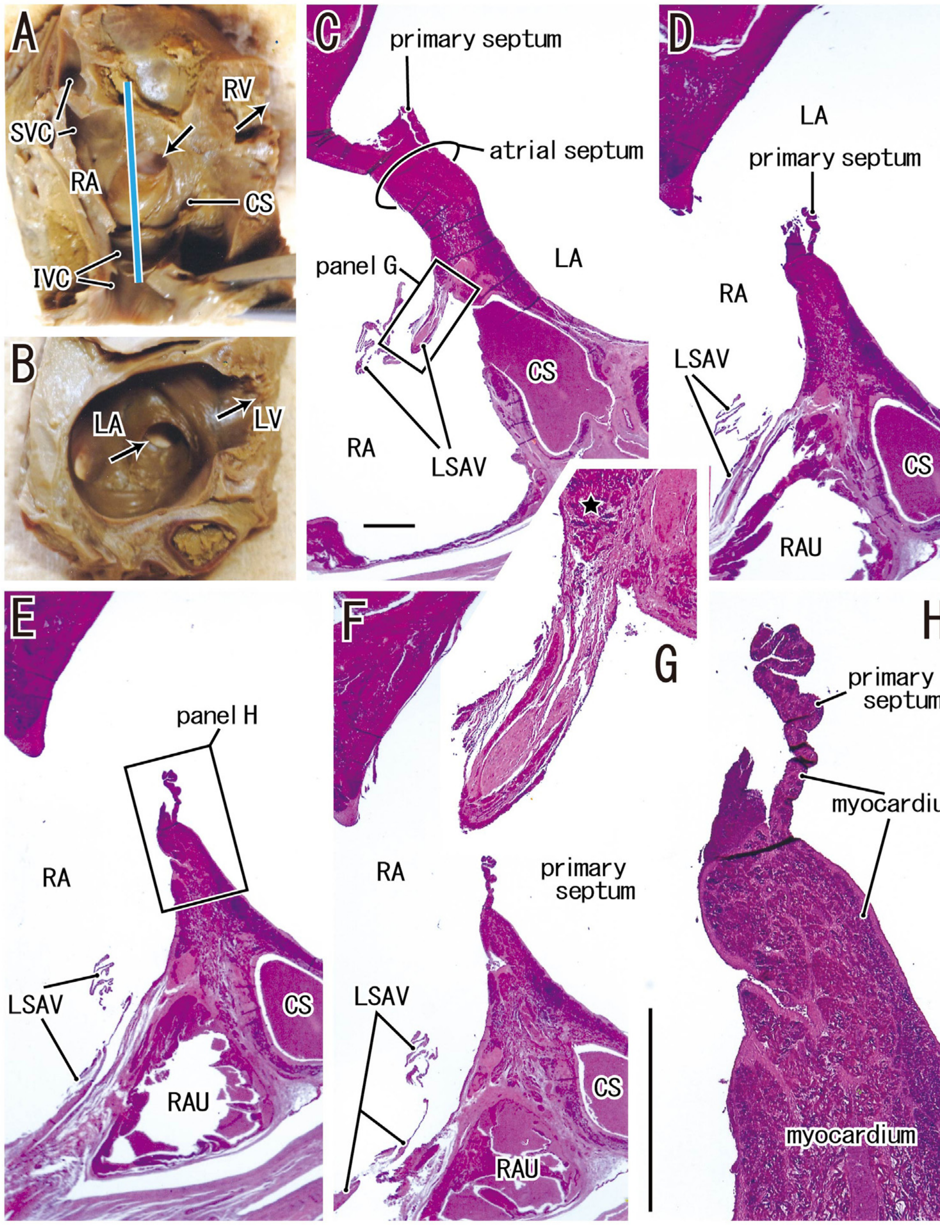

Fig. 4. Macroscopic observations and histology of a primary septum-derived folded valve associated with the left sinuatrial valve in a specimen with a CRL of 288 mm. Macroscopic views of the right and left atria (LA, RA; panels A and B) before preparation for histology (panels C–H); arrows indicate an opening of the foramen ovale and the blue line indicates the sectional plane (almost sagittal). Panels C–F are at low magnification and panels G and H show views of the squares in panels C and E at high magnification (scale bars in C and H: 1 mm). Panel C shows the most anterior site in this specimen. The candidate primary septum is short, highly folded (panel H), and attached to the left atrial aspect of the muscular septum (panels C–E). The left sinoatrial valve (LSAV) is attached to the right atrial side of the muscular septum (panels C and D). The myocardium continues to the candidate primary septum (panel H), but does not enter the sinoatrial valve (star in panel G). CS, coronary sinus; IVC, inferior vena cava; LV, left ventricle; RAU, right auricle; RV, right ventricle; SVC, superior vena cava. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

SA valve. Thus, the thick and high superior rim of fossa at the left atrial face was likely to connect with abnormal attachments of the primary septum-derived valve, resulting in a macroscopically open foramen.

3.2. Histological observations

Nine of the specimens assessed macroscopically could not be assessed histologically due to damage of the atrial septa during tissue dissection, washing of aggregated blood, and histologic procedures. Thus, we performed histological analysis of 21 fetal hearts. The ovale fossa was difficult to identify in sagittal and almost sagittal sections because it could not be observed from the atrial cavity (Figs. 2–6). Instead, the upper and lower parts of the thick atrial septum, which contain abundant myocardium, consistently sandwiched a large slit (hereafter simply referred to as the foramen). The foramen was partly covered or closed entirely by a membranous or plate-like structure. In taking photographs, we took care to show the SA valve at the inferior caval orifice, along with the FO valve, when they were close together in a section. We observed three types of FO valves (Fig. 7). Type 1 hearts (n = 10) each had a candidate primary septum-derived FO valve covering the foramen from the left atrial face (Figs. 2 and 3); type 2 hearts (n = 7) each had a candidate primary septum-derived small valves associated with normal left SA valves (Fig. 4); type 3 hearts (n = 4) each had a large

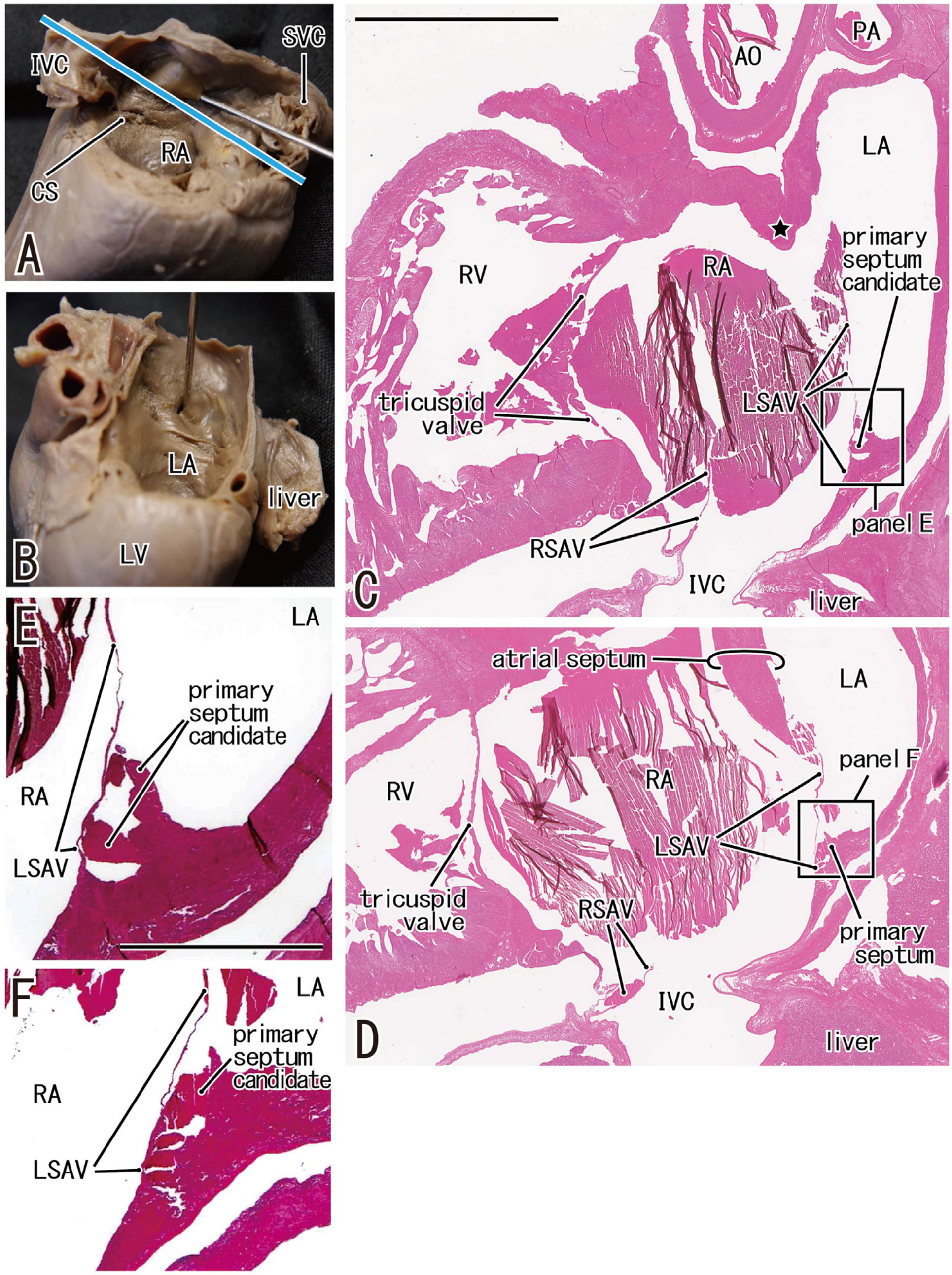

Fig. 5. Macroscopic observations and histology of a left sinuatrial valve that appears to cover the foramen ovale in association with a highly folded primary septum in a specimen with a CRL of 310 mm.
Macroscopic views of the right and left atria (LA, RA; panels A and B) before preparation for histology (panels C–F); a pin was inserted into the opening of the foramen ovale and the blue line indicates the sectional plane (almost sagittal). Histologic examination showed that the RA contained a blood clot due to inadequate washing after dissection. The scale bars in panels C and E are 5 mm and 1 mm, respectively. In contrast to the small right sinuatrial valve (RSAV), the left valve (LSAV) was long and wide and extended into the LA (panels C and D). The primary candidate septum was small, folded, and fragmented and its major part was attached to the left sinuatrial valve from the left atrial side (panels E and F). The star in panel C indicates an infolding of the atrial roof that continues to the muscular atrial septum in panel D. AO, ascending aorta; CS, coronary sinus; IVC, inferior vena cava; LV, left ventricle; PA, pulmonary artery; RV, right ventricle; SVC, superior vena cava. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

FO-like valve, but it appeared to arise from the inferior caval orifice and a nearby site (Figs. 5 and 6).

Each of the type 1 hearts had a candidate primary septum-derived valve which contained myocardium that was continuous with the myocardium of the muscular atrial septum (Figs. 2E and F and 3 G). The type 1 valve extended along the left atrial face (Fig. 2C and D); in contrast, the type 2 valve had a small part attached to the right atrial face of the rims of fossa (Fig. 3C). The left SA valve was identified in the right atrial side of the atrial septum (Fig. 3F). Two type 1 specimens each had a probe patent foramen (not shown) and the other eight each had a macroscopically open foramen (Figs. 2A and B and 3 A and B).

Each of the type 2 hearts had a folded valve that contained myocardium and was attached to the left atrial face of the rim (Fig. 4H), but the valve was too small to cover the foramen (Fig. 4D and E). Instead, the left SA valve approached and attached to the muscular atrial septum at the right atrial face. The core of the SA valve was quite different from the myocardium (Fig. 4G) in that it

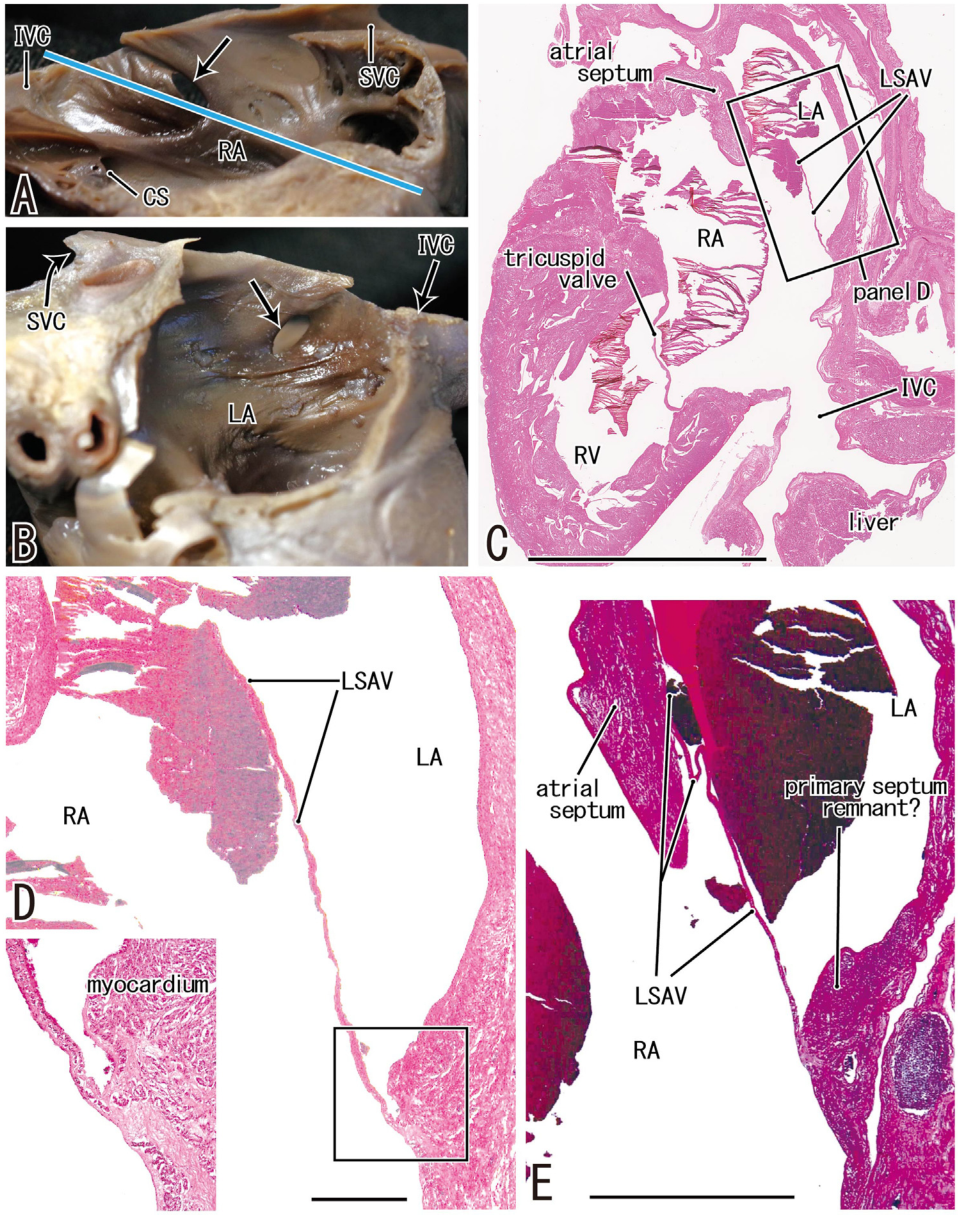

Fig. 6. Macroscopic observations and histology of a left sinuatrial valve extending into the left atrium in association with a remnant primary septum in a specimen with a CRL of 272 mm.
Macroscopic views of the right and left atria (LA, RA; panels A and B) before preparation of samples for histology (panels C–E); arrows indicate an opening of the foramen ovale, and the blue line indicates the sectional plane (almost sagittal). Panels C and D are at low magnification, and panel E and the insert of panel D are at high magnification (Scale bars: 5 mm in panel C; 1 mm in panels D and E). There is no myocardium entering into the valve (panel D), the left sinuatrial valve (LSAV) was long and extended into the LA (panels C and D), but the small right valve was not evident in this section. A plane 1 mm anterior to panel C shows the left valve attached to the left atrial aspect of the muscular septum (panel E). In contrast, the candidate primary septum provided a small mass attached to the left sinuatrial valve from the left atrial side. CS, coronary sinus; IVC, inferior vena cava; SVC, superior vena cava. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

was continuous with the subendocardial fibrous tissue. Each of the seven type 2 hearts had a macroscopically open foramen (Fig. 4A and B). Two of these hearts each had a foramen at the right atrial face that was associated with a macroscopically long and narrow plate that arose from the inferior caval orifice (Fig. 1C).

It was more difficult to interpret the histology of type 3 hearts. The FO valve appeared to continue to the left SA valve, which was contralateral to the right SA valve (Fig. 5C). However, the right SA valve was much smaller than the left valve, and a large left valve was not evident in any of the sections (Fig. 6C). Actually, the superior rim of the FO (or a muscular atrial septum) was derived from an infolded atrial roof (Fig. 5C). However, the other muscular structure for the inferior attachment of the FO valve was only an irregularly-shaped, small myocardial structure at the left atrial face. We consider this myocardial structure as a highly folded primary septum (Fig. 5E and F), in contrast to the septum in type 2 hearts (Fig. 4H), although it appeared to be no more than a myocardial mass in Fig. 6D and E. All of the myocardial structures appeared to be derived from the primary septum. Therefore, each of the type 3 hearts lacked a muscular septum-like structure that provides an inferior margin of the fossa ovalis. Two of the four type 3 hearts each had a probe patent foramen (Fig. 5A and B), and the other two each had a macroscopically open foramen (Fig. 6A and B). Macroscopically, at the right atrial face, one of the type 3 hearts had a long and narrow plate that arose from the inferior caval orifice.

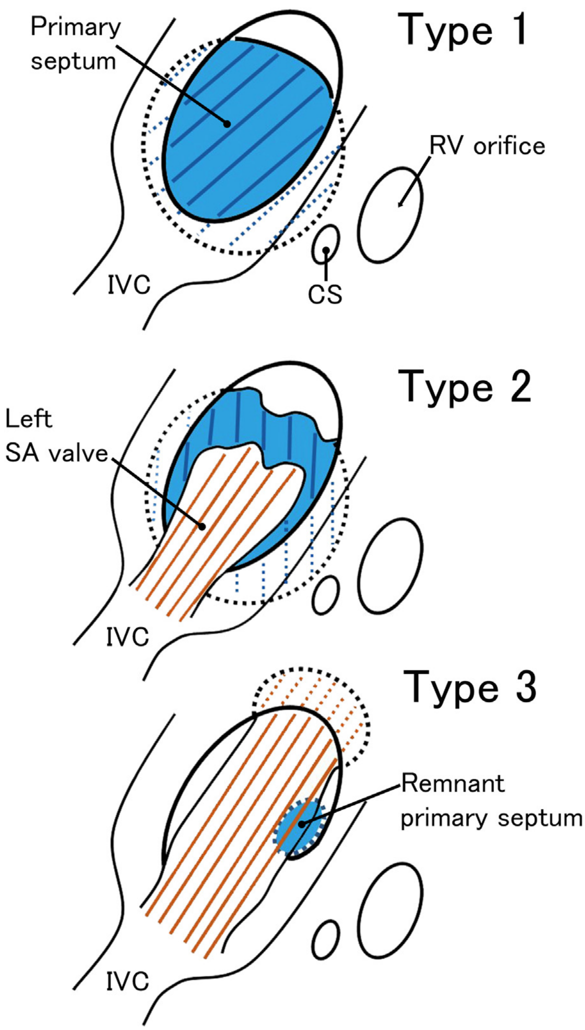

Fig. 7. Three types of FO valves identified in fetal hearts.
Viewed from the right atrial face of the fossa. A type 1 heart has a candidate primary septum-derived valve (complete) covering the foramen from the left atrial face (10 specimens). A type 2 heart has a candidate primary septum-derived valve (incomplete) associated with a well-developed, left sinoatrial valve (7 specimens). A type 3 heart has a large valve, but it appears to arise from the inferior caval orifice and its nearby site and is associated with a candidate remnant of the primary septum (4 specimens). CS, coronary sinus; IVC, inferior vena cava; RV, right ventricle.

Consequently, each of the examined hearts had a primary septum-derived valve as a myocardium-containing membrane that extended along the left atrial face. In contrast, a candidate SA valve-derived membrane was continuous with the subendocardial fibrous tissue, in that it originated from the inferior caval orifice and nearby sites, and likely extended toward the interatrial area because of the highly folded or remnant primary septum. In all specimens examined, we found no anomalies in the coronary sinus orifice, atrioventricular valves, and topographical relationships among the four chambers. Comparisons of sections of the same regions indicated no distinct differences from gestational age 30–40 weeks in the presence of minor coronary veins (Kim et al., 2018), epicardiac and myocardiac nerves (Cho et al., 2019), and internal topographical anatomy.

4. Discussion

Our most striking finding is the considerable morphological variation in the FO valve and fossa ovalis among near-term fetuses. To our knowledge, no previous study reported macroscopic and histologic observations of so many fetal hearts that had macroscopically open FOs, especially viewed from the left atrial face of the FO. We cannot exclude the possibility that some of the observed variations were due to cardiac teratology. However, Patten et al. (1929) also found distinct open FOs in 36.2% of 69 normal fetuses at term. Moreover, our descriptions of the internal morphologies of fetal hearts are consistent with those of Keen (1942) and Sweeney and Rosenquist (1979). Thus, the topographical anatomy described in our schematic (Fig. 7) seems to be within the normal range. We considered that the type 2 and type 3 hearts had a primary septum that was highly folded, or that even became a remnant. Whether the fetal FO was probe-patent or macroscopically open seemed unrelated with severity of the abnormality of the primary septum, because there were also probe-patent hearts in type 3 and type 1.

Because there were no anomalies in the coronary sinus or atrioventricular junction, our type 2 and type 3 hearts differ from the well-known anomaly "ostium primum defect", which is caused by a complete lack of the vestibular spine (Anderson et al., 2015). However, the possibly abnormal primary septum, especially in type 3 hearts, might be a consequence of a poorly developed vestibular spine during embryogenesis. A baby with a remnant primary septum might not die at or soon after birth if it was able to grow more than 30 weeks *in utero* and because the large left SA valve appeared to compensate for the flap valve function by closing the macroscopically open foramen. Therefore, it might be better to consider the abnormal morphologies we described here as a spectrum of variations, from a primary-septum derived FO valve to a left SA valve-derived valve. In addition, based on views from the "right" atrial face of adult hearts, Klimek-Piotrowska et al. (2016) described an FO with a high rim, and another morphology with a low and dull rim that included a patent foramen. However, they did not describe morphologies viewed from the left atrial face.

Most textbooks, citing the work of Christie (1963), explain that the FO valve originates largely from the primary septum, and there is a limited contribution of the left SA valve for the inferoposterior crescent (Hamilton and Mossman, 1978; Skandalakis and Gray, 1994; Williams, 1995; Sadler, 1995; O'Rhahilly and Műller, 1996; Moore and Persaud, 1998). Our Figs. 2 or 3 seem to exhibit such a crescent, but it was provided by the left SA valve attaching to the right atrial face of the fossa ovalis. Christie (1963) examined 15 specimens that had CRLs of 25–210 mm, but only assessed one specimen (CRL of 50 mm) histologically after macroscopic photos were taken during dissection. Two other specimens (CRL 5 mm and 26 mm) were only assessed histologically, and 12 were only assessed macroscopically. Therefore, the conclusion that there was degeneration of the left SA valve was based largely on macroscopic observations. Christie did not find a macroscopically plate-like FO valve at the right atrial face, nor a valve with a high superior rim at the left atrial face, either of which is likely associated with a left SA valve-derived FO valve. The crescent might also correspond to the primary septum remnant.

The classical interpretation is that the muscular secondary septum grows dorsocaudally, as a continuation of the sinus septum, and it has a width greater than the interseptovalvular space. Thus, the dorsal attachments of the primary septum and the left SA valve extend into the interior of the atrium on its left and right surfaces (Williams, 1995). Naito et al. (2015) demonstrated three types of anteroposterior arrangements of the coronary sinus, sinus septum, and SA valves. These variations seem to affect the morphology of the coronary sinus valve in adults. The origin of the sinus septum is a major subject in embryonic heart research (Steding et al., 1990). The incorporation of the sinus venosus into the right atrium indicates the sinus septum has an intra-atrial position (Steding et al., 1990). However, a right border of the left atrium is still not evident in early fetuses when the atrial roof infolding is ongoing (Kim et al., 2014). A slight difference in timing and topographical anatomy of the sinus septum may explain the SA valve extending into the left atrium, and this may result in a folded primary septum.

Finally, a limitation of this study is that all examined sections were stained only with H&E (from previous studies). If we had used additional stains, such as Masson trichrome, it may have been possible to confirm whether the flap valves contained myocardium.

Authorship contribution

DS contributed to data acquisition and writing of the manuscript. JHK designed the study and contributed to data acquisition, interpretation and writing the manuscript. GM designed the study and contributed to data interpretation, and critical revision of the manuscript. SS and HA contributed to data interpretation and the critical revision of the manuscript. JFRV contributed to data interpretation and critical revision of the manuscript. All authors agreed with the submission.

Ethical standards

The authors assert that all procedures contributing to this work complied with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1995, as revised in 2000, and that the study was approved by the relevant institutional committees (No. 1428).

References

Anderson, R.H., Spicer, D.E., Brown, N.A., Mohun, T.J., 2014. The development of septation in the four-chambered heart. Anat. Rec. 297, 1414–1429.

Anderson, R.H., Mohun, T.J., Brown, N.A., 2015. Clarifying the morphology of the septum prinum defect. J. Anat. 226, 244–257.

Cho, K.H., Kim, J.H., Murakami, G., Abe, H., Rodríguez-Vázque, J.F., 2019. Nerve distribution in myocardium including the atrial ventricular septa in late stage human fetuses. Anat. Cell Biol. 52, 1–9.

Christie, A., 1930. Normal closing time of the foramen ovale and the ductus arteriosus. Am. J. Dis. Child. 40, 323–326.

Christie, G.A., 1963. The development of the limbus fossae ovalis in the human heart — a new septum. J. Anat. 97, 45–54.

Gardner, E., O'Rahilly, R., 1976. The nerve supply and conducting system of the human heart at the end of the embryonic period proper. J. Anat. 121, 571–587.

Hamilton, W.J., Mossman, H.W., 1978. Human Embryology, 4th edition. Williams & Wilkins, London, pp. 247.

Jensen, B., Spicer, D.E., Sheppard, M.N., Anderson, R.H., 2017. Development of the atrial septum in relation to postnatal anatomy and interatrial communications. Heart 103, 456–462.

Keen, J.A., 1942. A note on the closure of the foramen ovale and the post-natal changes of the ventricles in the human heart. J. Anat. 77, 104–109.

Kim, J.H., Hwang, S.E., Rodríguez-Vázquez, J.F., Murakami, G., Cho, B.H., 2014. Upper terminal of the inferior vena cava and development of the heart atriums: a study using human embryos. Anat. Cell Biol. 47, 236–243.

Kim, J.H., Chai, O.H., Song, C.H., Jin, Z.W., Murakami, G., Abe, H., 2018. Observations of fetal heart veins draining directly into the left and right atria. Folia Morphol., in press.

Klimek-Piotrowska, W., Hołda, M.K., Koziej, M., Piątek, K., Hołda, J., 2016. Anatomy of the true interatrial septum for transseptal access to the left atrium. Ann. Anat. 205, 60–64.

Moore, K.L., Persaud, T.V.N., 1998. The Developing Human, 6th edition. WB Saunders, Philadelphia.

Naito, M., Yu, H.C., Kim, J.H., Rodriguez-Vazquez, J.F., Murakami, G., Cho, B.H., 2015. Topographical anatomy of the fetal inferior vena cava, coronary sinus and pulmonary veins: variations in Chiari's network. Clin. Anat. 28, 627–637.

Odgers, P.N.B., 1934. The formation of the venous valves, the foramen secundum and the septum secundum in the human heart. J. Anat. 69, 412–422.

O'Rhahilly, R., Müller, F., 1996. Human Embryology and Teratology, 2nd edition. Wiley-Liss, New York, pp. 194–201.

Patten, B.M., Sommerfield, W.A., Paff, G.H., 1929. Functional limitations of the foramen ovale in the human foetal heart. Anat. Rec. 44, 165–178.

Patten, B.M., 1931. The closure of the foramen ovale. Dev. Dyn. 48, 19–44.

Pauza, D.H., Skripka, V., Pauziene, N., Stropus, R., 2000. Morphology, distribution, and variability of the epicardiac neural ganglionated subplexuses in the human heart. Anat. Rec. 259, 353–382.

Röse, C., 1890. Beitrage zur vergleichenden Anatomie des Herzens der Wirbelthiere. Morph. Jahrb. 16, 27–96.

Sadler, T.W., 1995. Langman's Medical Embryology, 7th edition. Williams & Wilkins, Baltimore.

Sizarov, A., Anderson, R.H., Christoffels, V.M., Moorman, A.F.M., 2010. Three-dimensional and molecular analysis of the venous pole of the developing human heart. Circulation 122, 798–807.

Skandalakis, J.E., Gray, S.W., 1994. Embryology for Surgeons, 2nd edition. Williams & Wilkins, Baltimore, pp. 924.

Steding, G., Xu, J.W., Seidl, W., Månner, J., Xia, H., 1990. Developmental aspects of the sinus valves and the sinus venosus septum of the right atrium in human embryos. Anat. Embryol. 181, 469–475.

Sweeney, L.J., Rosenquist, G.C., 1979. The normal anatomy of the atrial septum in the human heart. Am. Heart J. 98, 194–199.

Williams, P.L., 1995. Gray's Anatomy, 38th edition. Churchill Livingstone, London, pp. 303–304.