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The Fibrous Skeleton in the Human Heart: Embryological and Pathogenetic Considerations

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Summary. The fibrous skeleton of the human heart is composed of several parts which are formed from different, mainly extracardiac sources. The atrioventricular valve rings are formed by invagination of sulcus tissue at the atrioventricular and bulboventricular transitions. The atrial part of the central fibrous body is formed from an ingrowth of tissue from the dorsal mesocardium, the ventricular part from ingrowth of sulcus tissue towards an endocardial structure, the left bulbar ridge. During valve development the atrioventricular endocardial cushions, initially situated between the developing atrial and ventricular parts of the central fibrous body, are almost completely removed downwards into the ventricular cavities. However, a small portion of these cushions remains on top of the ventricular septum, is "trapped" by the surrounding sulcus tissues and becomes incorporated in the central fibrous body. These embryological findings on this centrally located area of the heart have implications for certain types of cardiac abnormalities. In this respect the atrioventricular conduction system, cor triatriatum sinistrum and atrioventricular defect are discussed.

Key words: Atrial septum – Central fibrous body – Heart: development – Heart: fibrous skeleton – Heart: malformations

The fibrous skeleton of the heart consists of the anuli of the atrioventricular and arterial orifices and the central fibrous body, which connects atrioventricular and aortic anuli. The membranous septum is in continuity with the right part of the central fibrous body. Directly above the point of junction of the atrioventricular node and the common bundle, a strip of connective tissue from the central fibrous body passes posteriorly through the atrial septum and is continuous with the Eustachian valve. This is the tendon of Todaro. The present study deals with the embryologic background of the fibrous skeleton of the heart and its relationship

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with the atrioventricular sulcus tissue. The importance of this mesenchymal tissue has been emphasized in various developmental processes. Wenink (1971) described the continuity of the atrioventricular sulcus tissue with the dorsocaudal extension of an endocardial structure, the left bulbar ridge, in the human embryo. He suggested that the fibrous casing of the bundle of His has its origin not only in this left bulbar ridge but also, for a smaller part, in the tissue of the sulcus.

Anderson et al. (1977b) stated that in certain forms of congenital heart block it was mainly sulcus tissue and not endocardial cushion that prevented contact between conducting tissue and atrial myocardium. Furthermore, it has been stressed that the sulcus tissue becomes the main constituent of the atrioventricular valves and valve rings (Van Gils 1979). The role of the endocardial cushions as a valvular apparatus seemed to be confined to young stages, whereas the contribution of cushion tissue to the definitive atrioventricular valves and valve rings was found to be minimal.

The heart is initially formed as two endocardial heart tubes, which fuse and remain connected dorsally for some time by means of an area of mesenchyme tissue, the dorsal mesocardium. The atrioventricular sulcus material originates from the tissue of the dorsal mesocardium which, after formation of the myocardium beginning at the venous pole of the heart, gradually covers the whole heart tube and thus forms the epicardial layer (Shimada and Ho 1980). In early stages the dorsal muscular atrial wall is incomplete and in close contact with this expanding tissue of the dorsal mesocardium (His 1885). Because of this gap in the atrial wall involvement of the tissue of the dorsal mesocardium in atrial development is conceivable.

The aim of our study was to investigate to what extent the sulcus tissue contributes to the fibrous skeleton of the heart, to what extent the endocardial cushions are involved and whether or not other sources participate in this developmental process. Finally our embryological findings were matched with present views on the pathogenesis of some cardiac defects.

Material and Methods

89 human embryos from 5 to 47 mm crown-rump(CR)-length present in the collection of the Department of Anatomy and Embryology were investigated. Serial sections were 10 mu thick and stained by routine histological methods. The relevant stages will be described.

A graphic reconstruction (Tinkelenberg 1979) was made of the heart of a 47 mm CR-length embryo.

Observations

In an embryo of 5 mm CR-length the dorsal muscular atrial wall has a gap in the midline. Through this gap rather dense mesenchymatous material from the dorsal mesocardium is continuous with loose mesenchymatous tissue inside the atrial cavity extending to the anterior atrial wall, where this wall faces the proximal part of the arterial trunk (Fig. 1). More caudally, it borders on the lower atrioventricular endocardial cushion. Thus, this mesenchymatous tissue is closely connected with the lower border of the developing septum primum.

In embryos of 6 mm CR-length, the mesenchymatous tissue in the atrial cavity contacts both upper and lower endocardial atrioventricular cushions. It forms the upper border of the foramen primum, i.e. the lower crest of the septum primum

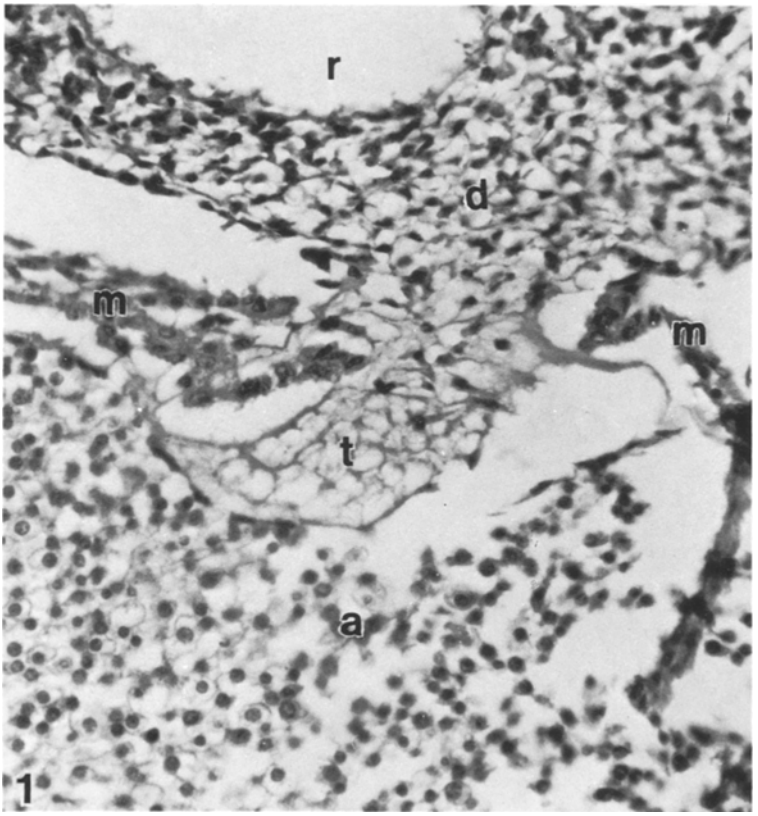

Fig. 1. Transverse section of heart of a 5 mm embryo to show the continuity of dorsal mesocardium (*d*) with mesenchymatous tissue (*t*) inside the atrial cavity (*a*). The dorsal muscular atrial wall (*m*) is interrupted in its midline. The atrial cavity is filled with erythroblasts. *r* right lung bud (×260, H-E)

(Fig. 2a, b). The appearance of its most anterior part is very like the endocardial cushions with their "empty", poorly staining appearance; towards the venous valves, it appears more readily stainable and dense. Dorsocaudally, its appearance is like the tissue of the dorsal mesocardium, with which it is continuous.

In an embryo of 9.5 mm CR-length, the foramen primum is almost completely closed (Fig. 3a, b). Following the series in a caudal direction, more mesenchymatous tissue is found in the base of the atrial septum primum (Fig. 3a, b). At the level where the septum primum contacts the lower atrioventricular endocardial cushion, it consists mainly of mesenchymatous tissue continuous with the dorsal mesocardium (Fig. 3b).

In an embryo of 17 mm CR-length a dense strip of mesenchymatous tissues lies upon the now fused atrioventricular endocardial cushions, between these and the atrial septum primum. Thus it prevents any direct contact between this septum and the endocardial cushions (Fig. 4a). Caudally, this strip can be followed behind the venous orifices being continuous with the tissue in the venous valves (Fig. 4b, c). This suggests that the mesenchymatous strip is continuous with the developing tendon of Todaro. Dorsocaudally, the strip is in continuity with the dorsal mesocardium.

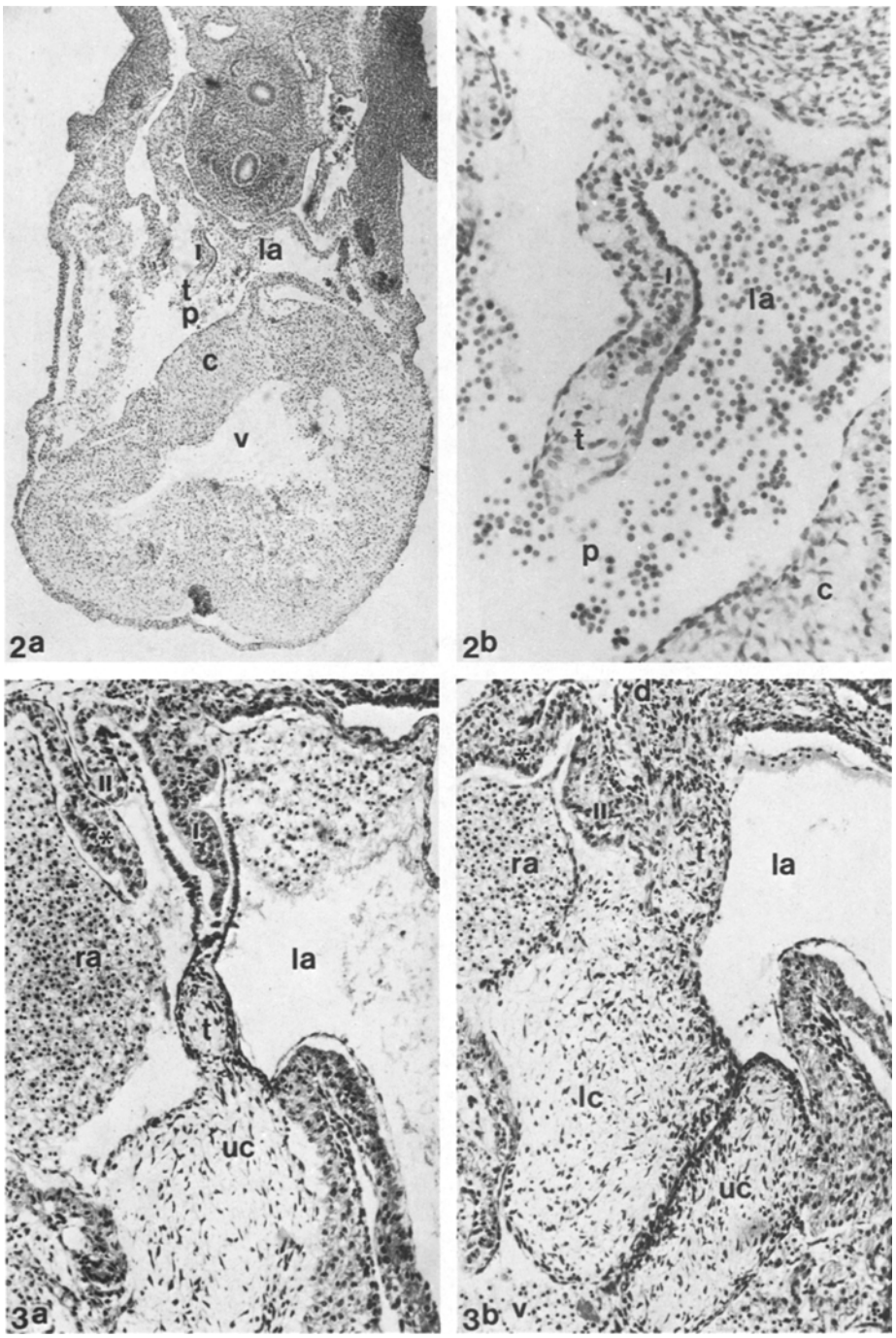

Fig. 2a, b. Transverse section of heart of a 6 mm embryo. **a** Mesenchymatous tissue (*t*) forms the lower crest of the septum primum (*I*) and upper border of the foramen primum (*p*). (× 105, H-E). **b** Detail. The mesenchymatous tissue is poorly stainable and "empty" alike the endocardial cushions (*c*). *la* left atrium; *v* ventricle (× 225, H-E)

Fig. 3a, b. Transverse section of heart of a 9.5 mm embryo. **a** The myocardial cells of the septum primum (*I*) are distributed in a random way, unlike the organized double-folded muscular layer of the septum secundum (*II*) and the venous valves (*). The mesenchymatous tissue (*t*) separates septum primum and upper atrioventricular endocardial cushion (*uc*). **b** More caudally the septum primum shows mainly mesenchymatous tissue (*t*) in contact with dorsal mesocardium (*d*) and lower atrioventricular endocardial cushion (*lc*). *la* left atrium; *ra* right atrium; *v* ventricle. (× 90, H-E)

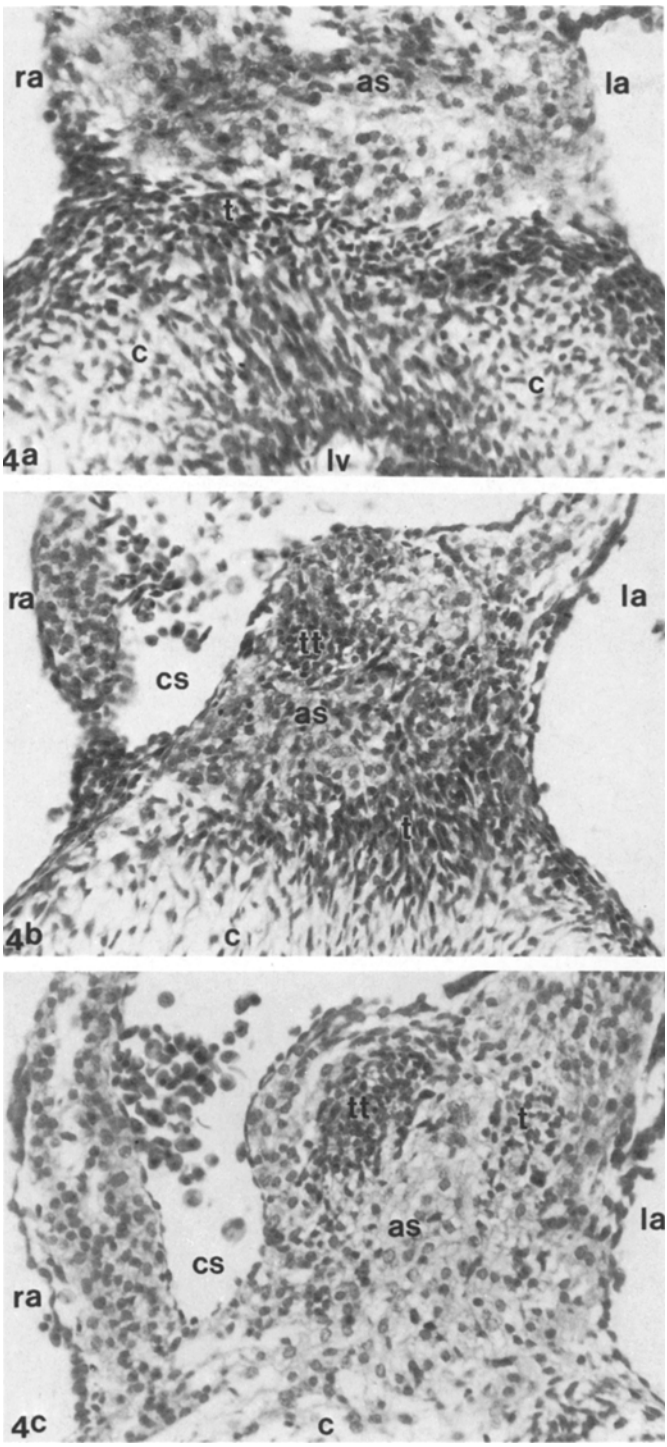

Fig. 4a–c. Transverse section of heart of a 17 mm embryo. **a** Mesenchymatous tissue (*t*) prevents contact of atrioventricular endocardial cushions (*c*) and atrial septum (*as*); its nuclei are more dense and appear to be cut in a different plane from the atrioventricular cushions. **b** In a lower section this tissue appears to be stretching out towards the area of the venous valves where the developing tendon of Todaro (*tt*) can be seen. **c** In a further section this tissue becomes continuous with tissue in the venous valves and thus with the tendon of Todaro. *cs* coronary sinus; *la* left atrium; *lv* left ventricle; *ra* right atrium. (×235, H-E)

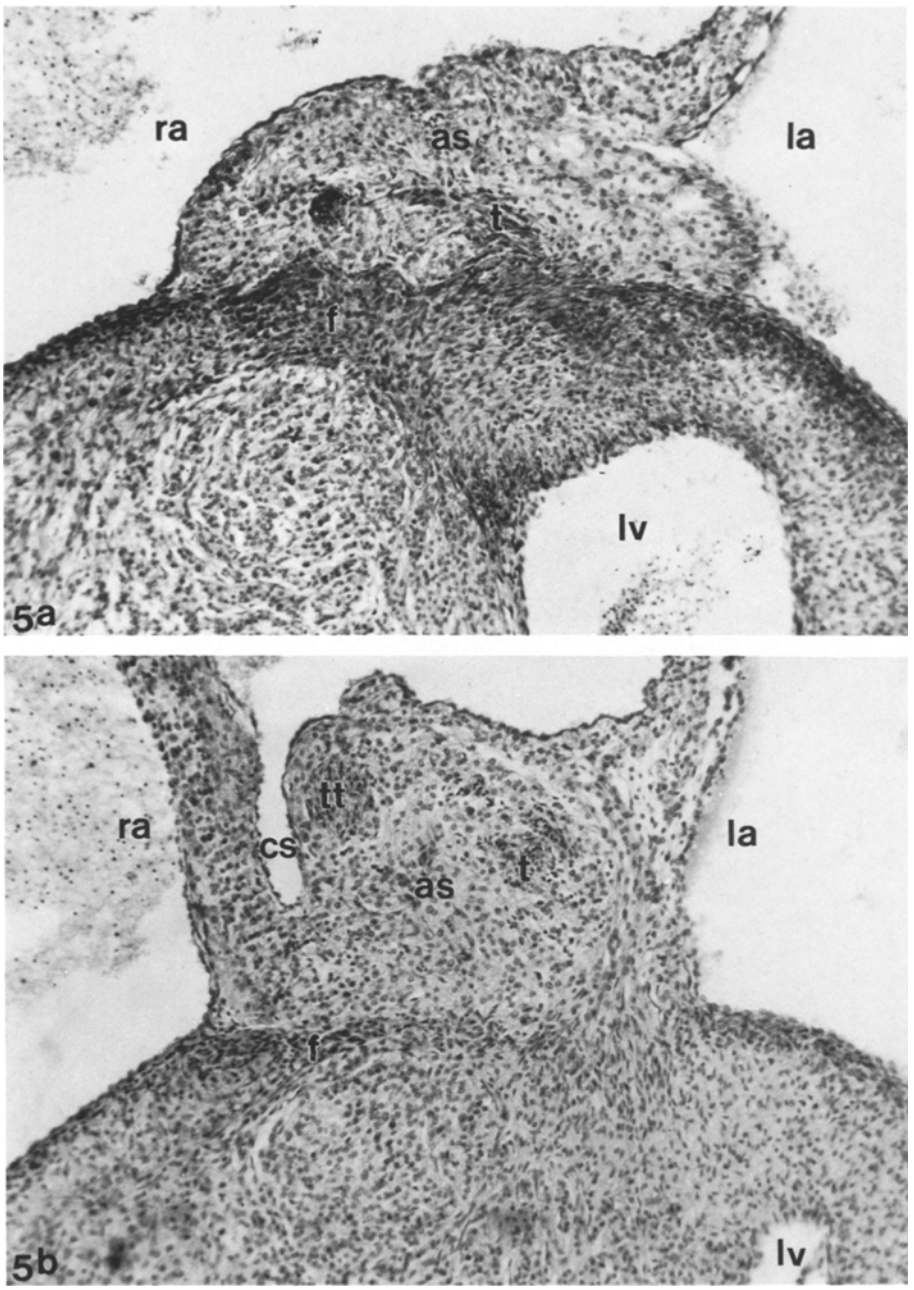

Fig. 5a, b. Transverse section of a heart of a 29.5 mm embryo. Collagen fibers appear in the developing fibrous skeleton of the heart (*f*). **a** Part of this fibrous skeleton, derived from the forementioned ingrowth of mesenchymatous tissue (*t*) stretches out into the lower crest of the atrial septum (*as*) towards the region where, in lower sections, the venous valves will be found. **b** In the venous valves the tendon of Todaro (*tt*) is present, whereas the mesenchymatous ingrowth (*t*) will reach it in the next few slides. The contact of ingrowth tissue with the dorsal mesocardium has become almost indistinguishable, as the interruption in the dorsal muscular atrial wall is almost closed in this stage *cs* coronary sinus; *la* left atrium; *lv* left ventricle; *ra* right atrium. (×210, Azan)

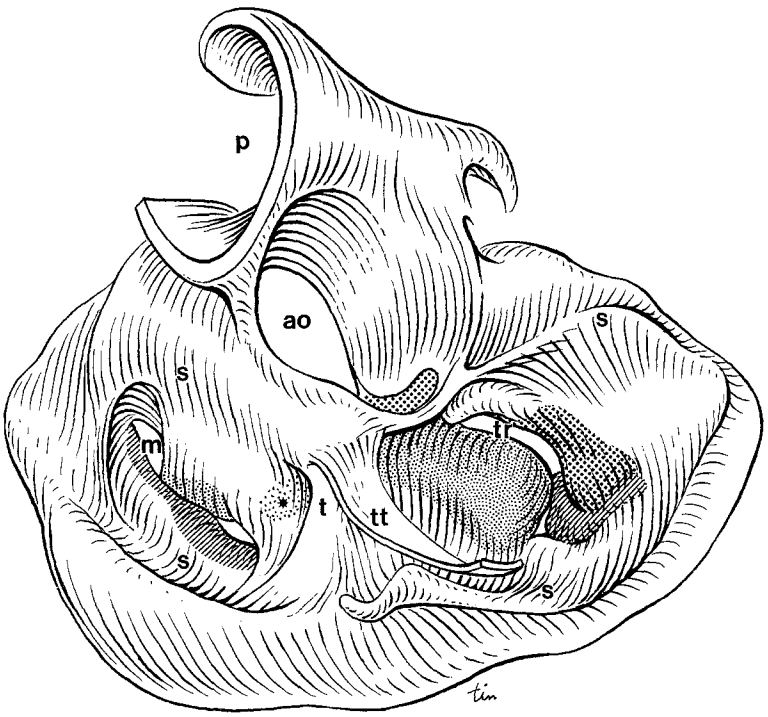

Fig. 6. Graphic reconstruction of the fibrous skeleton of the heart of a 47 mm embryo; craniodorsal view. The atrioventricular valve anuli and valves are formed from ingrowth of sulcus tissue which has become collagenized at this stage (*s*). Cushion tissue can still be found at the apical parts of the valve leaflets (*dotted and shaded areas*). Some cushion tissue remains visible on top of the ventricular septum (*). Above it the ingrowth from the dorsal mesocardium forms a sagittal rim (*t*) whereupon the muscular atrial septum rests. As myocardial tissue is not depicted, there appears to be a gap between the visualized tendon of Todaro (*tt*) and the base of the atrial septum. *ao* aorta; *m* mitral orifice; *p* pulmonary trunk; *tr* tricuspid orifice. (×37)

In an embryo of 29.5 mm CR-length, collagen fibers are present in the mesenchymatous tissue. The endocardial cushion tissue is found only in the apical parts of the developing valve leaflets at the distal part of the ingrowing sulcus material. This forms the atrioventricular anuli and valves as a fibrous "cylinder". A small remnant of cushion tissue still covers the top of the muscular ventricular septum.

At the atrial side, the dense mesenchymatous tissue extends towards the dorsocaudal part of the atrial septum (Fig. 5a, b). Muscular continuity in the dorsal atrial wall is still interrupted.

From an embryo of 47 mm CR-length, cut in a sagittal plane, a graphic reconstruction was made of the fibrous skeleton, the developing atrioventricular valves and the endocardial cushions (Fig. 6). The tissue in the atrioventricular sulcus surrounds both atrioventricular orifices. From this sulcus tissue two "cylinders" of collagenous material descend into the ventricles at the inner aspect of the atrioventricular transition. These cylinders are the developing atrioventricular valves. Cushion tissue is found in the apical, distal part of these atrioventricular

valves. As in the embryo of 29.5 mm CR-length, some cushion tissue remains visible on top of the ventricular septum, i.e. in the basal part of the central valve leaflets. Cranial to this, a fibrous ridge extends from the anterior atrial wall – behind the proximal part of the ascending aorta – towards the dorsocaudal part of the atrial septum, separating the cushion tissue from the atrial septum. In this stage the dorsal muscular atrial wall is complete. The atrioventricular node can be found at the right atrial side of this fibrous bridge whereas the common bundle penetrates it to gain access to the ventricles.

Discussion

This study shows that in an embryo of 5 mm CR-length a bridge of mesenchymatous tissue exists at the atrial side of the atrioventricular cushions, thus separating these cushions from the atrial septum. This bridge appears to be continuous with the dorsal mesocardium. It forms the atrial, upper part of the central fibrous body, which latter structure is the central part of the fibrous skeleton of the heart, extending between atrial and ventricular septum (Fig. 7). Davis (1927) described how, as the heart originates from the mesenchyme anterior to the foregut, the area of contact of this mesenchyme and the developing heart becomes a somewhat elongated and thin strip of mesenchyme, the dorsal mesocardium. This concurs with the description of Los (1960) and Langemeyer (1977) that the "coelomic organ", i.e. the mesenchymatous wall of the coelomic cavity, expands considerably and can be considered as the precursor of the venous pole of the heart. Laane (1978) also emphasized its relationship with development at the arterial pole of the heart.

At the area of contact of atrial wall and dorsal mesocardium, mesenchyme protrudes into the atrial cavity through an interruption of the dorsal atrial wall. In successive stages, this mesenchyme of the dorsal mesocardium gradually becomes more abundant in the atrial cavity; already at an early stage it is in contact with both atrioventricular cushions and the developing atrial septum primum (Fig. 3a). Thus, it is evident that the classical view of Mall (1912), that the "septum primum" fuses with the endocardial cushions has to be modified. It is not the "muscular" septum primum that fuses with the endocardial cushions. Instead an interjacent fibrous bridge of mesenchymatous tissue is formed along the lower border of the septum primum, which bridge prevents fusion of this septum with the atrioventricular endocardial cushions. This half-moon shaped cushion-like material seems to be identical to the structure that His named the spina vestibuli (1885). In early embryonic stages Puerta Fonollá and Orts Llorca (1978) described the beginning of this spina vestibuli as an ingrowth in the dorsocaudal part of the atrium starting from a cellular structure similar to that of the endocardial cushions. However, they do not mention the continuity with tissue of the dorsal mesocardium, which was very obvious as far as the 17 mm embryo.

We found that the ingrowing tissue remained visible throughout all stages of subsequent development and became more fibrous at an earlier stage than the atrioventricular cushions. In later embryonic stages the continuity with the dorsal mesocardium disappears as the interruption in the atrial myocardium is closed.

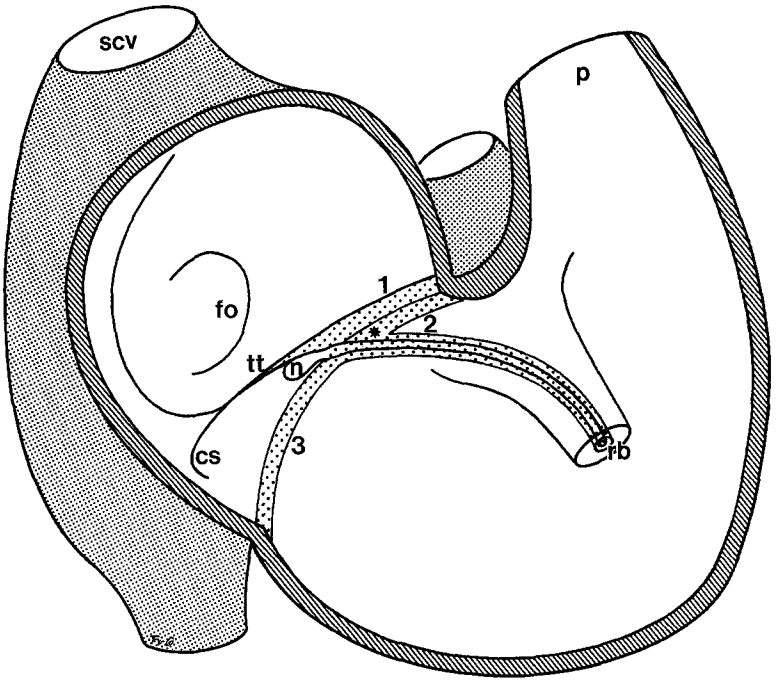

Fig. 7. Diagram illustrating the various contributions to the fibrous skeleton. 1. Atrial part (formed by ingrowth from the dorsal mesocardium). 2. Ventricular part and ensheathment of right bundle branch (ingrowth of posterior atrioventricular sulcus towards left bulbar ridge). 3. Valve anulus (invagination of sulcus tissue). * Incorporated part of cushion tissue on top of ventricular septum. *cs* coronary sinus; *fo* fossa ovalis; *n* atrioventricular node; *p* pulmonary trunk; *rb* right bundle branch; *scv* superior caval vein; *tt* tendon of Todaro, ending in both venous valves

From the 17 mm CR-length stage on, its posterior aspect is continuous with an expanding area of dense mesenchymatous tissue, stretching out to the right until it is behind the venous orifices and situated cranial to the atrioventricular node. Because of its location, this tissue appears to form the tendon of Todaro (Figs. 4, 5).

Shimada and Ho (1980) described that the tissue of the dorsal mesocardium forms the epicardial tissue, starting in the region of the sinus venosus. It is interesting to note that the successive outgrowth over the external surface of the heart, as described by them, concurs with the ingrowth into the interior of the heart described in this paper.

It is evident that the atrial part of the central fibrous body appears to be of extracardiac origin. The ventricular part is also of extracardiac origin, as is described in the literature (Wenink 1971). He described that the endocardial structure separating the ventricular septal myocardium from the atrioventricular endocardial cushions, is the left bulbar ridge. Ingrowth of tissue from the posterior atrioventricular sulcus towards the left bulbar ridge results in the ensheathment of the conducting tissues, as it courses for a long distance between the atrioventricular cushions and the ventricular septum. Due to this tissue bridge, fusion between

atrioventricular endocardial cushions and muscular ventricular septum is prevented and the ventricular, lower part of the central fibrous body is formed (Fig. 7).

The fibrous skeleton of the heart is closely linked to the atrioventricular valve rings. During atrioventricular valve development, most cushion tissue is removed downwards into the ventricles, whereas invaginating tissue of the atrioventricular sulcus forms the main part of the valves (Van Gils 1979). Parts of the bulboventricular sulcus also contribute to valve development (Anderson 1978; Meredith et al. 1979; Wenink 1980; Wenink in press). This implies that the atrioventricular valve rings are formed by extracardiac sulcus tissue (Fig. 6).

Although during valve development the greater part of the cushion tissue is removed downwards into the ventricles, a small remnant persists on top of the ventricular septum. This cushion remnant could very well be the tissue that was described by Walmsley (1929) and Wenink (1971) as taking part in the formation of the membranous septum which structure may be considered to be part of the fibrous skeleton (Bargmann 1963). The cushion remnant becomes embedded in material from extracardiac – sulcus – origin, which is gradually converted to fibrous tissue (Anderson et al. 1977a; Anderson et al. 1977b; Wenink 1971). Only in later stages of development, when it is already completely enclosed by collagenous material derived from sulcus tissue, does the cushion remnant become completely collagenized. This implies that this remnant of the atrioventricular cushions is included in the central fibrous body as it is "trapped" by the surrounding sulcus tissue (Fig. 7).

Ingrowth of tissue from the dorsal mesocardium contributes to the atrial part of the central fibrous body and is continuous with the tendon of Todaro. Invagination of sulcus tissue from the posterior atrioventricular sulcus towards the dorsocaudal extension of the left bulbar ridge results in the formation of the fibrous sheath of the conducting tissue and of the ventricular part of the central fibrous body. An invagination at the atrioventricular transition, coalescing with part of the bulboventricular transition zone, results in the formation of the atrioventricular valve rings. Finally, a small part of the atrioventricular endocardial cushions remains on top of the ventricular septum, is "trapped" by the surrounding sulcus tissues and thus incorporated in the central fibrous body.

Analysis of the embryonic development of the fibrous skeleton of the heart has certain implications for our present views on cardiac maldevelopment. The first example where embryology and pathology are closely related is the atrioventricular conduction system. This paper describes the formation of the inferior edge of the atrial septum in normal hearts by an ingrowth from the dorsal mesocardium, which covers the atrioventricular node and common bundle. It forms the atrial part of the central fibrous body and from there the tendon of Todaro proceeds towards the venous valves (Fig. 7). Close to the inferior edge of the atrial septum the atrioventricular node and common bundle can be found. In the normally developed heart the primordium of the deep component of the definitive atrioventricular node is formed by an invagination of the posterior atrioventricular myocardial ring. It is separated from the ventricular myocardium by the enveloping atrioventricular sulcus tissue. In passing beneath the endocardial cushions and anterior sulcus tissue it becomes separated from the atrial myocardium and contacts the primordium of

the atrioventricular bundle (Anderson et al. 1977a). The nature of the tissues contributing to the superficial atrial nodal components is entirely dependent upon the mode of formation of the lower portion of the atrial septum. They are derived firstly from the forward projection of the sinus venosus, secondly from the posterior invagination of the anterior atrioventricular myocardial ring, and finally from the primitive atrial component of the atrial septum (Anderson et al. 1976, 1977a). It has been suggested that the deep nodal component is separated from the atrial septum by sulcus tissue (Anderson et al. 1977a) but this statement has to be further specified. We know that an ingrowth from the dorsal mesocardium stretches out along the inferior edge of the atrial septum primum from the aspect posterior to reach directly behind the ascending aorta anterior. This means that this ingrowth separates the atrioventricular node and proximal part of the common bundle from the atrial myocardium. Sulcus tissue partially envelops the deep nodal component, but for the distal part and common bundle the separation from the atrial septum mainly results from the mesocardial ingrowth. This forms a fibrous intermediate layer, part of the central fibrous body. We have observed that the thickness of the intermediate layer may be variable, nevertheless it should prevent electrophysiological contacts between atrial myocardium and bundle to avoid conduction disturbances. Indeed, absence or poor formation of this fibrous intermediate layer, resulting in bypass tracts between atrial myocardium and common bundle, has been described. Several of these hearts did not exhibit any electrocardiographic abnormalities (Rossi 1969), others showed pre-excitation (Lev et al. 1966; Brechenmacher et al. 1974).

Both under, over or mal-development of ingrowing mesocardium tissue may influence cardiac development. In the second anomaly to be considered, cor triatriatum sinistrum, an abnormal diaphragm, typically diagonally oriented in the left atrial cavity, divides the left atrium into two compartments. The principal hypotheses on the morphogenesis of cor triatriatum concerns either abnormal development of the atrial septum, the "malseptation hypothesis" (Fowler 1881), or a deficient incorporation of the embryonic pulmonary vein into the left atrium, the "malincorporation hypothesis" (Griffith 1903; Loeffler 1949; Thilenius et al. 1976). Van Praagh and Corsini (1969) indicated the weak points in both hypotheses and offered a new concept, the "entrapment hypothesis", which incorporates both previously mentioned hypotheses. They suggested that the common pulmonary vein becomes entrapped by the relatively large mass of right horn sinus venosus tissue beneath which the vein runs early in its development. The left atrial ostium of the common pulmonary vein appears to get "roofed in" by fibroelastic tissue from the right sinus horn, thereby preventing normal incorporation. This implicates that the apparent cause of malincorporation of the common pulmonary vein into the left atrium is sinus venosus tissue, which is intimately related to septum primum. Indeed, this tissue is described by Van Praagh and Corsini (1969) as having "... the well-recognized endothelial property of forming fibroelastic tissue ...". What they describe could well be the mesenchymatous ingrowth from the dorsal mesocardium instead of "... endothelial (endocardial cushion) tissue ...". Apparently, this mesocardial tissue normally forms the lower rim of the atrial septum but it is possible that it may also expand into another direction, thus contributing to the formation of an intraatrial diaphragm.

In cases of atrioventricular defect it has been described that the inferior edge of the atrial septum consists, for the main part, of the tendon of Todaro and the central fibrous body, from which this tendon emerges anteriorly (Wenink et al. 1978). Based on our observations we can now postulate that this inferior edge is mainly formed by ingrowth from dorsal mesocardium tissue, whereas, more posteriorly, the tendon of Todaro emerges from it towards the venous valves. It is evident that the marked hypoplasia of the posterior part of the ventricular septum in atrioventricular defect prevents a normal attachment with the atrial septum, as it only contacts the atrial septum posteriorly (Thiene & Anderson 1978). As the inferior edge of the atrial septum is nevertheless complete, the atrial septum may be underdeveloped but its essential components are present! (Thiene et al. in press) This suggests that the atrial septum may vary greatly in appearance from apparently poor formation to complete development. The latter has been described recently (Piccoli et al. 1979).

As the inferior edge of the atrial septum is present in atrioventricular defect – though possibly hypoplastic –, we do not favor the term "septum primum defect". The malseptation of the atrioventricular canal has been described as the primary disorder in atrioventricular defect, which pleads against the use of the term "endocardial cushion defect" (Wenink et al. 1978). This explains our adoption of the term "atrioventricular defect".

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