Congenitally Complete Heart Block
Developmental Aspects

ROBERT H. ANDERSON, M.D., ARNOLD C. G. WENICK, M.D.,
TOM G. LOSEKOOT, M. D., AND ANTON E. BECKER, M.D.

SUMMARY Three cases of congenitally complete heart block are described of hearts in which other minor congenital malformations were not in themselves severe enough to disrupt the atrioventricular conduction system. The cases fitted well into the categorization of complete heart block suggested by Lev. Two exhibited lack of communication between the atrial and conducting tissues, the other had discontinuity of the penetrating atrioventricular bundle. In an attempt to explain why this discontinuity between different segments of the conducting tissues occurs, we re-examined several series of graded human embryos. This investigation suggested that the anulus fibrosus in the normal heart is derived from sulcus tissue of the atrioventricular junction, the endocardial atrioventricular cushions playing a minor role in the separation of atria from ventricles. The relationships between the sulcus tissues and the different components of the atrioventricular junctional area are discussed in terms of an explanation both for the existence of different types of congenitally complete heart block and for persistence of Mahaim (nodo-ventricular and nodo-fascicular) fibers.

CONGENITALLY COMPLETE HEART BLOCK results from failure of communication between the atrial and ventricular myocardial tissues as a consequence of lack of continuity of the atrioventricular conducting system across the fibrous atrioventricular anulus. It has been argued that, in an otherwise normal heart, such lack of continuity can either result from post-formative disruption of a normally developed conducting system or failure of fusion during development of parts of the conducting system derived from different embryological sources. Histopathological studies of congenital heart block, as reported in a recent review article, tend to support the latter concept, particularly since the studies of Lev and his colleagues have shown that there are two basic divisions of the dysrhythmia.

The first is that in which the atrial myocardial tissues fail to contact the compact atrioventricular node. The second group comprises those hearts in which a normally formed atrioventricular node is separated by fibrous tissue from the ventricular conducting tissues and myocardium. We recently examined an example of the first variety of complete heart block and suggested that such hearts were indeed best explained on the basis of interposition of fibrous tissue septa between differing embryological components of the specialized junctional tissues. We espoused a similar explanation for the second type of block, but at that time we were unable to explain why fibrous tissue should form between the different components of the node and bundle. We have now studied three further cases of congenitally complete heart block, and in the light of the findings in these hearts we have re-examined the embryological material at our disposal. We believe that our findings endorse the hypothesis of nodal development previously advanced, and show why fibrous tissue can form between the different conducting tissue components and thus produce congenitally complete heart block. At the same time our findings provide information regarding the development of the central fibrous body relative to the atrioventricular node and penetrating atrioventricular bundle of the normal heart.

From the Departments of Paediatrics, Cardiothoracic Institute, Brompton Hospital, London, England; Anatomy, State University of Leiden; Paediatrics, Binnen Gasthuis, University of Amsterdam; and Pathology, Wilhelmina Gasthuis, University of Amsterdam, The Netherlands.

Dr. Anderson was a Medical Research Council Travelling Fellow, U.K., during the course of this investigation. He is now a British Heart Foundation Senior Research Fellow.

Address for reprints: Dr. Anton E. Becker, Department of Pathology, Wilhelmina Gasthuis, Eerste Helmerstraat 104, Amsterdam, The Netherlands.

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Materials and Methods

The three cases of congenitally complete heart block were all admitted to the Binnen Gasthuis, University of Amsterdam, and despite treatment, all died. A complete autopsy was performed in each case. For histopathological examination of the conducting tissues, the entirety of the interatrial septum including the origin of the superior vena cava together with the proximal 1 cm of the interventricular septum was removed from the heart as a single block of tissue (fig. 1). The block was prepared for sectioning in routine manner, and following embedding in paraffin wax it was serially sectioned. In two instances sectioning was performed at right angles to both the atrioventricular junction and the plane of the septum (fig. 1). In the third case, the plane of section was parallel to the atrioventricular junction (fig. 4). Sections were cut at ten micron thicknesses, and each section was retained. Initially one section in each 50 was mounted and stained with a trichrome technique. Following examination of the original sections, further sections were mounted and stained as deemed necessary, mounting each section in areas of especial significance.

In order to determine the developmental history of the central fibrous body, we re-examined the graded series of human embryos previously studied and published.3, 10-13 The embryos comprised the collections of the University of Leiden, the University of Manchester and the Institute of Child Health, University of Liverpool.

Results

Case 1

This female child was born spontaneously at term weighing 4100 grams following an uncomplicated pregnancy. Directly after birth a slow heart rate was noted. At physical examination, there was no cyanosis but the liver was palpated 5 cm below the costal margin and the femoral pulses were impalpable. A precordial thrill was noted with irregular heart sounds, but no murmurs were audible. Laboratory tests were normal apart from a slight metabolic acidosis. Chest X-ray revealed gross cardiomegaly with small vascular pedicles and normal vascular markings. The electrocardiogram (fig. 2) revealed complete heart block with an atrial rate of 150 beats/min and a ventricular rate of 50 beats/min. High, peaked P waves were present with narrow QRS complexes of 0.06 msec duration. The QRS morphology suggested a high left ventricular septal site for the ventricular pacemaker. Multifocal ventricular extrasystoles were occasionally seen. Since a complex intracardiac malformation was suspected, cardiac catheterization was performed. This revealed an atrial communication with right-to-left shunting. Systolic pressures were equal in right

Figure 1. Photograph of the block of tissue removed for sectioning from case 1 (fig. 1A) and a drawing (fig. 1B) showing the plane of sectioning. Note that the block constitutes the entirety of the interatrial septum, including the ostia of superior (SVC) and inferior (IVC) vena cavae, the origin of the aorta (Ao), the crista supraventricularis (CSV) and the proximal part of the interventricular septum (IVS). TV = tricuspid valve; ASD = atrial septal defect; CS = coronary sinus. The lines a-a through d-d indicate the plane of section, and photomicrographs of these sections are illustrated in figure 3.
and left ventricles and the pulmonary artery and aorta. The ductus arteriosus was patent. Angiocardiography revealed marked isthmal hypoplasia with filling of the descending aorta through a large patent ductus arteriosus. Otherwise the cardiac chambers were normally formed and connected and the ventricular septum was intact.

The infant was treated with digoxin and diuretics, and initially made good progress. However, progressive vomiting of unknown cause supervened, necessitating intravenous therapy, to which a low dosage of aleudrine was added because of a decrease in ventricular rate to 40 beats/min. This produced an increase in ventricular rate, but this could not be maintained after discontinuation of intravenous medication, despite administration of aleudrine by rectum. Despite therapy the infant deteriorated and died at the age of 18 days.

Autopsy examination confirmed normal connections of the cardiac chambers with an atrial septal defect (fig. 1), isthmal hypoplasia and a patent ductus arteriosus. Histopathological examination revealed presence of a normal sinoatrial node, which made normal contact with atrial myocardium. The entire lower part of the atrial septum beneath the septal defect was found to be devoid of myocardial tissue (fig. 3a). The inferior limbus of the fossa ovalis was composed only of loose fibrous tissue. In this tissue were numerous large venous channels and multiple nerve bundles (fig. 3b). The anulus fibrosus was unexpectedly thick and was composed of dense fibrous tissue. A prominent artery ran through the anulus in the anticipated position of the atrioventricular node, and a few scattered bundles of small specialized-like cells surrounded the artery. These bundles did not penetrate the anulus, and no evidence was present apart from a few remnants in the central fibrous body (fig. 3c) of the penetrating atrioventricular bundle. However, the remnant continued as the bifurcating atrioventricular bundle, which was normally formed astride the ventricular septum, and which gave rise to a normal left bundle branch (fig. 3d). The right bundle branch could not be identified.

Case 2

A male child, weight 3250 grams, was born after a pregnancy of 42 weeks. During the pregnancy a fetal brady-cardia had been noted, and echocardiography (Dr. G. E. Freud) demonstrated the presence of complete heart block. Following birth, the presence of complete atrioventricular dissociation was confirmed. Examination revealed a pulse rate of approximately 50 beats/min. The liver was enlarged but there was no cyanosis or edema. Peripheral pulses, however, were poor. Auscultation revealed normal heart sounds with a grade 2/6 systolic murmur audible at the left sternal edge. There were multiple extrasystoles. Laboratory investigations were normal apart from a metabolic acidosis.
The chest X-ray revealed gross cardiomegaly. The ECG showed evidence of complete heart block, with an atrial frequency of 150 beats/min and a ventricular frequency of 50 beats/min. The QRS complexes were narrow, and their morphology suggested an origin for the ventricular pacemaker high in the left aspect of the septum. There were multiple ventricular extrasystoles.

The child was treated with oxygen and intravenous therapy to counteract the acidosis. Although permission for pacemaker implantation was requested, this procedure was not permitted by the child’s parents. The infant deteriorated and died on the second day.

At autopsy, the positive findings were confined to the heart. The chambers and great arteries were normally connected and related. The foramen ovale was probe patent and the ductus arteriosus closed. The lower segment of the atrial septum was grossly deficient, and transillumination revealed absence of musculature in the entire inferior limbus (fig. 4a).

Histopathology revealed the presence of a normal sinoatrial node, which at its margins merged with working atrial myocardium. In the region of the inferior limbus, the atrial septum was found to be composed entirely of fibrous tissue, with endothelial channels and conspicuous nerve bundles coursing anteriorly from the atroventricular sulcus (fig. 4a). An extensive penetrating bundle was identified coursing toward the atrial septum, but this structure never succeeded in passing through the anulus fibrosus. It was always enclosed by fibrous tissue on its atrial aspect, but there were multiple connections identified inferiorly between the conducting tissue and the underlying ventricular myocardium (fig. 4b). When traced anteriorly, the bundle gave rise to a normal left bundle branch (fig. 4c). A right bundle branch was not identified.

Case 3

The patient was a female child born spontaneously weighing 2330 grams after pregnancy of 36 weeks. During pregnancy, fetal bradycardia had been noted, and found by echocardiography to be due to complete heart block (Dr. G. E. Freud). The intrauterine ventricular rate had been 55 beats/min, but this fell to 35 beats/min at birth. At examination, the infant was noted to have an anal atresia. She was dyspneic with a rate of 40 beats/min. The liver was palpated 5 cm beneath the costal margin in a distended abdomen and the eyelids were edematous. Cardiomegaly was observed and at auscultation the first heart sound was found to vary in intensity with the second sound being single. No murmurs were audible. Laboratory tests were normal apart from the finding of a metabolic acidosis. Chest roent-
genology revealed gross cardiomegaly with normal vascular markings. The electrocardiogram (fig. 5) revealed complete heart block with an atrial rate of 140 beats/min and a ventricular rate of 44 beats/min. The P waves were high and peaked, and the QRS morphology suggested the ventricular focus to be high and in the right aspect of the ventricular septum. The duration of the QRS complex was 0.05 seconds.

The anal atresia was perforated and dilated, with initial success. However, subsequently the heart rate slowed further to 30 beats/min, and the cardiac failure became worse. Despite intensive medical therapy the infant died 24 hours after admission at the age of 2 days.

Autopsy examination revealed that the cardiac chambers were normally formed and connected, although they exhibited an unusual exterior appearance with prominence of the right ventricle and both atrial appendages. The foramen ovale was probe patent and the ductus arteriosus was closed. Histopathological studies demonstrated presence of a normally situated sinoatrial node, which communicated with atrial myocardium via short transitional cells. The internodal myocardium was of ordinary "working" variety, and "Purkinje-like" cells were not identified. The atrioventricular node was a well formed structure situated in its anticipated position. A prominent compact node was identified (fig. 6b) which bifurcated posteriorly (fig. 6a) as in the normal heart. Normally formed transitional cells effected the communication between atrial myocardium and the compact node. Anteriorly the node diminished in size, and disappeared completely in the anticipated area of the central fibrous body (fig. 6c). The central fibrous body itself was very poorly formed, and the arrangement of the valve attachments was unusual, being at the same level (fig. 6c) rather than the mitral attachment being higher as in the normal heart. Although relatively hypoplastic, this central portion of the fibrous anulus did, however, prevent any communication between the proximal junctional area and the ventricular myocardial tissues. Beneath the anulus, the bifurcating atrioventricular bundle was normally related to the interventricular component of the membranous septum and normal right and left bundle branches were identified (fig. 6d).

Embryological Findings

Re-examination of the embryos in our collections10-12 confirmed that the specialized tissues of the heart are derived from the four junctional rings of tissue which, in the young embryo, are situated between the five basic segments of the
cardiac tube (fig. 7). As described previously, the processes of bulbo-ventricular looping and atrioventricular separation bring three of the junctional rings into apposition at the atrio-ventriculo-bulbar junction, and the specialized atrioventricular junctional area is formed at this site (fig. 8). The ventricular specialized tissues are formed in situ astride the bulboventricular septum, while the compact atrioventricular node is derived from an invagination from the posterior part of the atrioventricular ring of specialized tissue formed pari passu with the posterior part of the interventricular septum (fig. 8 and 9). The transitional cell zones of the junctional area are derived in part from a forward extension of the sinus venosus, encased within the sinoatrial ring of junctional tissue; in part from the septum primum (which Van Praagh and Corsini have suggested grows up from sinus venosus tissue), and in part from a posterior evagination from the anterior segment of the atrioventricular junctional tissue (fig. 10).

These findings indicate that the definitive atrioventricular junctional area can only be completed after the formation of the atrial septum has permitted all these transitional cell zones to establish contact with the axis formed by compact node and the penetrating bundle astride the ventricular septum. However, completion of atrial septation merely brings these nodal components into juxtaposition.

In order for muscular continuity between the segments to be established therefore, our findings suggest that it is necessary for there to be effacement of the atrioventricular sulcus tissue, which at this stage completely encases the nodal-bundle axis (fig. 10). Following the process of bulboventricular looping, the atrial and ventricular myoblastic tissues are continuous throughout the circumference of the atrioventricular junction. The separation of these tissues is accomplished by an ingrowth of the atrioventricular sulcus tissue, which initially surrounds the epicardial aspect of this junction. At the stage at which it proves possible to identify the nodal-bundle axis of specialized tissue astride the ventricular septum (fig. 9), our studies show that a complete sheet of sulcus tissue, continuous with the epicardial atrioventricular sulcus tissue, surrounds both the primordia of the compact node and the penetrating bundle. This tissue separates the specialized tissue both from the underlying ventricular septum and the overlying atrial tissues (fig. 9).

Further sheaths, composed of similar "clear" cells and continuous with the posterior sheath, separate the ventricular specialized tissues from the ventricular myoblastic tissues. In the region of the developing atrial septum, the atrioventricular endocardial cushions are also situated so as to separate the developing and ingrowing atrial septal tissues from the nodal-bundle axis of specialized tissue (figs. 8 and 10). Effacement of the sulcus tissue occurs initially in the region of the posterior atrial wall, so that the compact

**Figure 5.** Electrocardiogram from case 3, showing complete heart block with an atrial rate of 140 beats/min and a ventricular rate of 44 beats/min. QRS morphology was interpreted as showing a high right septal focus for ventricular activation.
nodal-bundle axis makes contact initially only with the posterior atrial wall and the sinus venosus tissue (fig. 10). If the junction of the compact node with the penetrating bundle is considered as the point at which the nodal-bundle axis enters the fibrous tissue primordia derived from sulcus tissue, then at this stage the penetrating bundle is excessively long as compared to the compact node (fig. 10).

With development of the atrial septum, however, the
anterior and superior segments of the sulcus tissue regress, permitting the sinus venosus, septum primum and anterior atrioventricular ring tissues all to establish direct myocardial contact with the nodal-bundle axis (fig. 11). When this process is completed, between six and eight weeks of development, the nodal-bundle axis is converted to a more definitive form, with a more extensive compact node and a shorter penetrating bundle (figs. 11 and 13.) The junction of node and bundle is now the point at which the axis passes into the sheath composed of sulcus tissue reinforced anteriorly by the atrioventricular endocardial cushion tissue (figs. 11–13). From the evidence, we conclude that the "sheath" enclosing the penetrating bundle has two segments.

The upper segment is composed of both sulcus and endocardial cushion tissue (figs. 10–13) and separates the specialized axis from the atrial tissues. The lower segment is composed solely of sulcus tissue, and this component separates the nodal-bundle axis from the underlying ventricular myocardium. Our findings suggest that it is the backward continuation of this sulcus tissue which forms the septal anulus fibrosus and separates the atrial working and specialized myocardium from the ventricular myocardial tissues of the posterior septum. Initially there are many myoblastic bridges which cross through the sulcus tissue and connect the nodal-bundle axis to the underlying ventricles (fig. 9). Even when the superior segment of sulcus tissue has regressed, permitting the definitive atrio-nodal connections to be formed, the inferior sulcus tissue is noted to be incompletely converted to fibrous tissue, so that multiple bridges of specialized tissue still persist between the nodal-bundle axis and the ventricular myocardium (fig. 13). Indeed, remnants of such bridges are to be found in the mature anulus fibrosus of many adult hearts, forming Mahaim fibers which connect both the node (nodo-ventricular fibers) and the bundle and proximal bundle branches (fasciculo-ventricular fibers) to the crest of the ventricular septum (fig. 4).

Discussion

Congenitally complete heart block can be divided into cases which occur in congenitally malformed hearts and
cases which occur in otherwise anatomically normal hearts. It is reasonable to presume that, in cases with severely malformed hearts, the developmental malfunction which produced the cardiac anomaly has also disrupted the cardiac conducting system. This is exemplified in several cases of abnormal hearts with complete heart block studied histopathologically in which the disposition of the specialized tissues bore little resemblance to the normal. In contrast, in hearts which are otherwise developed normally, or in which a defect, if present, bears no relationship to the conduction system, it can be hypothesized that a primary malformation of the conduction tissue itself is responsible for the heart block.

It has been suggested that such malformations result from division of the conducting system by fibrous tissue after its formation. This hypothesis was based upon the premise that the ventricular conducting system "migrated" from the atrioventricular node. There is now considerable evidence to suggest that this is not so, and that the conducting tissue is developed in situ, being made up from several segments of differing embryological origin. (See reference for review of previous evidence, and references 3, 10, 13.)

This concept of multiple origins accords well with a further categorization of complete heart block occurring in "normal" hearts which was suggested by Lev and his colleagues. They divided the dysrhythmia into cases with discontinuity between the atria and the node, and cases with discontinuity between the node and the ventricular conduct-
FIGURE 11. Frontal sections of a 29 mm human embryo showing the stage at which effacement of the sulcus tissue permits the development of atrio-nodal continuity. Note that right and left are reversed relative to the sections illustrated in figures 3 and 6, i.e., the sections are viewed from the front rather than the back, as one would view a chest X-ray. Fig. Al is posterior to fig. Bl. In figure Al there is contact (closed arrow) through the sulcus tissue between atrial myocardium and compact node (CN). Stipples are as in the previous diagram. In figure Bl the specialized tissue axis is still surrounded by sulcus tissue (open arrow). By definition, therefore, this is penetrating bundle (PB). RA = right atrium; RV, LV = venous valves; SPr = septum primum; LA = left atrium; To = tricuspid orifice; RV = right ventricle; LV = left ventricle; IVS = interventricular septum. The area within the square in fig. 11B1 is enlarged in figure 12.

FIGURE 12. Enlargement of area of penetrating bundle in a 29 mm human embryo (see fig. 11B1). Note how it is sulcus tissue (arrowed) which surrounds the axis (PB), cutting it off from the atrial septum. Note also the components of sinus venosus, septum primum (1°) and anterior atrio-ventricular ring tissue (AAVRT) which contribute to the septum. The endocardial cushion tissue are not directly related to the bundle. The inferior segment of sulcus tissue is poorly developed. Orientation as for figure 11. T of T = tendon of Todaro.
genetic role. Indeed, this difference was previously noted by Odgers but has received little emphasis of late. Thus, we believe that our findings indicate that the atrioventricular conducting axis during its development is enclosed by sheaths of sulcus tissue which are discrete and distinguishable from the endocardial atrioventricular cushions.

We submit that the sulcus tissue rather than the cushion tissue itself is responsible for effecting separation of atrial and ventricular myocardial tissues. This change of emphasis, although perhaps minor in the context of the subject as a whole, is we believe important since cases exhibiting atrio-nodal discontinuity are difficult to explain on the basis that the endocardial cushions provide all the tissue enclosing the nodal-bundle axis. They are much easier to explain on the basis of failure of regression of sulcus tissue which, according to our observations, entirely encloses the conducting tissue axis during early development, preventing any contact between it and the atrial myocardium above the level of the endocardial cushions as delineated by us. The degree of development of the nodal-bundle axis itself would determine the amount of specialized tissue encased in the fibrous sheath, varying from an extensive compact node as in our case 2 and cases 1–3 of Lev et al. to a short penetrating bundle as in our case 1 and other cases described by Lev. The feature common to all these cases is that a fibrous sheath encloses the conducting tissue, separating it from the atrial tissues. It is also noticeable that in the majority of cases the inferior limbus of the atrial septum is itself composed of fibrous tissue, and devoid of myocardial fibers.

It may therefore be possible that normal development of the atrial septal musculature is a necessary prerequisite for absorption of the atrioventricular sulcus tissue. Further evidence pointing to a separate role of cushion tissue vis-a-vis sulcus tissue is found in the cases with a discontinuous nodal-bundle axis. It is possible that the endocardial cushion tissue itself does interpose between node and bundle. However, we submit that our embryological findings again suggest that this is not the case, since the endocardial cushion tissue is always on the atrial aspect of the conducting tissue axis. In cases with discontinuity of the nodal-bundle axis we
would therefore suggest an alternative explanation, namely that the cleavage point of the conducting system is the site of union between the atrioventricular and bulboventricular rings of specialized tissue (fig. 9). The previous studies by one of us referred to above indicated that both these components are enclosed in sheaths of sulcus-like tissue, but that the tissue surrounding the ventricular component is derived from a source other than the atrioventricular sulcus. The possibility must therefore be considered that the fibrous tissue of the two sheaths persists between the two conducting tissue components, thus preventing atrioventricular muscular continuity. Further ancillary evidence pointing to the possible role of the sulcus tissue in separating atria and ventricles is to be found from gross dissection, since an epicardial tissue plane can be traced from the posterior atrioventricular groove directly into the atrioventricular junctional area.

Finally, the significance of the atrioventricular sulcus tissue must be emphasized with regard to the connections described between the nodal-bundle axis of conducting tissue and the posterior ventricular septum, such as seen in our case 2. These fibers are initially present throughout the length of the axis, and can therefore be divided into those which connect the node to the ventricular septum, nodo-ventricular fibers, and those which connect the bundle to the ventricular septum, fasciculo-ventricular fibers. The entire group of fibers can alternatively be considered together as Mahaim fibers. In our experience, only with maturation of the anulus are these bridges disrupted, and frequently this disruption is not completed by birth. It is our belief that these bridges are also responsible for the remnants of conducting tissue described within the anulus fibrosus of both neonatal hearts also and in many adult hearts.

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