Accessory Atrioventricular Myocardial Connections in the Developing Human Heart
Relevance for Perinatal Supraventricular Tachycardias

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Background—Fetal and neonatal atrioventricular (AV) reentrant tachycardias can be life-threatening but resolve in most cases during the first year of life. The transient presence of accessory AV myocardial connections during annulus fibrosus development may explain this phenomenon.

Methods and Results—A total of 45 human embryonic, fetal, and neonatal sectioned hearts (4 to 36 weeks of development) were studied immunohistochemically. Accessory myocardial AV connections were quantified and categorized according to their specific location, and 3D reconstructions were made. Between 4 and 6 weeks of development, the atrial and ventricular myocardium was continuous at the primitive AV canal. At 6 to 10 weeks, numerous accessory myocardial AV connections were identified in the left (45%), right (35%), and septal (20%) regions of the AV junction. Most right-sided accessory connections comprised distinct myocardial strands, whereas left-sided connections consisted of larger myocardial continuities. At 10 to 20 weeks, all accessory AV connections comprised discrete myocardial strands and gradually decreased in number. The majority of accessory connections were located in the right AV junction (67%), predominantly in the lateral aspect (45%). Seventeen percent of the accessory connections were observed in the left AV junction, and 16% were observed in the septal region. 3D reconstructions of the developing AV nodal area at these stages demonstrated multiple AV node–related accessory connections. From 20 weeks until birth, and in neonatal hearts, no further accessory AV myocardial connections were observed.

Conclusions—Isolation of the AV junction is a gradual and ongoing process, and right lateral accessory myocardial AV connections in particular are commonly found at later stages of normal human cardiac development. These transitory accessory connections may act as substrate for AV reentrant tachycardias in fetuses or neonates.

Key Words: arrhythmia  ■  cardiac development  ■  embryology  ■  immunohistochemistry

Atrioventricular reentrant tachycardia (AVRT) that requires the presence of an accessory atrioventricular (AV) myocardial pathway (AP) is the most common type of supraventricular tachycardia in both the fetus and the newborn. AVRT is a potentially life-threatening problem in this young age group, and these tachycardias are sometimes difficult to control with antiarrhythmic drug therapy. However, most tachycardias resolve spontaneously within the first months of life, and >60% of patients require no antiarrhythmic drug therapy and remain free of symptoms after the age of 1 year. This self-limiting character of most perinatal AVRTs suggests that the majority of the APs involved eventually disappear after birth; furthermore, a discontinuation of tachycardia-initiating events may also explain the disappearance of these type of arrhythmias. It is unknown whether APs involved in perinatal AVRT have a different origin from APs involved in AVRT that present later in life. We hypothesize that self-limiting perinatal AVRT can be explained by the transitory presence of accessory myocardial connections during the normal process of isolation of the AV junction in cardiac development.

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Shortly after the formation of the primary heart tube, the heart is subjected to extensive remodeling processes. Previous studies have shown that around the seventh week of human development, separation of the atrial and ventricular myocardium at the primitive AV canal has begun. From the 12th week of development, the atrial and ventricular myocardium are separated by a layer of fibrous tissue called the...
annulus fibrosus, through which the AV conduction axis is the only myocardial continuity.7 Recently, electrophysiological studies in avian4 and mouse,10 models have shown that multiple accessory AV myocardial connections were present until the late stages of cardiac development. These accessory connections demonstrated retrograde10 and antegrade AV conduction and gradually decreased in number at subsequent developmental stages.8 In addition, an electrophysiological study in mice demonstrated the onset of AVRT at early stages of development.10 In the present study, we investigated the presence and specific locations of APs in relation to the process of formation of the annulus fibrosus during the different stages of normal heart development in humans.

Methods

Hearts

Human embryonic, fetal, and neonatal hearts (n = 45) were obtained from the collection of the Department of Anatomy and Embryology of the Leiden University Medical Center, The Netherlands. The study was approved by the local medical ethics committee. Only specimens with a normal karyotype and structurally normal hearts were included in the present study. All hearts were already sectioned either in the transverse, frontal, or sagittal plain and immunohistochemically stained with different myocardial (human muscle actin [HHF35], DAKO, Glostrup, Denmark; myosin, α-myosin heavy chain [MHC] and β-MHC, kindly supplied by A.F.M. Moorman) and fibrous (fibronectin, A245, DAKO, Glostrup, Denmark; collagen VI, Southern Biotechnology, Birmingham, Ala; and laminin, PU078, BioGenex, San Ramon, Calif) tissue markers. Furthermore, histologically stained sections were used: hematoxylin and eosin, resorcin-fuchsin–iron hematoxylin–picric acid–thiazin red (modified Verhoff-Van Giesen stain), and Azan. A detailed description of staining protocols can be found in previous publications.11,12 All embryos, fetuses, and neonates were separated into 4 groups of successive gestational stages of development according to pregnancy duration and crown-rump-length (CRL): group 1, from 4 weeks/CRL 5 mm to 6 weeks/CRL 11 mm (n = 2); group 2, from 6 weeks/CRL 11 mm to 10 weeks/CRL 40 mm (n = 7); group 3, from 10 weeks/CRL 40 mm to 20 weeks/CRL 164–170 mm (n = 27); and group 4, from 20 weeks/CRL 164–170 mm to birth/neonates (n = 9).

The hearts were studied carefully section by section for the presence of accessory AV myocardial connections in the left, right, and septal areas of the AV junction with an Olympus BH-2 light microscope (Olympus, Center Valley, Pa). An AP was defined as an area of accessory AV myocardial tissue located in addition to the AV conduction axis in postseptated hearts.

All accessory myocardial connections in embryonic or fetal hearts were categorized on the basis of their specific location in the AV junction. Accessory myocardial connections related to the developing AV node (AVN) were described separately.

Immunohistochemistry

Additional immunohistochemical experiments were performed with myosin light chain (MLC)-2a and peristin-specific antibodies as additional myocardial and fibrous tissue markers, respectively. All embryonic hearts were fixed in 4% paraformaldehyde; after dehydration, they were embedded in paraffin. The embedded hearts were sectioned (5-μm sections) and mounted in a 1:6-10 order onto protein/glycerin-coated slides, so 6 different staining procedures could be performed on 1 embryo. After dehydration of the slides, inhibition of endogenous peroxidase was performed for MLC-2a with a solution of 0.3% H2O2 in PBS for 20 minutes. For peristin, antigen retrieval was performed in 0.01 mol/L citric buffer (pH 6.0) at 97°C for 12 minutes, followed by inhibition of endogenous peroxidase in a solution of 0.3% H2O2 in PBS for 20 minutes. Overnight incubation with the primary antibody was performed with the following antibodies: 1:2000 anti-atrial MLC-2a (a gift from S.W. Kubalak) and 1:1000 anti-peristin (a gift from R.R. Markwald). The primary antibodies were dissolved in PBS-Tween 20 with 1% BSA (Sigma-Aldrich, St Louis, Mo). The slides were rinsed between subsequent incubation steps with PBS (2×) and PBS-Tween 20 (1×). For both MLC-2a and peristin, a 40-minute incubation with the secondary antibodies was performed with 1:200 goat anti-rabbit biotin (Vector Laboratories, Burlingame, Calif; BA-100) and 1:66 goat serum (Vector Laboratories; S1000) in PBS-Tween 20. Thereafter, a 40-minute incubation with ABC reagent (Vector Laboratories; PK 6100) was performed. For visualization, all slides were incubated with 400 μg/mL 3,3′-diaminobenzidine tetrahydrochloride (DAB; Sigma-Aldrich; D5637) dissolved in Tris-maleate buffer pH 7.6, to which 20 μL of H2O2 was added for 10 minutes. Then, 0.1% hematoxylin (Merck, Darmstadt, Germany) was used to counterstain the slides (MLC-2a 10 seconds and peristin 5 seconds), followed by rinsing with tap water for 10 minutes. Finally, the slides were dehydrated and mounted with Entellan (Merck).

AMIRA Reconstruction

Reconstructions were made of the developing AVN region, as described previously,3 with the Amira software package (Mercury/TGS, Berlin, Germany).

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Four Weeks/CRL 5 mm to 6 Weeks/CRL 11 mm (n = 2)

At 4 weeks (CRL 5 mm) of development, the heart tube had looped, and the common atrium was positioned completely above the primitive left ventricle. Large endocardial cushions were observed in the region of the common outflow tract and on the anterosuperior and posteroinferior luminal sides of the primitive AV canal. At this stage, the atrial and ventricular myocardia were continuous at the region of the primitive AV junction. At 5 weeks (CRL 7 mm), formation of the right ventricle had begun, and the future left and right ventricles were clearly discernible. In the AV canal region, the myocardium of the primitive atria and the ventricles was continuous (data not shown).

Six Weeks/CRL 11 mm to 10 Weeks/CRL 40 mm (n = 7)

Between 6 and 7 weeks, the AV cushions had fused, and the future tricuspid and mitral valve orifice of the AV junction became visible. Almost all atrial and ventricular myocardium was still continuous at the AV junction. Around the seventh week of development, ventricular septation was nearly completed, thereby separating the left and right bloodstreams. The separation of atrial and ventricular myocardium had clearly commenced at the right dorsal aspect of the embryonic heart and to a lesser extent on the left dorsal side. At 7 to 8 weeks, ventricular septation was completed, and formation of the partially AV-cushion–derived tricuspid valves at the right AV junction and of the mitral valves at the left AV junction had begun. At the end of the ninth week, AV cushion tissue was no longer observed, and well-shaped mitral and tricuspid valves were present at the AV junction. At this stage, the atrial and ventricular myocardia were almost completely separated by the fibrous tissue of the developing annulus fibrosus. On the dorsal side of the fetal heart, a distinct AV
myocardial continuity was observed that corresponded to the developing AV conduction axis, comprising the developing AVN and the bundle of His. Between 6 and 10 weeks of development, many parts of the AV junction showed an incomplete isolation at the annulus fibrosus (Figure 1A through 1C). Accessory AV myocardial connections were found in the left (45%), right (35%), and septal (20%) regions of the AV junction (Figure 1D). Most of the accessory myocardial connections were identified as broad accessory AV myocardial continuities. At the dorsal aspect of the right AV junction, accessory connections consisted of small, single myocardial strands.

At the right AV junction, the so-called right atrioventricular ring (RAVR) bundle could easily be distinguished from the atrial myocardium as a separate structure. The RAVR bundle, considered part of the embryonic AV conduction system, formed a ring of myocardium around the tricuspid annulus on the atrial side (Figure 2A through 2C).13 Most of the accessory myocardial connections were identified as broad accessory AV myocardial continuities. At the dorsal aspect of the right AV junction, accessory connections consisted of small, single myocardial strands.

Interestingly, the majority (65%) of the right-sided accessory myocardial AV connections were located subendocardially and made contact with the RAVR bundle. In all examined hearts, the isolating tissue between the RAVR bundle and the ventricular myocardium was not as extensive as at other locations at the AV junction. Frequently, only a single layer of fibrous tissue was observed between the RAVR bundle and the ventricular myocardium.

Ten Weeks/CRL 40 mm to 20 Weeks/CRL 164–170 mm (n=27)

Between 10 (CRL 40 mm) and 20 (CRL 164 to 170 mm) weeks of development, annulus fibrosus and valve formation had progressed further, and cardiac development was dominated by growth. At the left AV junction, the annulus fibrosus had become a firm structure with a thick layer of fibrous tissue isolating the left atrial and ventricular myocardium (Figure 2D through 2F). The developing AVN was positioned in the right posteroseptal region and was continuous with the bundle of His traversing the annulus fibrosus behind the aorta. At the right AV junction, the annulus fibrosus was more fragile, and accessory myocardial AV connections were found frequently, especially adjacent to the RAVR bundle (Figure 2A through 2D), which could still be observed in most hearts up to 20 weeks.

Between 10 and 20 weeks, broad accessory AV myocardial continuities, as seen at earlier embryonic stages, could no longer be detected. However, up to 20 weeks of development, numerous accessory myocardial AV connections were identified (Figure 3A through 3E). At these stages, all accessory myocardial AV connections consisted only of single strands of myocardium crossing the annulus fibrosus (Figure 3C through 3E). As expected, the majority (67%) of accessory myocardial AV connections were now located in the right AV junction, and only 17% were located in the left AV junction. Furthermore, 16% of accessory myocardial AV connections...
were observed in the midseptal and posteroseptal regions of the AV junction (Figure 3F). Right-sided connections (45%) were located subendocardially at the lateral aspect of the right AV junction, primarily related to the RAVR bundle (Figure 3C and 3E).

Twenty Weeks/CRL 164–170 mm to Birth/Neonatal Stages (n=9)
The annulus fibrosus of 5 fetal and 4 neonatal hearts was examined completely. In both fetal and neonatal hearts, no accessory myocardial AV connections were observed in the left, right, or septal areas of the AV junction (data not shown).

Accessory Connections Related to the Developing AVN
The developing AVN and bundle of His were examined during different stages of fetal heart development. The cardiomyocytes of the AVN were large, pale, rounded cells and could be easily distinguished from the adjacent atrial working myocardium (data not shown). From 10 weeks onward, the developing AVN remained positioned anterior to the coronary sinus ostium to the midatrial septum, immediately adjacent to the tricuspid annulus (Figure 4A). Shortly after completion of ventricular septation, the bundle of His was a prominent structure that crossed the annulus fibrosus in the midseptal region, continuing at the ventricular side and divided into a left and right bundle branch. With fetal heart development, the bundle of His was better isolated and could be identified easily from the surrounding structures. During subsequent stages of development and continuing until birth, numerous small strands of cardiomyocytes originating from the AVN region penetrated the annulus fibrosus. These accessory AV nodal extensions of large, pale, rounded cardiomyocytes connected to the ventricular septal myocardium but had no relationship with the penetrating bundle of His (Figure 4A and 4B). Sections and a 3D reconstruction of the AVN region and AV nodal accessory connections of a 14.2-week-old fetal heart are shown in Figure 4.

Discussion
Supraventricular tachycardias affect ∼0.1% of fetuses and newborns. In most cases, the substrate for arrhythmia is an abnormal electrical conduction through an accessory AP, which causes a circus movement between atria and ventricles. However, the majority of children presenting with AVRT in the fetal or neonatal period have no recurrences after the age of 1 year, and approximately one third of the patients show a disappearance of ventricular preexcitation and noninducibility of AVRT by transesophageal electrophysiological studies. This self-limiting character of most AVRTs in fetuses and newborns is an intriguing clinical phenomenon, but the mechanism has not yet been elucidated. AVRT in this age group has been speculated to originate from the transient presence of conducting APs during the normal process of maturation of the annulus fibrosus. The development of this isolating structure involves several processes in which the endocardial cushions that line the luminal side of the primitive AV canal, together with the inward migration of
The epicardially located AV sulcus tissue, play an important role. Recently, it has been shown in more detail that a combination of bone morphogenetic protein signaling, periostin (an osteoblast-specific factor), and epicardium-derived cells that enter the heart at the AV sulcus play a key role in this process.

The cause of APs has not been elucidated. The majority of APs conduct antegrade, as seen in patients with Wolff-Parkinson-White (WPW) syndrome (OMIM No. 194200; incidence in general population 1.5 per 1000 persons; the prevalence of WPW syndrome in children under 13 years of age is lower, at 0.07%). In adults, 25% of APs involved in....

Figure 3. Separation of atrial and ventricular myocardium at 10 to 20 weeks of development. Between 10 and 20 weeks of development, several accessory myocardial AV connections bypassing the AV conduction axis were present. A, Modified Verhoeff-Van Gieson-stained frontal section of a 15.3-week-old fetal heart in which myocardium is stained yellow-brown and fibrous tissue is stained red. B, Boxed area in A showing detail of the annulus fibrosus of the right AV junction, which is in continuity with the base of the tricuspid valve (arrows in A and B). C, Detail of boxed area in B showing the RAVR bundle, which is in continuity with the ventricular myocardium, thereby creating an accessory myocardial AV connection (arrow in C). D, Frontal section of right AV junction of a fetal heart at 19.6 weeks of development. Arrows indicate the tricuspid valve in continuity with the fibrous tissue of the annulus fibrosus (red). E, Magnification of the boxed area in D showing an accessory myocardial AV connection in contact with the RAVR bundle (arrow in E). A total of 27 hearts were investigated for the presence of accessory myocardial AV connections at the developing AV junction (F) between 10 and 20 weeks of development. The red numbers indicate the total number of hearts in which accessory myocardial AV connections were present at a specific location at the AV junction, and the percentages represent the amount of accessory myocardial AV connections at a specific location at the AV junction compared with the total number of accessory myocardial AV connections in the entire AV junction. RA indicates right atrium; RV, right ventricle; and AO, aorta. Scale bars: A and D, 1 mm; B, 200 μm; C and E, 100 μm.
AVRT are concealed, which indicates that they only have retrograde conducting properties. In infants, the percentage of concealed APs is higher, ~60%. In the majority of cases of WPW syndrome, there is no familial involvement; however, a significant minority of cases are inherited as a single-gene disorder or occur as part of a syndrome with a strong genetic basis. Recently PRKAG2 gene missense mutations have been identified to be involved in familial WPW syndrome, often in association with cardiac hypertrophy. Animal studies have shown that mutations in the Alk3 gene result in disrupted formation of the annulus fibrosus, which causes ventricular preexcitation via posterior paraseptal bypass tracts. The differences in location and specific electrophysiological properties of APs, as well as their association with structural heart diseases such as hypertrophic cardiomyopathy and congenital heart disease, indicate that not all APs share the same causative pathway.

Previous studies have demonstrated the presence of accessory myocardial AV connections between atrial and ventricular myocardium during normal embryological and fetal heart development in humans and other mammals. However, the present study for the first time systematically describes the presence and specific locations of gradually disappearing accessory AV myocardial connections that cross the developing annulus fibrosus in human embryonic, fetal, and neonatal hearts. We demonstrate that atrial and ventricular myocardia were continuous at the primitive AV canal at early stages of development. First separation of atrial and ventricular myocardium by the developing annulus fibrosus was observed at the right dorsal AV junction at ~7 weeks of development, and myocardial continuity persisted longer near the left junction. Total separation of atrial and ventricular myocardium was completed at ~10 to 11 weeks, which corresponds to other studies regarding the formation of the annulus fibrosus in developing human hearts. However, numerous accessory AV myocardial connections can be identified until the end of the second trimester of pregnancy. Comparable to other studies, these accessory AV myocardial connections were observed at the subendocardial aspect.
of both the right and left lateral AV junction of the heart. In the second and third trimesters, the left AV ring becomes firmly isolated by a thick layer of fibrous tissue, followed by isolation of the right AV ring.

Isolation of the right AV ring is particularly weak, and frequently, it consists only of very thin layers of fibrous tissue. Up to 20 weeks of gestation, small AV myocardial strands remain present near the lateral side of the tricuspid valve, mainly located subendocardially. The high frequency of these right-sided accessory myocardial AV connections and the weak isolation of this part of the AV junction in particular might be associated with the normal developmental process of the right ventricular inflow tract. In early stages of heart development, as observed in the present study, the common atrium is positioned completely above the left ventricle. Formation of the right ventricular inflow tract starts with a groove that is embedded in the myocardium of the primary fold. As a result of the expansion and outgrowth of this myocardial groove, the right ventricular inflow tract will be formed, which eventually establishes the right part of the AV junction. Formation of the right ventricular inflow tract might result in a weaker isolation and a high frequency of accessory myocardial AV connections, because this part of the AV junction develops subsequent to the existent left AV junction. The right-sided AV myocardial connections frequently are located in close relationship to the RAVR bundle. This semicircular structure forms part of the temporary embryologically specialized AV conduction system and is continuous with the AVN posteriorly. In the fetus, it can be identified as a ring of nodelike cells in the right atrium just above the tricuspid valve, which later disappears. These accessory myocardial AV connections appear to correspond to the presumed multiple AV nodes and pathways originally reported by Kent and reviewed by Anderson et al. The relationship of right-sided accessory myocardial AV connections with the RAVR bundle could explain the decremental properties seen in some of the right-sided APs.

Within the developing AVN, small myocardial extensions can be identified that cross the annulus fibrosus and connect the developing AVN with the ventricular septal myocardium. These AV nodal extensions remain present until birth. The presence of the so-called nodovenricular connections in fetal and neonatal hearts has been reported previously, and this phenomenon has been described as fetal dispersion of the AVN. In the first months after birth, extensive remodeling of the fibrous heart skeleton, including the AVN area, takes place, in which the AVN becomes a more solid structure. AV nodal extensions appear to be a common finding in neonatal hearts, although this has been associated with sudden infant death syndrome in the past. In theory, nodovenricular pathways could provide the substrate for supraventricular tachycardia, but to the best of our knowledge, this rare form of reentrant tachycardia has not been documented in the perinatal period.

Recently, the temporary presence of functional accessory myocardial AV connections has been demonstrated by electrophysiological studies in avian hearts up to late stages of fetal development. These connections appeared to have antegrade conducting properties, as was demonstrated by unipolar electrogram recordings that showed premature left and right ventricular base activation in postseptated hearts. Furthermore, studies performed in mammals showed that in normal mouse embryos, conducting accessory AV pathways are present during cardiac development that can actually create the substrate for reentrant tachycardias. Some of these pathways even appeared to have decremental properties, as observed in the Mahaim preexcitation syndrome. In normal human fetuses, the conducting properties of transient accessory AV connections, which are dependent on factors such as intercellular coupling, remain to be elucidated, as does their ability to establish a pathway for AVRT. However, these accessory myocardial AV connections in human fetuses and their specific locations show strong similarities to the conducting accessory myocardial AV connections demonstrated in birds and mice.

APs in adult patients with AVRT are primarily found around the mitral valve orifice, and ≈60% are located in the left ventricular free wall. In the pediatric age group, the incidence of APs around the tricuspid annulus appears to be higher. APs around the tricuspid valve are usually located at the subendocardial aspect of the heart, whereas left-sided APs can also have a more epicardial course in the AV sulcus. This implies that the persistence of subendocardially located accessory myocardial AV connections demonstrated in normal fetuses could only partially explain the pathogenesis of APs in patients with AVRT. However, the delayed disappearance of fetal APs, as reported in the present study, offers a good explanation for the onset and disappearance of fetal and neonatal AVRT. One third of fetuses and neonates with AVRT have WPW syndrome, with ventricular preexcitation on the postnatal ECG; the others have concealed APs with only retrograde conduction. Although late recurrences of tachycardia after 8 to 10 years have been reported in neonates with WPW syndrome, the majority of these children remain free of symptoms for the rest of their lives. Recently, it has been reported that the group of neonates with concealed APs has an even better prognosis, and >80% remain asymptomatic after the first year, with no recurrences later in life. In the present study, we have demonstrated that accessory myocardial AV connections remain present up to the late stages of fetal heart development, which indicates that the process of isolation of the AV junction is a continuous process that has not finished by the time of birth. The temporary presence of these accessory myocardial AV connections could serve as a substrate for perinatal AVRT.

Study Limitations

The present study demonstrated the presence of accessory AV connections in normal heart development; however, none of the hearts investigated were from fetuses or neonates with known episodes of supraventricular tachycardia. Therefore, it
cannot be determined whether the accessory connections served as functional substrate for AP-mediated supraventricular tachycardia.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Atrioventricular reentrant tachycardias presenting in fetal or neonatal life can be life-threatening but also tend to resolve in the majority of patients in the first year of life. The origin of accessory pathway–mediated tachycardias in the perinatal period has not been elucidated. In early embryonic development, the atrial and ventricular myocardia are continuous in the primitive atrioventricular canal. The atrioventricular conduction axis will then develop, which coincides with separation of the atrial and ventricular myocardium by formation of the annulus fibrosus. Annulus fibrosus development involves several processes in which the endocardial atrioventricular cushions that line the luminal side of the primitive atrioventricular canal, together with the inward migration of the epicardially located atrioventricular sulcus tissue, have an important role. In postseptated human hearts, we demonstrated the presence of numerous accessory atrioventricular myocardial connections around both the mitral and tricuspid annulus during normal cardiac development. At the end of the second trimester, the connections gradually decreased in number and size and were located primarily around the tricuspid annulus. The persistence of fetal atrioventricular connections may serve as substrate for atrioventricular reentrant tachycardia in the fetus and newborn. The self-limiting character of most of these tachycardias could be explained by loss of the substrate due to the ongoing development of the annulus fibrosus, a process not completely finished by the time of birth.
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