J. of Cardiovasc. Trans. Res. (2013) 6:187–196
DOI 10.1007/s12265-012-9433-0

The Anatomy of the Conduction System: Implications for the Clinical Cardiologist

Robert H. Anderson · Mark R. Boyett · Halina Dobrzynski · Antoon F. M. Moorman

Received: 23 October 2012 / Accepted: 27 November 2012 / Published online: 15 December 2012

Abstract It is just over 100 years since details emerged of the anatomical arrangement of the histologically specialised cardiomyocytes responsible for initiation and propagation of the cardiac impulse. Shortly thereafter, histological criteria were established to permit their location in autopsied human hearts. These criteria retain their value, but can now be enhanced by molecular and immunohistochemical findings. The new techniques have advanced our knowledge of the location and detailed structure of the sinus and atrioventricular nodes, along with the atrioventricular conduction axis. They also reveal the presence of additional areas of specialised myocardium, such as the paranodal area of the terminal crest, and the atrioventricular ring tissues. In contrast, they offer no support for the notion that the pulmonary venous sleeves are histologically specialised, but do provide insights to the substrates for outflow tract tachycardias. This article is part of a *JCTR* special issue on Cardiac Anatomy.

Keywords Specialised myocardium · Sinus node · Atrioventricular node · Atrioventricular conduction axis · Arrhythmias

R. H. Anderson
Institute of Genetic Medicine,
Newcastle University, Newcastle, UK

M. R. Boyett · H. Dobrzynski
Institute of Cardiovascular Medicine, Manchester University,
Manchester, UK

A. F. M. Moorman
Department of Anatomy, Embryology & Physiology, Academic Medical Centre, University of Amsterdam, Amsterdam,
The Netherlands

R. H. Anderson (✉)
60 Earlsfield Road,
London SW18 3DN, UK
e-mail: sejjran@ucl.ac.uk

Introduction

It would be most appropriate simply to describe the impulse-generating and propagating tissues of the heart, but it is unrealistic to imagine that the particular subsets of cardiomyocytes will be described as anything but the conduction tissues. In this review, we describe these tissues as seen in the human heart, making comparisons, when appropriate, with findings in other animal species. Using the criteria long established to permit their distinction from the working cardiomyocytes, we show that the cells satisfying their distinction as being histologically specialised are more widely distributed than generally anticipated, altough the function of some of the specialised areas identified using new immunohistochemical criteria has still to be established. We also show how criteria based on immunohistochemical and molecular analysis contribute to ongoing debates concerning the origins of some specific arrhythmias, such as atrial fibrillation and outflow tract tachycardias.

Recognition of the Conduction Tissues

Although a description of the atrioventricular bundle was provided by His in the final decade of the nineteenth century [1], Keith had doubted the existence of any muscular structure connecting the atrial and ventricular muscle masses [2]. The situation at that time was further confused by the claims of Kent that multiple muscular structures crossed the plane of atrioventricular insulation, and were responsible for normal atrioventricular conduction [3]. The structures observed by Kent do exist, but only in abnormal circumstances do they give rise to atioventricular muscular connections [4]. It was the investigation of Tawara that clarified the location of the solitary muscular axis that, in the normal heart, provides the electrical pathway from the atrial to the ventricular chambers [5]. Shortly thereafter, Keith and Flack [6] revealed the location of the sinus

node. Like Tawara [5], they used serial histologic sections to demonstrate the location and morphology of the specialised areas. Others, in contrast, were not as rigorous in their use of serial histological sections. Thus, Thorel [7] had claimed that discrete pathways for conduction could be found in the atrial myocardial walls between the sinus and atrioventricular nodes. This claim, which was not widely accepted, prompted Aschoff [8], and Monkeberg [9], to propose criteria for the histological demonstration of pathways within the heart. Taking as their example the ventricular conduction pathways demonstrated by Tawara [5], they argued that, to form a discrete conducting pathway, cardiomyocytes should be histologically distinct, followed from section to section, and most importantly, should be insulated by fibrous tissue from the adjacent working cardiomyocytes. It is the first two of the these criteria that serve to permit recognisiton of the cardiac nodes. When used for the express purpose of identifying, in standard histological sections, the cardiomyocytes specialised to generate and propogate the cardiac impulse in the normal human heart, these criteria retain their value. Those claiming to have identified specialised internodal atrial tracts during the twentieth century [10] took no note of the criteria [11]. Neither did those claiming that nodal cells were to be found in the pulmonary venous myocardial sleeves [12]. The classic criteria, nonetheless, can now be endorsed by more accurate criteria for recognition of specialised cardiomyocytes, specifically those provided by molecular [13] and immunohistochemical [14] techniques.

Modern Day Criteria for Recognition of the Conducting Tissues

For those using experimental animal tissues, and for those using fresh human tissues, demonstration of the molecular phenotype of the working cardiomyocytes permits their distinction from those specialised to generate and disseminate the cardiac impulse [13]. Use of laser capture of the areas occupied by the specialised cardiomyocytes then permits demonstration of the differences in ion channels relative to those found in the working cardiomyocytes [14]. Thus, when viewed from the molecular stance, working cardiomyocytes express genes such as Nkx2.5, and contain fast-conducting gap junctions composed of connexin 40, whereas the cardiomyocytes of the sinus node do not [13, 15]. Furthermore, during their development, the specialised cardiomyocytes express the transcription factor Tbx3, and continue to express this factor in the postnatal heart. The specialised cardiomyocytes also express HCN4, the gene encoding the ion channel responsible for the so-called funny current, or I_f. The concentrations of these various proteins, and their encoding mRNAs, can now be determined for the different cardiac tissues (Fig. 1). With these opportunities in mind, and considering the pulmonary venous sleeves, if it could be shown that isolated cardiomyocytes within the sleeves did not express Nkx2.5 and connexin 40, yet expressed Tbx3 and HCN4, a reasonable claim could be made for the individual cells to have a pacemaking function. Understanding is not helped, however, if the cells, being scattered through the myocardial walls, are described as being “nodal”. A node, within the context of the cardiac conduction tissues, is a collection of histologically specialised cardiomyocytes identifiable using the criteria initially established by Aschoff and Monkeberg [8, 9]. It will remove confusion if the cells are said to be potentially pacemaking cells. This distinction will become feasible in the future since, using the technique of laser capture, differences in ion channels have been demonstrated not only between the cardiomyocytes making up the sinus and atrioventricular nodes as compared to the working cardiomyocytes, but also in the paranodal area of the terminal crest [14], and in the terminal parts of the atrial vestibules [16]. Use of the molecular and immunohistochemical criteria, therefore, combined with continued application of the German criteria [8, 9], can permit unequivocal recognition of those components of the cardiac walls that are specialised to permit generation and propogation of the cardiac impulse. They also reveal the presence of additional areas to which, as yet, we cannot prescribe a specific function.

The Components of the Conduction System

The molecular and ion channel criteria confirm the importance of the well-recognised components of the conduction system, such as the sinus node, the atrioventricular node, the atrioventricular conduction axis, and the ventricular conducting pathways, or Purkinje cells. The new criteria show that the structures illustrated initially by Kent [3] are part of a ring of cardiomyocytes occupying the insertions of the atrial walls into the atrioventricular junctions, and well described as the atrioventricular ring tissues [16]. They show additionally the presence of a more extensive area of cells with some pacemaking properties adjacent to the sinus node [14]. Cardiomyocytes with comparable potentially pacemaking properties, at least in experimental animals, are to be found on the epicardial aspect of the arterial valvar sinuses. In the developing heart, significantly larger areas of the heart share the features of the cardiomyocytes that eventually become the components of the cardiac nodes [17]. This points to the presence of additional areas within the heart that, potentially, might function as substrates for arrhythmias because of their developmental heritage.

The Sinus Node

The cardiomyocytes making up the sinus node satisfy two of the three criteria established by the German pathologists [8, 9]. They are histologically discrete, and can be followed from

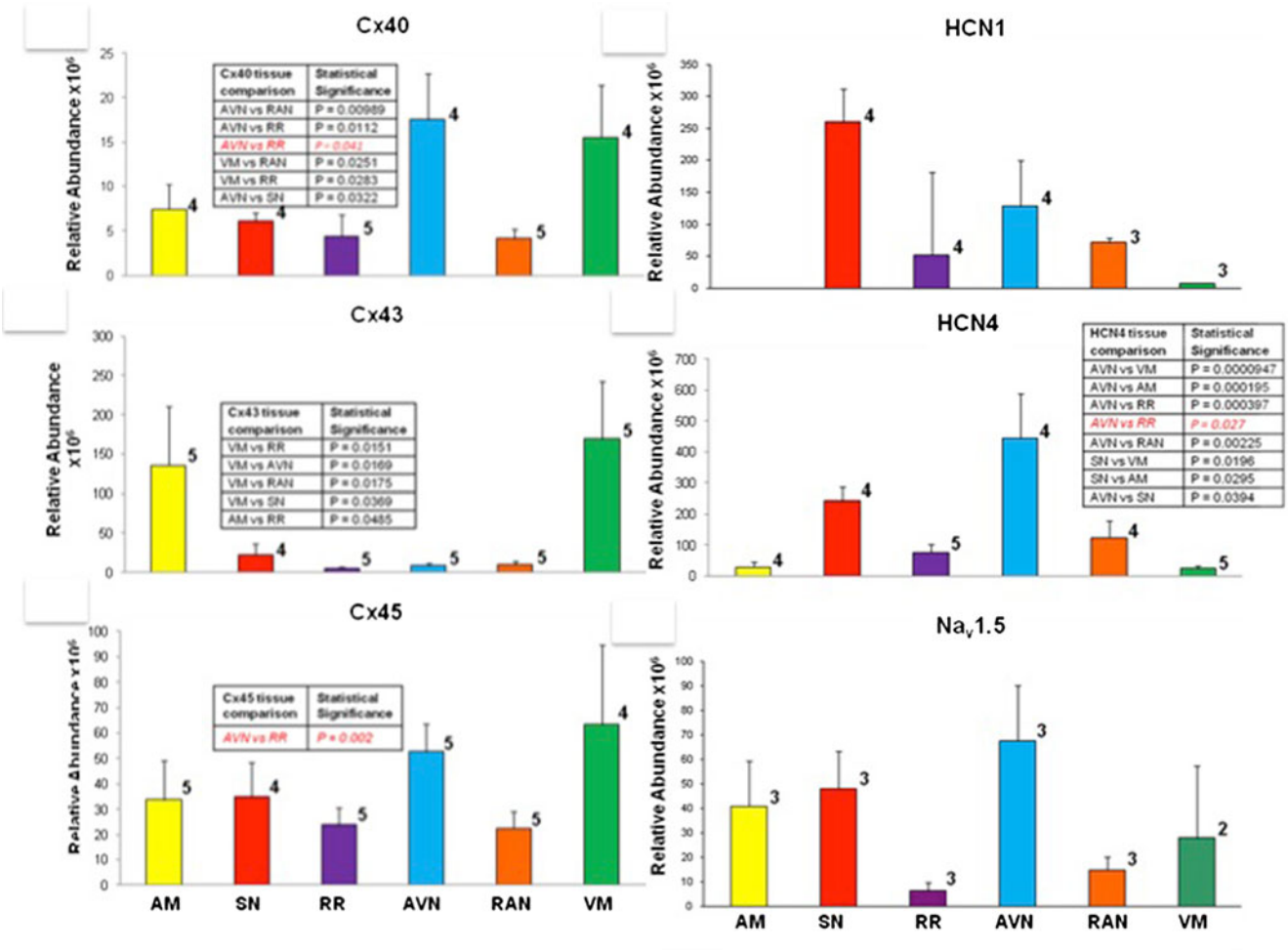

Fig. 1 The graphs show the relative aboundance of expression of mRNA as found in different cardiac tissue from six rat hearts. The total RNA was isolated by means of laser assisted microdissected tissue sections, and converted to cDNA. qPCR was carried out using specific primers (connexins are shown in the *left panels* and ion channels in the *right panels*) and Syber green technology. Data was analysed using the delta-Ct method, and one-way ANOVA was used for statistical analysis. Mean values are shown plus or minus standard deviations. Abbreviations: *AM* atrial muscle; *AVN* atrioventricular node; *RAN* retroaortic node; *RR* right ring tissue, *SN* sinus node; *VM* ventricular muscle. *Cx40*, *Cx43*, and *Cx45* are gap junction channels responsible for electrical coupling between heart cells. *HCN1* and *HCN4* are the so-called "funny channels" partly responsible for pacemaking in conduction tissues. Nav1.5 is the main cardiac sodium channel responsible for the cardiac sodium current, which is responsible for the fast upstroke of the action potential in the working myocardium. Note that in this analysis, no attempt was made to differentiate the different components of the atrioventricular node

section to section. At the boundaries of the node in the human heart, short areas of histologically transitional cardiomyocytes insert into the musculature of the terminal crest (Fig. 2) [18]. In nine tenths of the human population, the node is positioned inferiorly within the terminal groove relative to the crest of the appendage (Fig. 3). In one tenth of the population, the node extends in horseshoe fashion across the crest of the appendage [19]. The node also possesses a well-formed tail, which extends inferiorly for variable distances towards the orifice of the inferior caval vein [20]. Apart from the short transitional tongues and the tail, there are no further extensions of nodal tissue within the atrial walls.

During early development, extensive areas of myocardium within the systemic venous sinus can be recognised to share the properties of the eventual nodal tissues [17, 21]. These areas of so-called primary myocardium are initially slowly conducting. With ongoing maturation, they become indistinct from the remainder of the atrial walls. In the postnatal heart, it is the ordered packing of the working cardiomyocytes that potentiates preferential atrial conduction, as pointed out by Bachmann when first describing the interatrial bundle that now bears his name [22]. The sinus node is ideally situated to activate preferentially this bundle, which runs through the anterior aspect of the superior interatrial groove.

The cardiomyocytes of the sinus node in the human heart aggregate around a prominent atrial artery, which arises from the initial part of the right coronary artery in just over half the population, and from the first part of the circumflex artery in

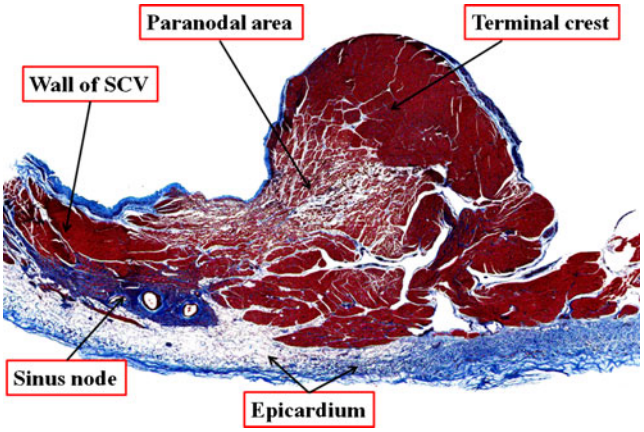

Fig. 2 The image shows a section across the superior cavo-atrial junction of the human heart, stained using the trichrome method, with fibrous tissue stained blue. The sinus node can be recognised lying subepicardially within the terminal groove. It is also possible to distinguish the paranodal area on the basis of its histological characteristics

just under half. Other origins can be found, such as lateral origin from the right coronary artery, or postero-inferior origin from the circumflex artery [23]. As it runs to supply the node, the artery can either cross over the crest of the appendage, pass behind the superior caval vein to enter the terminal groove, or branch to form a circle, supplying the node from both ends. In the rabbit, in contrast, the node forms the full thickness of the atrial wall, and does not possess a central artery [24]. The advent of laser capture and immunohistochemistry revealed, in the human heart, a paranodal area within the terminal crest, intermediate in terms of molecular make-up and content of ion channels between the cells of the sinus node and the working atrial cardiomyocytes [14]. The precise function of the paranodal area remains to be determined, but computer simulations suggest that it is an integral part of normal atrial activation [14].

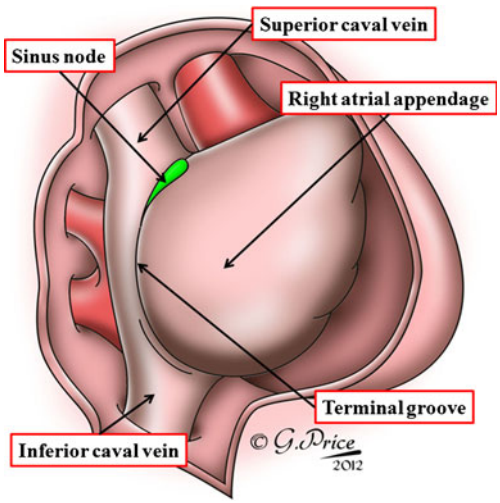

Fig. 3 The cartoon shows the usual position of the sinus node, lying subepicardially within the terminal groove, and inferior relative to the crest of the right atrial appendage. In one tenth of individuals, the node extends across the crest of the appendage in horseshoe fashion

The Internodal Atrial Myocardium

For an extended period of the latter half of the twentieth century, purportedly specialised pathways were believed to connect the sinus and atrioventricular nodes [10]. Tracts do not exist within the atrial walls, however, that are insulated from the working myocardium in the fashion of the ventricular conduction pathways. The impulse generated by the sinus node is conducted more rapidly along the long axis of the atrial muscles bundles than it is transversely [25]. Thus, the main pathways for conduction towards the atrioventricular node are the terminal crest, and the margins of the oval fossa (Fig. 4). Conduction to the left atrium is preferentially through Bachmann's bundle [22], although additional pathways occur through the margins of the oval fossa, and through the muscular connections between the walls of the coronary sinus and the left atrium [26]. During development, the walls of the systemic venous sinus are exclusively composed of primary myocardium, and pathways within these walls can be identified in prenatal stages [17]. Primary myocardium, however, is slowly-conducting, so such pathways would not represent areas of preferentially rapid conduction.

The Atrioventricular Node

The atrioventricular node delays the cardiac impulse prior to its propagation through the ventricular conduction pathways. As yet, in the human heart, the precise parts of the nodal area producing the delay have still to be identified. Functional correlations have largely been obtained using experimental

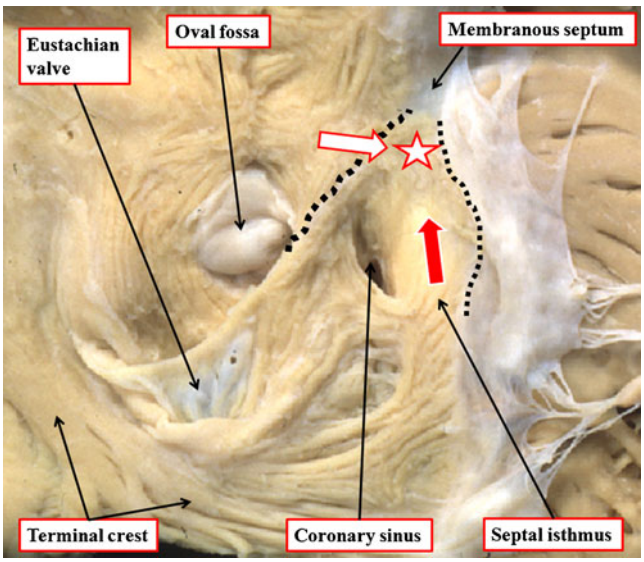

Fig. 4 The image shows the septal surface of the right atrium of the human heart, having removed the endocardium to show the alignment of the major aggregates of the working cardiomyocytes. The *dotted lines* show the boundaries of the triangle of Koch, with the *white arrow* showing the location of the fast pathway, and the *red arrow* showing the slow pathway into the atrioventricular node (*star*)

animals, but there are marked differences between mammalian species in the arrangement of the nodal area. It does not follow, therefore, that results in experimental animals, such as the rabbit or mouse, are directly referable to the human situation.

In the human heart, the atrioventricular node is located at the apex of the triangle of Koch (Fig. 4). The nodal cells form an oblique half-oval set against the sloping surface of the ventricular septum, with the insulating tissues of the atrioventricular groove separating the nodal cells from the ventricular musculature (Fig. 5a). Cells from the right atrial wall feed directly into this compact node, as do cells from the left atrial wall and the atrial septum. Many of these cardiomyocytes are slender and elongated, forming transitional pathways from the working to the nodal cardiomyocytes (Fig. 5a). When traced inferiorly, two extensions of nodal cardiomyocytes run towards the vestibules of the tricuspid and mitral valves (Fig. 6) [27]. In the developing human heart, the atrioventricular ring was shown to be in continuity with the atrioventricular bundle, itself part of an interventricular ring of specialised cardiomyocytes [28]. The part of this interventricular ring that encircles the developing left ventricular outflow tract is broken in subsequent development. The part remaining within the ventricles, extending along the septum beyond the branching atrioventricular bundle, forms a dead-end tract [29]. The dorsal component of the interventricular ring is part of the definitive atrioventricular node, continuous with the atrioventricular bundle. In the mouse heart, this basal part of the node is readily distinguished on the basis of both its molecular phenotype and developmental origin. It expresses connexin40, as does the atrioventricular bundle. The larger part of the body of the compact node expresses neither connexin43 nor connexin40

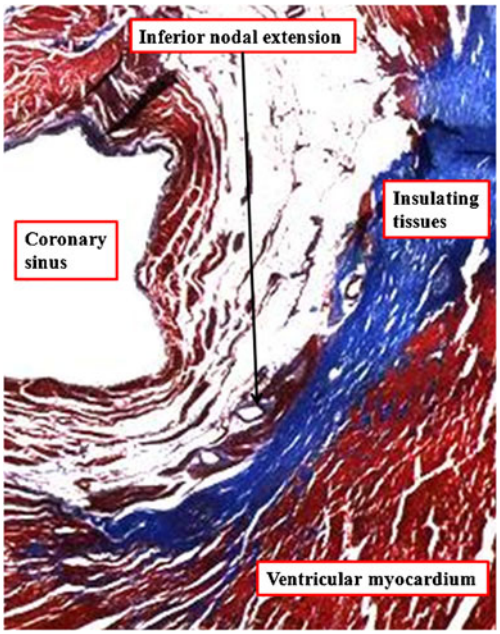

Fig. 6 The section shows the inferior extension of the atrioventricular node in a human heart. The extension was traced through serial sections, and could be identified as being histologically specialised using the criteria established by Aschoff [8] and Monckeberg [9]. Laser capture microdissection revealed the extension also to have the immunohistochemical characteristics of specialised myocardium

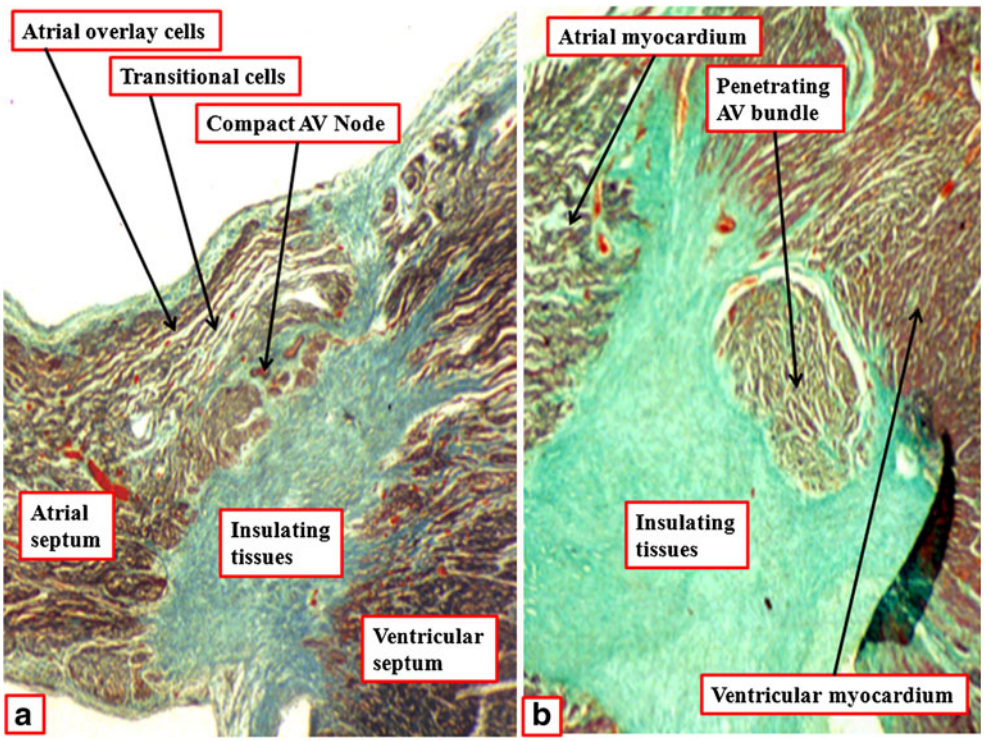

Fig. 5 The histological sections, stained with the trichrome method, with fibrous tissue stained green, show the features (**a**) of the atrioventricular (AV) node and (**b**) the penetrating atrioventricular bundle

[30]. Such an arrangement is also found in the human heart [31].

The rightward component of the atrioventricular ring system emerging inferiorly from the atrioventricular node is part of the slow nodal pathway [32]. The cardiomyocytes forming the ring initially possessed a primary phenotype, and hence would certainly have conducted slowly. In one heart studied after ablation of the slow pathway, no evidence was found of histologically specialised cells extending into the area destroyed by the ablative lesion [33]. The inferior extension from the node, nonetheless, would have passed through the ablated region. The anatomical evidence now indicates that a comparable slow pathway will enter the compact node from the left atrial side as a second inferior extension. The fast pathway into the node is made up of the working atrial cardiomyocytes. These merge with the compact node having coursed antero-superiorly relative to the oval fossa (Fig. 4).

The Atrioventricular Conduction Axis

The atrioventricular conduction axis has atrial, penetrating, and ventricular components. The penetrating part is formed when the cells making up the axis become insulated from the atrial myocardium by the fibrous tissues of the atrioventricular junction [5]. In the human heart, the penetrating part as thus defined, in other words the bundle of His, is a relatively short column of longitudinally oriented and histologically specialised cardiomyocytes (Fig. 5b). Having penetrated the fibrous insulating plane, the axis is usually positioned on the crest of the muscular ventricular septum, where it has a short non-branching segment before giving rise to the fascicles of the left bundle branch. The bundle itself continues on the crest of the septum as the dead-end tract, with the right bundle branch taking origin from the axis at the site of most distal left-sided fascicles. In some individuals, the branching part of the axis is located beneath the septal crest on its left ventricular aspect [34]. Having taken origin from the axis, the cardiomyocytes of the left bundle branch fan out subendocardially on the smooth surface of the muscular ventricular septum, forming superior, septal, and inferior ramifications [35, 36]. The right bundle branch runs down the right ventricular aspect of the septum as a discrete thin column of cells, being buried within the septum in its initial course. It ramifies at the apex of the right ventricle, with one bundle crossing the ventricular cavity within the moderator band. The specialised cardiomyocytes within the bundle branches remain insulated from the ventricular myocardium until they reach the ventricular apexes, but then merge with the working cardiomyocytes.

In species such as the rabbit [37, 38] and the dog [39], there is marked cellular diversity within the penetrating component of the axis. The penetrating component in the rabbit has often been identified as being part of the atrioventricular node [37]. When using the criterion suggested by Tawara [5], this histologically heterogeneous part of the axis, since it is insulated by fibrous tissues from the atrial myocardium, should not be considered part of the node, In terms of activation, the cells cannot directly be influenced by atrial events. Recognition of such subtle morphological features is crucial if we are to identify the precise sites of atrioventricular delay, and the functions of the pathways into and through the atrioventricular node [40].

The Atrioventricular Ring Tissues

In the normal heart, there is but a solitary muscular pathway joining together the atrial and ventricular muscular masses [5]. Although the tissues within the atrial vestibules had been recognised by Kent and others [41], and histochemical techniques had endorsed their specialised nature [42], it was the availability of more sophisticated immunohistochemical techniques that permitted demonstration of their full extent [16]. These showed columns of cardiomyocytes discrete from the working cells to extend inferiorly from the compact atrioventricular node in the hearts of mice and rats. The columns, located within the atrial vestibules, encircle both atrioventricular valvar orifices, and come together antero-superiorly in a retroaortic node (Fig. 7), with the tricuspid ring crossing over the penetrating component of the atrioventricular conduction axis so as to reach the retroaortic node (Fig. 8). This retroaortic node, occupying the base of the atrial septum, can also be identified using the classical histological criteria of Aschoff [8] and Monkeberg [9] (Fig. 9). Remnants of the ring tissues themselves had similarly been demonstrated in human hearts

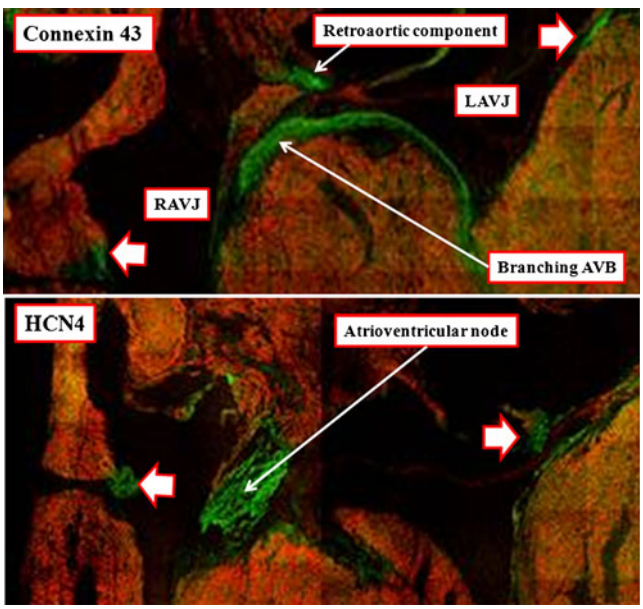

Fig. 7 The images show sections across the atrioventricular junctions of the rat heart, processed to show (*top*) connexin 43, and (*bottom*) HCN4. The immunohistochemical techniques reveal the specialised characteristics of the atrioventricular ring tissues (*arrows*)

by using the German criteria [43]. During development of the human heart, the ring of tissue encircling the embryonic interventricular foramen also includes the retroaortic node [28]. It is the anterior continuation of this ring from the branching atrioventricular bundle that persists as the dead-end tract [29].

Postnatal persistence of other parts of the rings accounts for the anomalously located atrioventricular nodes that give rise to atrioventricular conducting bundles when the heart is congenitally malformed and there is atrioventricular septal malalignment [44–46]. Such nodes are also found at the atrial origin of the reentry circuits responsible for so-called Mahaim pre-excitation [4]. In contrast to the suggestion of some investigators [47], however, the anteriorly located ring tissue does not form part of the definitive atrioventricular node [16].

Potential Substrates for Atrial Tachycardias

In the clinical situation, abnormal atrial rhythms can be initiated at several sites along the terminal crest. These sites coincide with the junction, in the developing heart, of areas of primary and working myocardium. With ongoing development, the cardiomyocytes initially possessing a primary phenotype become indistinguishable, when using standard histological techniques, from the working cardiomyocytes. It is likely that the atrial arrhythmias have their origin in those cardiomyocytes of primary myocardial lineage [13]. Clinical

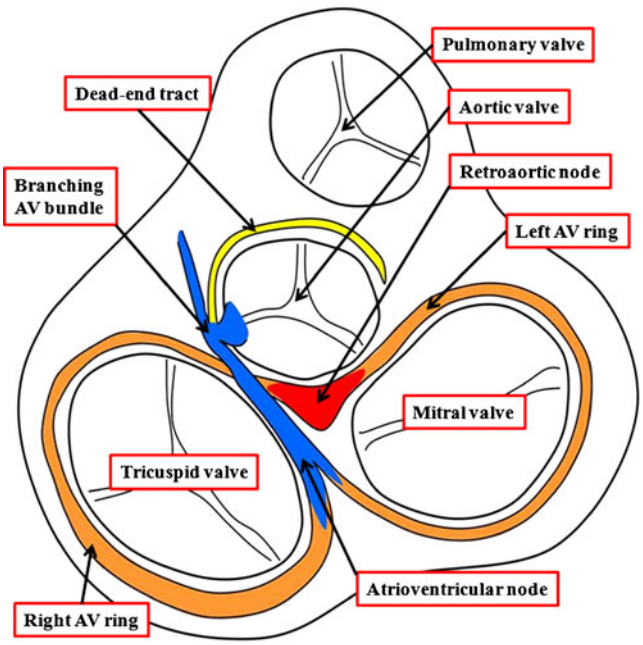

Fig. 8 The cartoon, showing the atrioventricular junctions as seen from the ventricular apex, illustrates the arrangement of the atrioventricular ring tissues as found in the adult rat heart. Note the break between the dead-end tract (*yellow*) and the retroaortic node (*red*). These structures are continuous in the developing heart

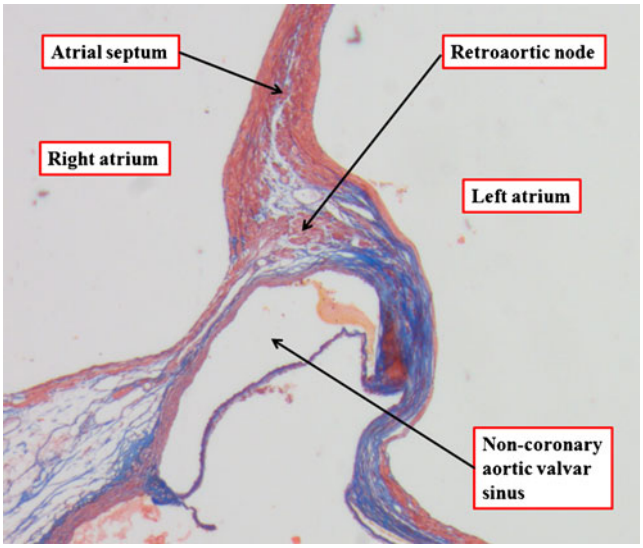

Fig. 9 The histologic section is from an adult mouse heart. It shows how the retroaortic node can be recognised as being histologically specialsied using the criteria established by Aschoff [8] and Monckeberg [9]

studies have also now demonstrated beyond doubt that the atrial fibrillation, in many instances, is initiated in the pulmonary venous myocardial sleeves. The abnormal rhythms have been said to be generated by nodal cardiomyocytes located within the sleeves [12]. The criteria used to support such a nodal origin for the cardiomyocytes are weak. Developmental lineage studies show that the cardiomyocytes making up the pulmonary venous sleeves have never possessed a primary phenotype [48]. It is more likely that atrial fibrillation is the consequence of acquired pathological changes occurring in the myocardial sleeves, most likely with the accretion of fibrous tissue setting the scene for micro-reentry [13]. Changes could occur, nonetheless, to permit working cardiomyocytes to achieve pacemaking potential. If so, then the transformed cells would show the immunohistochemical criteria for pacemaking. As yet, to the best of our knowledge, such changes have not been demonstrated in material taken from patients suffering from atrial fibrillation. If found, it would also be preferable to describe any such cardiomyocytes as being potentially pacemaking, rather than nodal.

Potential Substrates for Ventricular Tachycardias

The distinction of cardiomyocytes known to have had a primary phenotype during development is equally pertinent to searches for the anatomic substrates of outflow tract trachycardias. During their development, the arterial valves are encased within a turret of myocardium, which initially possessed a primary phenotype [13]. The extensions of myocardium identified by some investigators [49] as potential arrhythmic substrates, however, are not remnants of this myocardial turret.

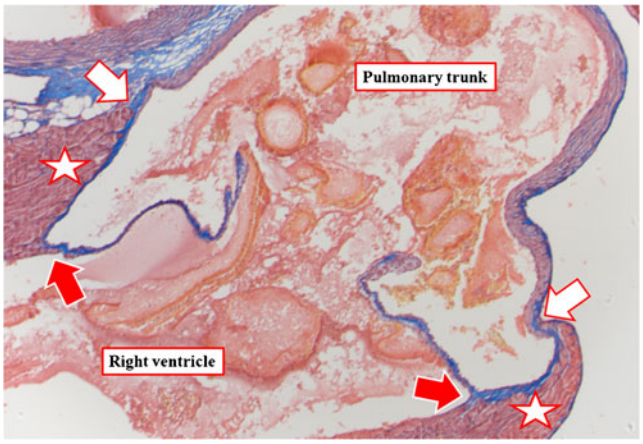

Fig. 10 The section shows the structure of the right ventriculo-arterial junction of the adult mouse heart. The basal attachments of the leaflets of the pulmonary valve are proximal (*red arrows*) relative to the anatomic ventriculo-arterial junction (*white arrows*). Because of this arrangement, the basal components of the valvar sinuses are composed of ventricular myocardium (*stars*), which initially possessed a primary phenotype. Note that there are no extensions of muscle beyond the anatomic ventriculo-arterial junctions

The largest structure identified by the group from Turkey is the free-standing subpumonary infundibular sleeve. Developmentally, the outflow myocardium is markedly heterogeneous [50]. Not only are the myocardial turrets surrounding the developing arterial valves of primary myocardial origin, but so also is the parietal wall of the right ventricular infundibulum. The components of the infundibulum adjacent to the aortic root are newly formed during development, with the myocytes populating the outflow cushions to produce the new myocardium [51] being derived from primary myocardial walls. Thus, the myocardial crescents to be found at the bases of each of the pulmonary valvar sinuses, known to be sites of abnormal rhythmicity, are derived initially from primary myocardium. With ongoing development, they become indistinguishable histologically from the remainder of the right ventricular cardiomyocytes (Fig. 10). At least in the rat, remnants of the sleeve of myocardium surrounding the developing arterial valves persist in the postnatal heart, and would have had potentially pacemaking characteristics (Fig. 11). Cardiomyocytes are also found in this location in human hearts [52]. These cardiomyocytes, therefore, would also likely have pacemaking properties. They would need to be ablated using lesions placed distal to the ventriculo-arterial junctions [53].

A similar situation exists in regard to the aortic outflow tract. The cardiomyocytes that invade the outflow cushions are subsequently recruited to form the free-standing muscular subpulmonary infundibulum. Small remnants of these tissues are also found at the base of the two aortic sinuses that give rise to the coronary arteries. The dead-end tract of the atrioventricular conduction axis also occupuies this part of the root (Fig. 11). All of these cardiomyocytes would have arrhythmogenic potential. The non-coronary aortic

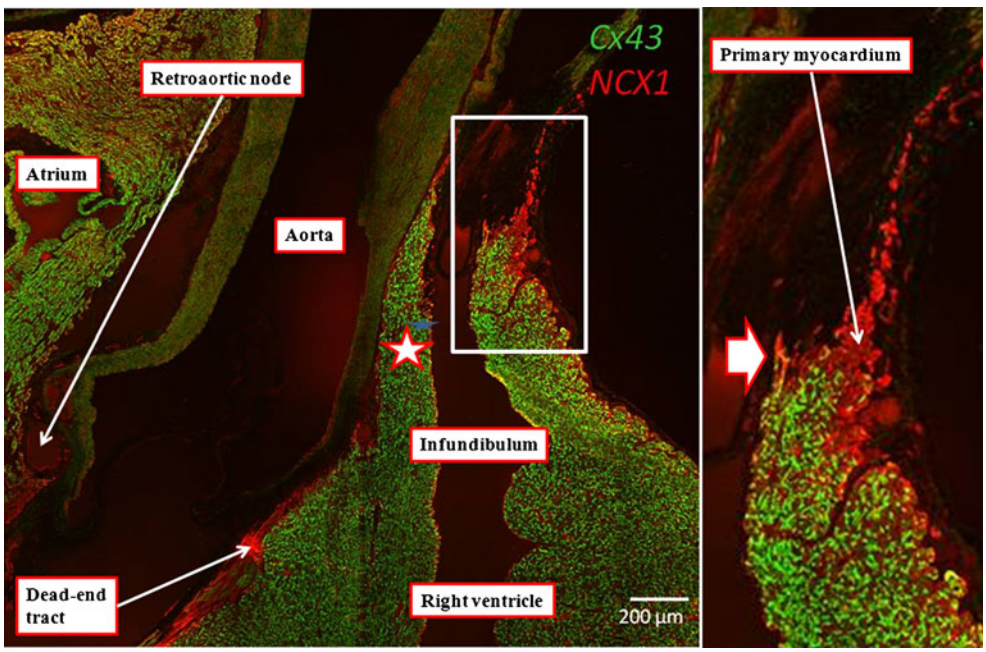

Fig. 11 The sections show the ventriculo-arterial junctions of the guinea pig heart processed to show connexin 43. The *inset* is magnified in the *right hand panel*. It shows how the base of the pulmonary valvar sinus is composed of cardiomyocytes lacking gap junctions containing connexin 43, indicating their origin as primary myicardium. Note how the free-standing sleeve of pulmonary infundibular myocardium overlaps the aortic root. This muscle should not be interpreted as a myocardial extension. It is normal infundibular anatomy. Note, however, that the dead-end tract and the retroaortic node, recognised because of their lack of gap junctions containing connexin 43, are intimately related to the aortic root

valvar sinus, in contrast, does not possess ventricular muscle at its base, since this sinus is related to the area of aortic-to-mitral valvar fibrous continuity. Some arrhythmias, however, are known to be ablated by lesions placed within this sinus [54]. Abnormal persistence of the myocardium of the inner heart curvature, which also possesses a primary myocardial phenotype, would provide a rational basis for these abnormal rhythms, the more so since it is known that a small proportion of otherwise normal human hearts can be found with a persisting subaortic muscular infundibulum [55].

Conclusions

Discovery of the cardiomyocytes specialised histologically so as to generate and propogate the cardiac impulse was very much a twentieth-century event. The emergence of new molecular and immunohistochemical techniques at the turn of the twenty-first century has now refined the early discoveries. The criteria put forward over a century ago to permit recognition of the histologically specialised cardiomyocytes in autopised human tissues, nonetheless, retain their utility and currency. When combined with those available using the newer techniques, the criteria reveal newly discovered areas, such as the paranodal component of the terminal crest, and the retroaortic node. The functions of these structures have yet to be established. Cardiomyocytes with an initially specialised phenotype also exist within the ventricular outflow tracts, and could be responsible for production of some outflow tract tachycardias.

References

1. His W. Die Tätigkeit des embryonalen herzens und deren bedeutung für die Lehre von der Hezebewegung beim Menschen. Arb med Klinik Leipzig. 1893; 14–19.
2. Keith, A. (1950). *An autobiography* (pp. 255–259). London: Watts.
3. Kent, A. F. S. (1893). Researches on the structure and function of the mammalian heart. *The Journal of Physiology, 14*, 233–254.
4. Anderson, R. H., Ho, S. Y., Gillette, P. C., & Becker, A. E. (1996). Mahaim, Kent and abnormal atrioventricular conduction. *Cardiovascular Research, 31*, 480–491.
5. Tawara, S. (1906). *Das Reizleitgssystem des Saugetierherzens*. Jena: Gustav Fischer.
6. Keith, A., & Flack, M. (1907). The form and nature of the muscular connections between the primary divisions of the vertebrate heart. *Journal of Anatomy and Physiology, 41*, 172–189.
7. Thorel, C. (1909). Vorlaufige Mitteulungen u¨ber eine besondere Muskelverbindung zwischen der Cava superior und dem Hisschen bundel. *Munch Med Woch, 56*, 2159–2161.
8. Aschoff, L. (1910). Referat uber die Herzstorungen in ihren Beziehungen zu den Spezifischen Muskelsystem des Herzens. *Verh Dtsch Pathol Ges, 14*, 3–35.
9. Mönckeberg, J. G. (1910). Beitrage zur normalen und pathologischen Anatomie des Herzens. *Verh Dtsch Pathol Ges, 14*, 64–71.
10. James, T. N. (1963). The connecting pathways between the sinus node and A–V node and between the right and the left atrium in the human heart. *American Heart Journal, 66*, 498–508.
11. Janse, M. J., & Anderson, R. H. (1974). Specialized internodal atrial pathways—fact or fiction? *European Journal of Cardiology, 2*, 117–136.
12. Perez-Lugones, A., McMahon, J. T., Ratliff, N. B., et al. (2003). Evidence of specialized conduction cells in human pulmonary veins of patients with atrial fibrillation. *Journal of Cardiovascular Electrophysiology, 14*, 803–809.
13. Bakker, M. L., Christoffels, V. M., & Moorman, A. F. (2010). The cardiac pacemaker and conduction system develops from embryonic myocardium that retains its primitive phenotype. *Journal of Cardiovascular Pharmacology, 56*, 6–15.
14. Chandler, N. J., Greener, I. D., Tellez, J. O., Inada, S., Musa, H., Molenaar, P., et al. (2009). Molecular architecture of the human sinus node: insights into the function of the cardiac pacemaker. *Circulation, 119*, 1562–1575.
15. Christoffels, V. M., Smits, G. J., Kispert, A., & Moorman, A. F. M. (2010). Development of the pacemaker tissues of the heart. *Circulation Research, 106*, 240–254.
16. Yanni, J., Boyett, M. R., Anderson, R. H., & Dobrzynski, H. (2009). The extent of the specialized atrioventricular ring tissues. *Heart Rhythm, 6*, 672–680.
17. Moorman, A. F. M., & Christoffels, V. M. (2003). Cardiac chamber formation: development, genes and evolution. *Physiological Reviews, 83*, 1223–1267.
18. Sanchez-Quintana, D., Cabera, J. A., Farre, J., Climent, V., Anderson, R. H., & Ho, S. Y. (2005). Sinus node revisited in the era of electroanatomical mapping and catheter ablation. *Heart, 91*, 189–194.
19. Anderson, K. R., Ho, S. Y., & Anderson, R. H. (1979). The location and vascular supply of the sinus node in the human heart. *British Heart Journal, 41, 28–32.*
20. Wiese, C., Grieskamp, T., Airik, R., Mommersteeg, M. T. M., Gardiwal, A., deGier-deVries, C., et al. (2009). Formation of the sinus node head and differentiation of sinus node myocardium are independently regulated by Tbx18 and Tbx3. *Circulation Research, 104*, 388–397.
21. Christoffels, V. M., & Moorman, A. F. (2009). Development of the cardiac conduction system: why are some areas of the heart more arrhythmogenic than others? *Circulation. Arrhythmia and Electrophysiology, 2*, 195–207.
22. Bachmann, G. (1916). The inter-auricular time interval. *American Journal of Physiology, 41*, 309–320.
23. Busquet, J., Fontan, F., Anderson, R. H., Ho, S. Y., & Davies, M. J. (1984). The surgical significance of the atrial branches of the coronary arteries. *International Journal of Cardiology, 6*, 223–234.
24. Dobrzynski, H., Li, J., Tellez, J., et al. (2005). Computer three-dimensional reconstruction of the sinoatrial node. *Circulation, 111*, 846–854.
25. Spach, M. S., Lieberman, M., Scott, J. G., Barr, R. C., Johnson, E. S., & Kootsey, J. M. (1971). Excitation sequences of the atrial septum and the AV node in isolated hearts of the dog and rabbit. *Circulation, 29*, 156–172.
26. Chauvin, M., Shah, D. C., Haissaguerre, M., Marcellin, L., & Brechenmacher, C. (2000). The anatomic basis of connections between the coronary sinus musculature and the left atrium in humans. *Circulation, 101*, 647–652.
27. Inoue, S., & Becker, A. E. (1998). Posterior extensions of the human compact atrioventricular node: a neglected anatomic feature of potential clinical significance. *Circulation, 97*, 188–193.
28. Wessels, A., Markman, M. W., Vermeulen, J. L. M., Anderson, R. H., Moorman, A. F. M., & Lamers, W. H. (1996). The development of the atrioventricular junction in the human heart. *Circulation Research, 78*, 110–117.

29. Kurosawa, H., & Becker, A. E. (1985). Dead-end tract of the conduction axis. *International Journal of Cardiology, 7*, 13–20.
30. Aanhanen, W. T., Mommersteeg, M. T., Norden, J., Wakker, V., deGier-deVries, C., Schuster-Gossler, K., et al. (2010). Developmental origin, growth, and three-dimensional architecture of the atrioventricular conduction axis of the mouse heart. *Circulation Research, 107*, 728–736.
31. Hucker, W. J., McCain, M. L., Laughner, J. I., Iaizzo, P. A., & Efimov, I. R. (2008). Connexin 43 expression delineates two discrete pathways in the human atrioventricular junction. *Anatomical Record, 291*, 204–215.
32. Inoue, S., Becker, A. E., Riccardi, R., & Gaita, F. (1999). Interruption of the inferior extension of the compact atrioventricular node underlies successful radio frequency ablation of atrioventricular nodal reentrant tachycardia. *Journal of Interventional Cardiac Electrophysiology, 3*, 273–277.
33. Ho, S. Y., McComb, J. M., Scott, C. D., & Anderson, R. H. (1993). Morphology of the cardiac conduction system in patients with electrophysiologically proven dual atrioventricular nodal pathways. *Journal of Cardiovascular Electrophysiology, 4*, 504–512.
34. Massing, G. K., & James, T. N. (1976). Anatomical configuration of the His bundle and bundle branches in the human heart. *Circulation, 53*, 609–621.
35. Atkinson, A., Inada, S., Li, J., Tellez, J. O., Yanni, J., Sleiman, R., et al. (2011). Anatomical and molecular mapping of the left and right ventricular His-Purkinje conduction networks. *Journal of Molecular and Cellular Cardiology, 51*, 689–701.
36. Stephenson, R. S., Boyett, M. R., Hart, G., Nikolaidou, T., Cai, X., Cooro, A. F., et al. (2012). Contrast enhanced micro-computed tomography resolves the 3-dimensional morphology of the cardiac conduction system in mammalian hearts. *Plos One, 7*(4), e35299. doi:10.1371/journal.pone.0035299.
37. Anderson, R. H. (1972). Histologic and histochemical evidence concerning the presence of morphologically distinct cellular zones within the rabbit atrioventricular node. *Anatomical Record, 173*, 7–24.
38. Li, J., Greener, I. D., Inada, S., Nikloski, V. P., Yamamoto, M., Hancox, J. C., et al. (2008). Computer three-dimensional reconstruction of the atrioventricular node. *Circulation Research, 102*, 975–985.
39. Ho, S. Y., Kilpatrick, L., Kanai, T., Germroth, P. G., Thompson, R. P., & Anderson, R. H. (1995). The architecture of the atrioventricular conduction axis in dog compared to man: its significance to ablation of the atrioventricular nodal approaches. *Cardiovascular Electrophysiology, 6*, 26–39.
40. Hucker, W. J., Sharma, V., Nikolski, V. P., & Efimov, I. R. (2007). Atrioventricular conduction with and without AV nodal delay: two pathways to the bundle of His in the rabbit heart. *American Journal of Physiology Heart, 293*, H1122–H1130.
41. Gossrau, R. (1971). Uber zusätzliches Reizleitungsgewebe im Goldhamsterherzen. *Zeitschrift für Zellforschung und Mikroskopische Anatomie, 115*, 587–592.
42. Anderson, R. H. (1972). The disposition and innervation of atrioventricular ring specialized tissue in rats and rabbits. *Journal of Anatomy, 113*, 197–211.
43. Anderson, R. H., Davies, M. J., & Becker, A. E. (1974). Atrioventricular ring specialized tissue in the normal heart. *European Journal of Cardiology, 2*, 219–230.
44. Anderson, R. H., Arnold, R., Thaper, M. K., Jones, R. S., & Hamilton, D. I. (1974). Cardiac specialized tissues in hearts with an apparently single ventricular chamber (double inlet left ventricle). *The American Journal of Cardiology, 33*, 95–106.
45. Anderson, R. H., Becker, A. E., Arnold, R., & Wilkinson, J. L. (1974). The conducting tissues in congenitally corrected transposition. *Circulation, 50*, 911–923.
46. Milo, S., Ho, S. Y., Macartney, F. J., Wilkinson, J. L., Becker, A. E., Wenink, A. C. G., et al. (1979). Straddling and overriding atrioventricular valves morphology and classification. *The American Journal of Cardiology, 44*, 1122–1134.
47. Blom, N. A., Gittenberger-De Groot, A. C., Deruiter, M. C., Poelmann, R. E., Mentink, M. M., & Ottenkamp, J. (1999). Development of the cardiac conduction tissue in human embryos using HNK-1 antigen expression: possible relevance for understanding of abnormal atrial automaticity. *Circulation, 99*, 800–806.
48. Mommersteeg, M. T., Christoffels, V. M., Anderson, R. H., & Moorman, A. F. (2009). Atrial fibrillation: a developmental point of view. *Heart Rhythm, 6*, 1818–1824.
49. Hasdemir, C., Aktas, S., Govsa, F., Aktas, E. O., Kocak, A., Bozkaya, Y. T., et al. (2007). Demonstration of ventricular myocardial extensions into the pulmonary artery and aorta beyond the ventriculoarterial junction. *Pacing and Clinical Electrophysiology, 30*, 534–539.
50. Boukens, B., Christoffels, V., Coronel, R., & Moorman, A. (2009). Developmental basis for electrophysiological heterogeneity in the ventricular and outflow tract myocardium as a substrate to life threatening arrhythmias. *Circulation Research, 104*, 19–31.
51. van den Hoff, M. J. B., Moorman, A. F. M., Ruijter, J. M., Lamers, W. H., Beddington, R. W., Markwald, R. R., et al. (1999). Myocardialisation of the cardiac outflow tract. *Developmental Biology, 212*, 477–490.
52. Cabrera, J. A., & Sanchez-Quintana, D. (2012). Education in heart. *Heart*, in press.
53. Timmermans, C., Rodriguez, L. M., Crijns, H. J., Moorman, A. F., & Wellens, H. J. (2003). Idiopathic left bundle-branch block-shaped ventricular tachycardia may originate above the pulmonary valve. *Circulation, 108*, 1960–1967.
54. Asirvatham, S. J. (2009). Correlative anatomy for the invasive electrophysiologist: outflow tract and supravalvar arrhythmia. *Journal of Cardiovascular Electrophysiology, 8*, 955–968.
55. Rosenquist, G. C., Clark, E. B., Sweeney, L. J., & McAllister, H. A. (1976). The normal spectrum of mitral and aortic valve discontinuity. *Circulation, 54*, 298–301.