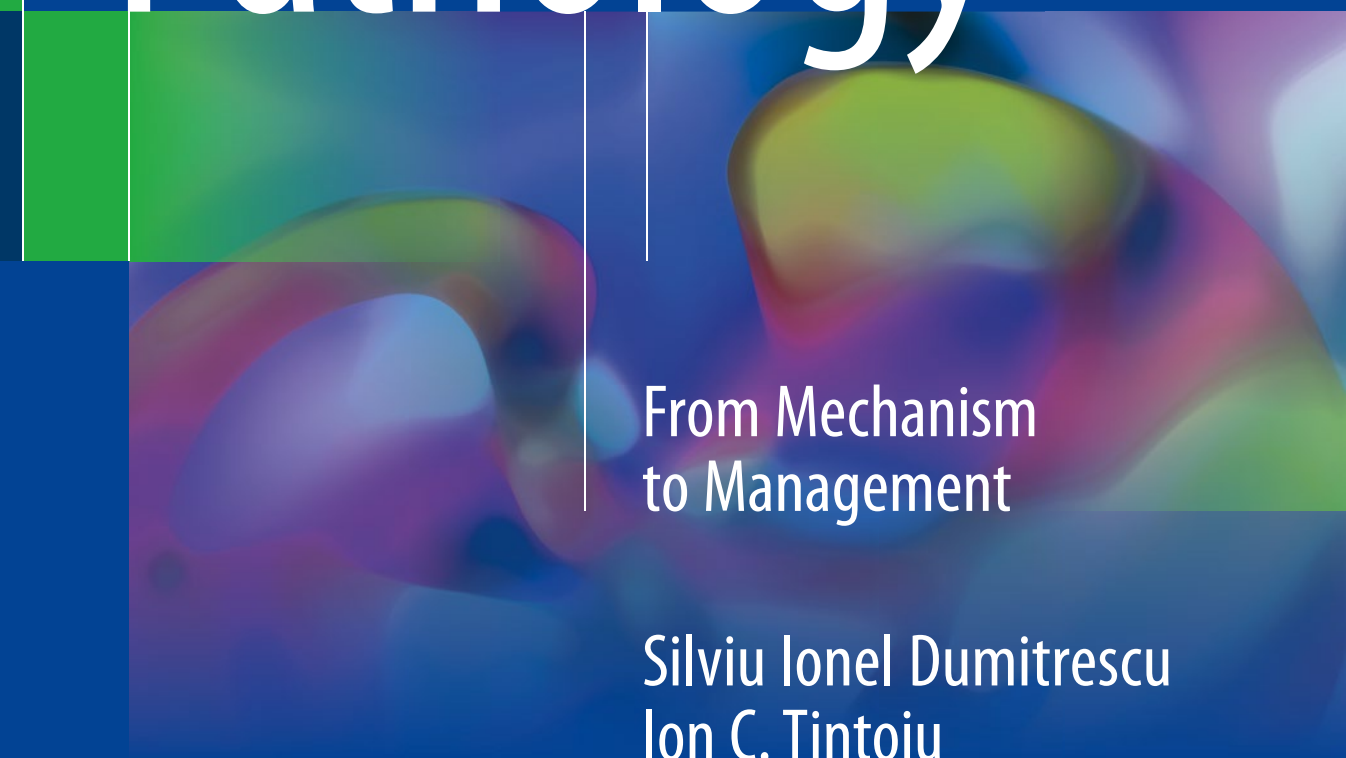
Right Heart Pathology



From Mechanism to Management

Silviu Ionel Dumitrescu
Ion C. Țintoiu
Malcolm John Underwood
Editors

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I dedicate this monograph to my professor Vasile Cândea, the mentor of the cardiac surgery school in our hospital.

Thanks to my wife Olga and my daughter Raluca for their patience with which they supported me in the realization of this monograph.

Ion C. Ţintoiu, MD, PhD, FESC

Foreword

Pathology of the right heart has been less studied by medical literature, therefore we have proposed to update the existing data in order to improve the therapeutic solutions.

On the whole, We have reviewed the main elements of embryology, genetics, anatomy, pathophysiology, diagnostic methods, right heart pathology, and up-to-dated therapeutic solutions. We have presented the pathology of the right heart from the point of view of its primary and secondary interests.

The objectives of this monograph were three. The first was to present the general data from anatomy to pathology. The second part of the study was to analyze the main diagnostic methods: exam, classical methods (cardiac catheterization, angiocardiography) as well as modern methods of echocardiography (TEE, 3D, 4D etc), MRI, Angio CT, etc. The third was to individualize the therapeutic solutions for medical and surgical treatments. The authors of this monograph are medical personalities who present their personal experience as well. Each chapter approaches the subject with arguments from literature, graphic examples, and iconography mainly from accumulated knowledge. Arrhythmias, pacing problems, ICD, and CRT are addressed in their complexity from the point of view of procedural techniques as well as complications. The tricuspid valve pathology is treated in its primary and secondary affection and in the context of pulmonary hypertension. The right ventricle dysfunction is presented in its systolic and diastolic components as well as in relation to the left ventricle. Pulmonary thromboembolism is specifically analyzed in a chapter which includes specific surgical and interventional treatment. The repercussions on right ventricle function after liver transplantation and pneumonectomy are tackled as well.

We would like to thank the authors and coauthors of this monograph for their participation in this project.

Bucharest, Romania — Ion C. Ţintoiu

Preface

Pathology of the right heart is less studied in the literature, and that is why we have proposed to update the existing data in order to improve the therapeutic solutions. We have reviewed the main elements of embryology, genetics, anatomy, pathophysiology, diagnostic methods, right heart pathology, and up-to-date therapeutic solutions. We have presented the pathology of the right heart from the point of view of both primary and secondary interests.

The monograph has three objectives. The first is to present the general data from anatomy to pathology. The second is to analyze the main diagnostic methods: exam, classical methods (cardiac catheterization, angiocardiography), and modern methods of echocardiography (TEE, 3D, 4D etc), MRI, Angio CT, etc. The third is to individualize therapeutic solutions for medical and surgical treatment. The authors of this monograph are medical personalities who present their personal experience as well. Each chapter addresses the subject with arguments from literature, graphic, and iconographic examples, generally personal. Arrhythmias, pacing, ICD, and CRT problems are addressed in their complexity from the point of view of procedural techniques and complications. The pathology of the tricuspid valve is treated in its primary and secondary affection and in the context of pulmonary hypertension. Right ventricular dysfunction is presented in its systolic and diastolic components as well as in relation to the left ventricle. Pulmonary thromboembolism is specifically analyzed in a chapter that includes specific surgical and interventional treatment. Repercussions on right ventricular function after liver transplantation and pneumonectomy are also addressed.

We would like to thank the authors and coauthors of this monograph for their participation in this project.

Bucharest, Romania — Silviu Ionel Dumitrescu
Bucharest, Romania — Ion C. Ţintoiu
Sha Tin, Hong Kong — Malcom John Underwood

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Part I

Overview

Heart Embryology: Overview

1

Florentina Radu-Ioniţă, Ecaterina Bontaş, Viorel Goleanu, Bogdan Cîrciumaru, Daniela Bartoş, Irinel Parepa, Ion C. Ţintoiu, and Adrian Popa

Abstract

Human heart has a complex embryological development process driven by genetic mechanisms that have successive and unitary progression in a global context together with other developments of organogenesis. The first elements of cardiogenesis occur prematurely from mesoderm where cellular differentiation at this level acquires cardiogenic specificity by creating the first heart field. From this stage, cellular multiplication is specific for myocardial, endothelial, and smooth muscle cells through the second heart field. Accordingly to up-to-date evidence, the mechanisms of this process are genetically coordinated mainly by NKX2.5, GATA4, Mef2, TBX5 and Hand which establish not only the structure of the embryonic cord but also the sequential evolution of the differentiation and completion of the cardiac structures including the inlet and outlet paths. First field and second field are the initial particular stages of cardiogenesis. In the primary heart tube, the differentiation into adult anatomical cardiac structures (the atrial and ventricular cavities) begins. The heart tube looping initi-

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ates the separation of the primitive atria, ventricle and outflow tract. The separation between these cavities is made by different but concordant mechanisms. Coronarogenesis is the last stage before embryonic heart becomes functional.

Keywords
Cardiogenesis · Cardiac morphogenesis Normal heart development · First and second heart fields · Linear and looped tube separation Jonctional differentiation · Angiogenesis Conduction system

The norm should be established; embryos should be arranged in stages.

Franklin P. Mall

1.1 Background

Importantly, Kloesel et al. stated that "the embryonic development of the human heart is a complex process" [1]. As well, understanding of cardiac development is based also on "genetics, molecular cell biology, embryology, systems biology and anatomy" [1]. It must also be emphasized that in the heart embryology numerous terms are currently existent for the similar cardiac structures. The extremely difficult molecular biology and genetic taxonomy differentiates a gene from a protein by a general agreement [1]. A human gene is described in italic uppercase letters (e.g., *GATA4*), while the protein obtained from this gene is described in nonitalic uppercase letters (e.g., GATA4) [1].

Recent data regarding cardiogenesis of Kloesel et al. have established nine main successive stages [1]: (1) gastrulation (three germ layers), (2) the first and second heart fields development, (3) heart tube, (4) heart tube looping, convergence, and wedging, (5) septa forming with common atrium and atrioventricular canal, (6) formation of outflow tract, (7) development of cardiac valves, (8) development of vessels (coronary arteries, aortic arches and sinus venous), (9) development of the conduction tissue. The first cardiac structures emerge from the "mesodermal precardiac cells" that shift to the superior part of the primary embryonic framework forming a special cardiac structure called "cardiac crescent" [2]. Equally important, the cardiogenesis process is sustained by transcription factors also known as "primordial genes" implied in cardiac morphogenesis. Therefore, the role of above mentioned genes is to differentiate mesodermal precardiac cells in the myocardial cells, endothelial cells and smooth muscle cells through the process called "the phenomenon of progressive lineage restriction" [3]. Transcription factors responsible for cardiogenesis such as NK2 Homeobox 5 (NKX2.5) [1, 4], GATA-binding protein 4 (GATA4) [1, 5], T-Box protein 5 (TBX5) [1], MADS-box protein (Mef2) [6], and Heart—and neural crest derivatives-expressed protein (Hand) family [6] ensure the control of cardiac differentiation. Specifically, the interrelation between the main three transcription factors (TBX5, GATA4, and NKX2.5) as well the individual action of these elements is fundamental to cardiogenesis.

Embryonic human cardiac development in Carnegie stages 15–23 has important knowledge for clinical and scientific research [7]. Of note, the evolution of the human embryo is based on the *Carnegie Institution of Washington* stages (CS) so that in the first 8 weeks are described 23 stages. Cardiac structures begin differentiation from stage 13 Carnegie and are finalized in stage 23 (see Table 1.1) [7]. Moreover, human embryos cardiac development from Carnegie stages 15–23 offer significant evidence looking embryogenesis, for instance regarding the ventricular trabeculation process [7, 8].

1.2 Heart Fields

At day 16 (CS6-7) of gestation, a part of epiblast cells form by migration the mesoderm with "four cell populations—cardiogenic mesoderm and the paraxial, intermediate, and lateral plate mesoderm" [1, 2]. Further, progenitor cardiogenic mesodermal cells also known as "precardiac cells" generate the first heart field (FHF) [1]. Equally important, the FHF generates further the

Table 1.1 Stages of human development with corresponding events in cardiac development

Carnegie stage (CS)	Human DPC	Characteristics
CS8	17–19	The cardiac crescent forms
CS9	19–21	The embryo folds, the pericardial cavity is placed in its final position, gully of myocardium forms, the endocardial plexus forms, cardiac jelly forms
CS10	22–23	The heart beats, the endocardial tubes fuse, the mesocardium perforates, looping starts, the ventricle starts ballooning
CS11	23–26	The atria balloon, the proepicardium forms
CS12	26–30	The septum primum appears, the right venous valve appears, the muscular part of the ventricular septum forms, cells appear in the cardiac jelly, epicardial growth starts
CS13	28–32	The AV cushions form, the pulmonary vein attaches to the atrium, the left venous valve appears, epicardial mesenchyme appears first in the AV sulcus
CS14	31–35	The AV cushions approach one another, the outflow ridges become apparent, capillaries form in the epicardial mesenchyme
CS15	35–38	The AV cushions oppose one another, the secondary foramen forms, the distal outflow tract septates, the outflow tract ridges reach the primary foramen
CS16	37–42	The primary atrial septum closes, the outflow tract ridges approach the interventricular septum, the entire heart is covered in epicardium
CS17	42–44	Secondary atrial septum appears, the sinus node becomes discernable, the left and right AV connection becomes separate, the proximal outflow tract becomes septated, the semilunar valves develop
CS18	44–48	Papillary muscles appear, the AV valves start to form
CS19	48–51	The left venous valve fuses with the secondary septum, the mural leaflets of the mitral and tricuspid valves are released
CS21	53–54	The main branches of the coronary artery become apparent
CS22	54–56	The chordae tendinae form
CS23	56–60	The septal leaflet of the tricuspid valve delaminates

DPC days postconception
Modified from Kussman and Miller-Hance [7] with permission.
See further reading section for comprehensive data

secondary heart field (SHF) that will create the greater part of the heart [1]. It has to be underlined that the transcription factor islet-1 (Isl1) is exhibited by SHF cells required for the development further in cardiomyocytes, smooth muscle cells and endothelial cells [2, 9]. Both, FHF and SHF form cardiac crescent at day 15 [1].

It is well established that progenitor cardiogenic mesodermal cells (precardiac mesodermal cells) are the first generators in cardiogenesis. Initially, embryonic mesoderm cells convert in "precardiac lineage" that exhibits Mesp-1 with the ability to develop multipotent "cardiac progenitor cells" (CPC, exhibiting NKX2.5). As already mentioned, CPC control by themself the capacity to develop cardiac myocytes, vascular smooth muscle cells, and endothelial cells (Fig. 1.1) [10]. It is postulated that the significant resource for the CPC is SHF that will generate the outflow tract (OFT). However, the increase and generation of both OFT and heart valves is accomplished by "non-mesodermal neural crest cells" (NCC) of the neural fold by migration in the endocardial cushion and the arterial pole through genetic control of Pax3 (see Fig. 1.1) [10].

Between days 15 and 21 (CS7-9) structural evolutionary transformations by cellular multiplication of FHF and SHF lead to linear heart tube development that represents the next step of cardiogenesis. At day 15, first locations of primitive atrial and ventricular cavities appear in FHF sequentially placed in lateral places of cardiac crescent. As well, SHF represents the inside padding of FHF [1].

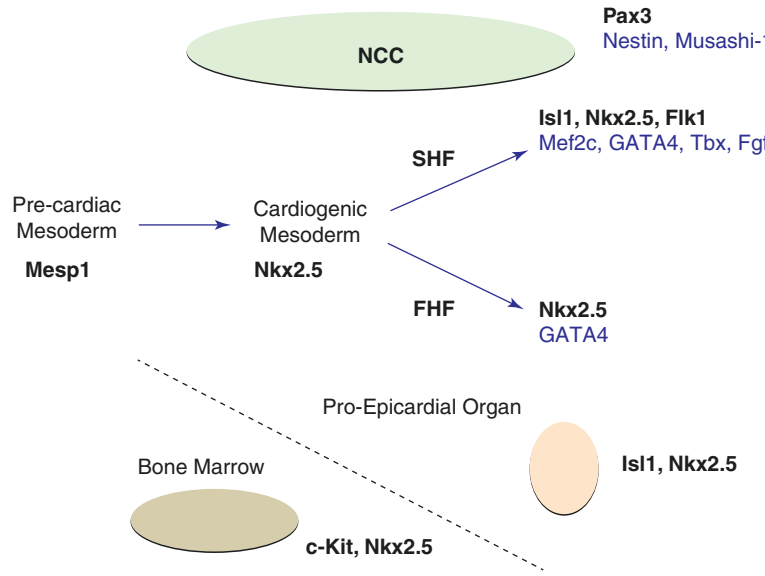

Fig. 1.1 Overview of myocardial CPC Markers in relation to their ontology. Pre-cardiac mesoderm cells express Mesp1 until differentiation to cardiogenic mesoderm, marked by the expression of Nkx2.5. The cardiogenic mesoderm differentiates to form two heart fields. Cells in the first heart field (FHF) express GATA4 in addition to Nkx2.5. Cells of the secondary heart field (SHF) express Isl1 and Nkx2.5. The SHF also becomes populated by neural crest cells (NCC) expressing Pax3. Markers associated with the heart field cells but showing greater variation in their expression are indicated in blue type. In addition to cardiogenic mesoderm, cells from the pro-epicardial organ and also of hematopoietic lineage have been identified in the myocardium. Abbreviations: *NCC* neural crest cells, *SHF* second heart field, *FHF* first heart field. From Chalajour et al. [10]. It is open access chapter.

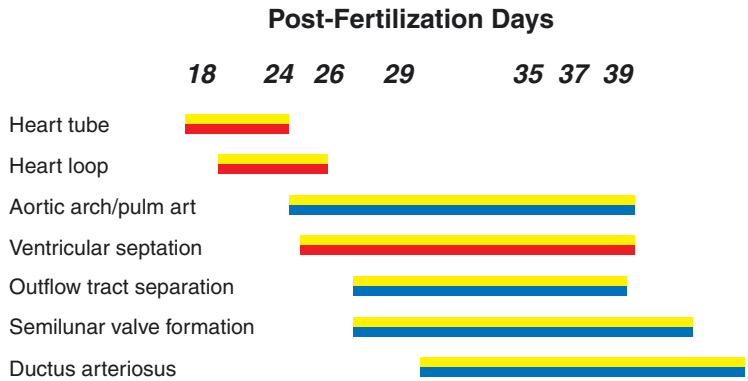

Fig. 1.2 Timeline of outflow tract and semilunar valve development post-fertilization. The colors represent contributions to cardiac development from different cell populations. These contributions are from the first heart field (red), second heart field (yellow) and cardiac neural crest (blue). Modified from Gittenberger-de Groot et al. [11]. From Martin et al. [12]. It is an open access article.

To sum up, FHF along with SHF and the migration of NCC into SHF participate in all stages of cardiogenesis (Fig. 1.2) [1, 10–12].

Consequently, at day 21, the first sites of atrium and ventricle cavities appear in FHF sequentially placed in lateral places of cardiac crescent. As already described above, SHF represents padding through cells placed inside FHF. From day 21 (CS9), cardiac crescent becomes linear heart tube which is a multicellular structure formed from the

upper part to down by truncus arteriosus, bulbus cordis, primitive ventricle and primitive atrium (Fig. 1.3) [1].

The hallmark of this phase is formation of the linear heart tube which initially has an arterial pole in the superior region and a venous one in the inferior region. Additional, Ward et al. showed that the right side of the SHF is partly responsible for the development to the left side of the outflow myocardium [14]. Moreover, the anterior component of the SHF ("anterior heart field") provide the myocardial cells from the right ventricle and the OFT [14].

1.3 Liniar Heart Tube

In the interval of days 19–21 (CS9), the linear heart tube is already built being a multicellular structure formed in the superior area from truncus arteriosus and bulb cordis, and in the lower part from the primitive ventricle and primitive atrium [1]. In fact, Kloesel et al. showed that the linear heart tube is already formed in day 21 (Fig. 1.3) [1]. By the day 28, the linear heart tube changes through the looping process (expansion and elongation of the heart tube) into the right (D-loop) to establish the future arrangement of the cardiac

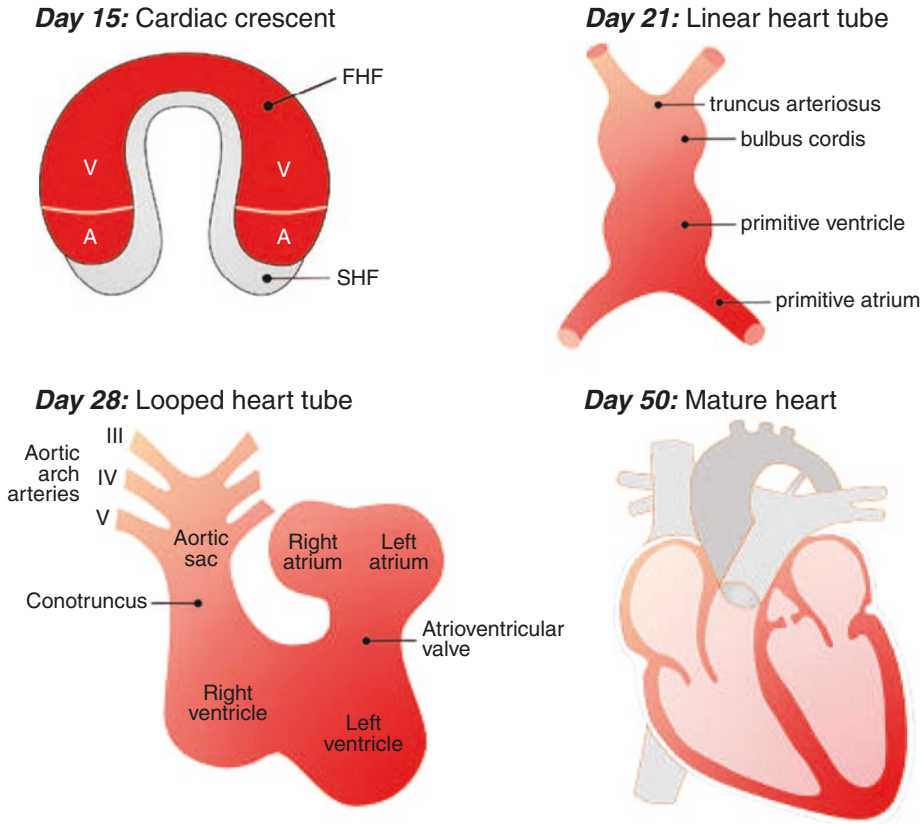

Fig. 1.3 Schematic representation of cardiac embryology. (**a**), Cardiac crescent at day 15. The first heart field is specified to form particular segments of the linear heart tube. The second heart field is located medial and caudal of the first heart field and will later contribute cells to the arterial and venous pole. (**b**) By day 21, cephalocaudal and lateral folding of the embryo establishes the linear heart tube with its arterial (truncus arteriosus) and venous (primitive atrium) poles. (**c**) By day 28, the linear heart tube loops to the right (D-loop) to establish the future position of the cardiac regions (atria [A], ventricles [V], outflow tract). (**d**) By day 50, the mature heart has formed. The chambers and outflow tract of the heart are divided by the atrial septum, the interventricular septum, 2 atrioventricular valves (tricuspid valve, mitral valve) and 2 semilunar valves (aortic valve, pulmonary valve). FHF indicates first heart field; SHF, second heart field. Adapted in modified form from Lindsey et al. [13]. From Kloesel et al. [1] with permission.

areas such as atria, ventricles and OFT (Fig. 1.3) [1, 13]. It has to be underlined that recent evidence shows that the mainly part of heart is created by migration of precursor cells from the SHF with the development of heart tube [1].

Consistently with above data, the comprehensive assessment of Kussman et al. (see Table 1.1) sustains that looping of heart tube has onset during days 22–23 (CS10) [7].

1.4 Looped Heart Tube

Between days 21 and 28 (CS9-13) the linear heart tube rotates and becomes a looped heart tube through the separation of atriums and ventricles; in which atrioventricular valve separates atrium cavities from left ventricle, and conotruncus separates aortic sac from right ventricle (Fig. 1.3) [1].

Of great interest is considerable evidence sustains that the primary linear heart tube under the control of genetic factors transforms through the inner curvature into a new form, process known as looping heart tube. Particularly, it has three fundamental elements in its structure: entry and exit points; and between above mentioned entry and exit points, the primitive atrial and ventricular cardiac cavities structures emerge. As a result, entry tract of the looping heart tube are sinus venosus (SV) and the sinoatrial ring (SAR) that continue with unique atrium. Additionally, an efferent looping pathway comes exclusively from SHT [15].

Gittenberger-de Groot et al. describe looping of the heart tube as the process characterized by "the differentiation of the primary heart tube into cardiac chambers (CC) and transitional zones (TZ)" [16]. Same team points up that many transitional zones are the components of the developing "septa, valves, conduction system, and fibrous heart skeleton" [16]. Moreover, these transitional zones will be in part included in the development of the final right atrium and left atrium, respectively in their right ventricle and left ventricle [16]. In addition, the team of Gittenberger-de Groot et al. showed that "from the venous to the arterial pole there are the sinus venosus and the sinoatrial ring (TZ), the primitive atrium (CC), the atrioventricular canal or ring (TZ), the primitive left ventricle (CC), the primary fold or ring (TZ), the primitive right ventricle (CC), and the ventricular OFT with a proximal and a distal part, also referred to as the ventriculoarterial ring (TZ)" (Fig. 1.4) [16].

The looping process of heart tube joins all above TZ together in the padding of the heart tube, specifically in the inner curvature [16].

Typically, from all TZ, the sinus venosus (SV) and primary fold do not generate endocardial cushions, while the AVC and OFT develop cushions. Importantly, the transition areas (TZ) of looped heart tube are the basic structures in the development of interatrial septum and interventricular septum, of the mitral valve, tricuspid valve, aortic and pulmonary valves, besides conduction tissue (see Fig 1.4) [16].

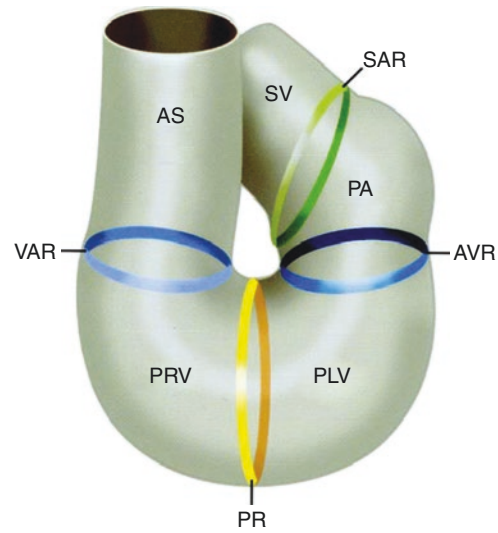

Fig 1.4 Schematic drawing of the looped heart tube with the cardiac chambers and the transitional zones. Following the blood flow from venous to arterial, we can distinguish the sinus venosus (SV), the sinoatrial ring (SAR), the primitive atrium (PA), the atrioventricular ring (AVR) encircling the atrioventricular canal, the primitive left ventricle (PLV), the primary fold or ring (PR), the primitive right ventricle (PRV), the outflow tract ending at the ventriculoarterial ring (VAR), and the aortic sac (AS) From Gittenberger-de Groot et al. [16] with permission.

1.5 Atrial and Ventricular Genesis

The genesis of atriums and ventricles cavities comprises the following stages: left from right ventricle separation, unique atrium, creation of the atrioventricular floor from the common atrioventricular channel, and the entry and exit separation from each ventricle (Fig. 1.5) [17].

Importantly, these processes are developing successively or concomitantly and are developed under genetic control. Precisely, Pitx2 gene determines left-right asymmetry, morphologic or structural differentiation among the right and left heart [18].

1.6 Atrial Septation

Separation of left atrium from right atrium is a progressive process starting with the "septum primum" or primary atrial septum that is covered by a mesenchymal cap and grows from the lowest part toward apex. Meanwhile, another dorsal mesenchymal protrusion advances parallel with septum primum in the common atrium and participate to the downward growing of primary atrial septum (Fig. 1.6) [1]. Before the primary atrial septum is getting to the endocardial cushion, a small hole named ostium primum persists. Moreover, in the cranial part appear fenestrations which become the ostium secundum by cell death mechanism [1].

Kloesel et al. state that around day 33, a second septum forms and further will develop the foramen ovale—a valve that lets the blood of the right atrium to pass on the left atrium during right-to-left shunting, also a feature of placental and systemic venous blood from gestation [1]. On the other hand, Kussman et al. show that during 35–38 days (CS15), the secondary foramen develops. Further, the primary atrial septum closes in CS16 [7]. The ostium primum is closed after joining of the primary atrial septum, mesenchimal cap, dorsal mesechimal protrusion along with the major atrioventricular cushions (Fig. 1.6) [1].

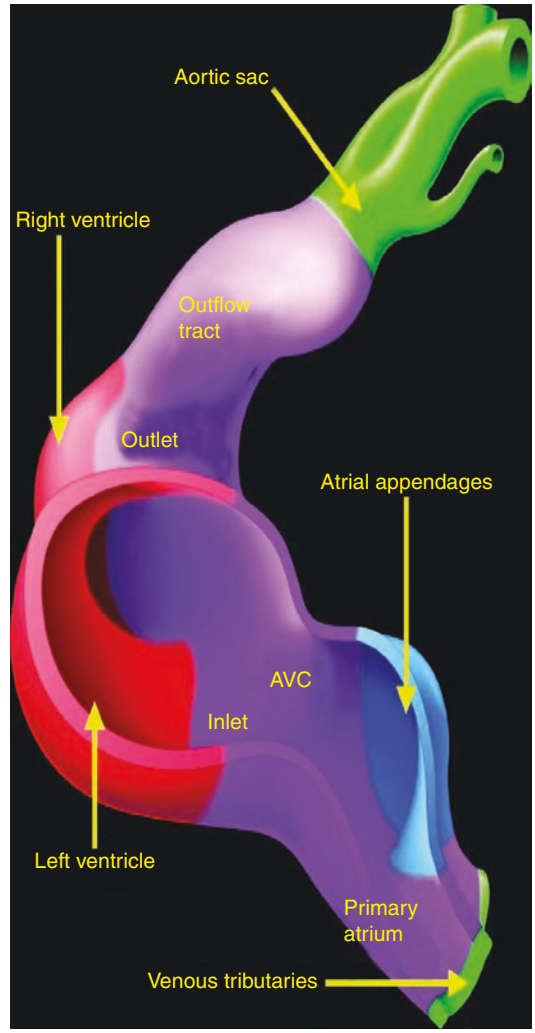

Fig. 1.5 This illustration shows the origin of the components of the developing atriums and ventricles. The myocardium of the primary heart tube is shown in purple, and makes up the primary atrium, the atrioventricular canal (AVC), the inlet and outlet components of the ventricular loop, and the outflow tract. Shown in green are the systemic venous tributaries, which are eventually incorporated within the right atrium, and the aortic sac with its arterial branches. The pulmonary vein is not shown, this being a new development appearing concomitant with the formation of the lungs. The atrial appendages, shown in blue, balloon in parallel from the primary atrial component of the heart tube. The apical parts of the ventricles, in contrast, balloon in series from the primary tube, with the apical part of the left ventricle growing from the inlet component, and the apical part of the right ventricle from the outlet component. From Moorman et al. [17] with permission.

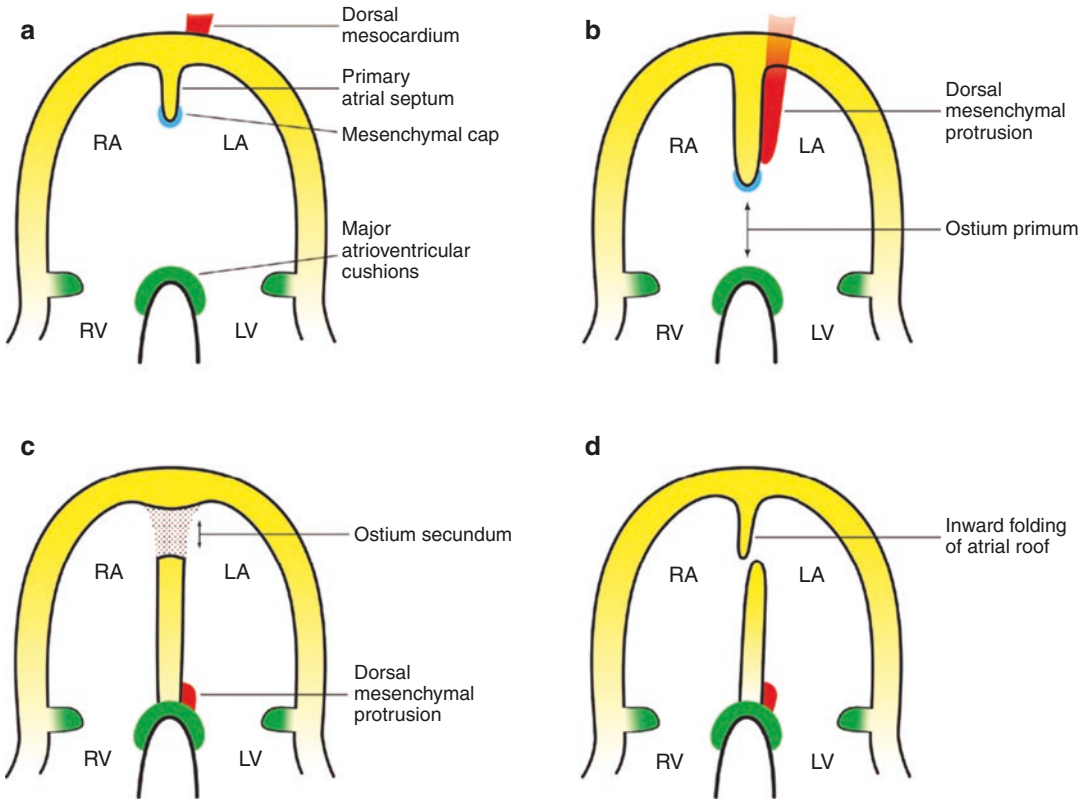

Fig. 1.6 Overview of processes leading to atrial septation. (**a**) Atrial septation begins with formation of the primary atrial septum (septum primum) that extends from the atrial roof downwards towards the major atrioventricular cushions. The leading edge of the primary atrial septum carries a mesenchymal cap. The venous pole of the heart is attached to dorsal mesocardium. (**b**) As the primary atrial septum continues its migration downwards and approaches the major atrioventricular cushions, it closes a gap known as ostium primum. Mesenchmal cells from the dorsal mesocardium have invaded the common atrium and join the downward growing primary atrial septum as the dorsal mesenchymal protrusion. (**c**) After fusion of the primary atrial septum, mesenchymal cap and dorsal mesenchymal protrusion with the major atrioventricular cushions, the ostium primum is closed. At the same time, part of the cranial septum primum breaks down and forms the ostium secundum. (**d**) Inward folding of the myocardium from the atrial roof produces the secondary atrial septum (septum secundum) which grows downwards to occlude the ostium primum by mechanism of a flap-valve (at birth, pulmonary vasculature dilates leading to a drop in right atrial pressure; the higher left atrial pressure pushes the primary atrial septum against the secondary atrial septum). From Kloesel et al. [1] with permission.

Finally, the secondary atrial septum (septum secundum) will occlude the ostium primum at birth (when pulmonary vasculature dilates causing decreasing in right atrial pressures) by mechanism of a flap-valve (Fig. 1.6) [1].

1.7 Ventricles Separation

Separation of the two ventricles starts from the looping heart stage when the univentricular cavity reshapes its primary structure as well as the future entry (inlet) and exit (outlet) paths align in the embryonic structure at the same level [19].

Importantly, the separation of primitive ventricle in the end to the left ventricle and the right ventricle is established by the interventricular septum that has distinctive muscular and mesenchymal constituents. Subsequently, the muscular structure comes up from the interventricular groove by myocardial development of the ventricular wall. Secondly, the mesenchymal constituent comes up above all by combination of the conotruncal endocardial cushions and

atrioventricular endocardial cushion. To same extent, Kloesel et al. concluded that "the complete ventricular septation depends on fusion of the outflow tract (conotruncal) septum, the muscular ventricular septum, and the atrioventricular cushions tissues" [1].

The basic helix-loop-helix (bHLH) transcription factors Hand1 and Hand2 have significant function keys in cardiogenesis [20]. Specifically, Hand1 (eHand, thing1, Hed) and Hand2 (dHand, thing2, Hxt) have important roles in heart development. Also, NKX2.5 and GATA4 genes are expressed in ventricular structures during cardiogenesis. The left ventricle develops under genetic control of Hand1 that is also implied in the formation of the interventricular septum and atrioventricular valve [2, 19]. Hand2 is compulsory for the right ventricle development [2, 19]. Especially, the presence and role of Hand2 in SHF have major contribution to the heart development, as well as the right heart ventricle [20]. Shortly, right ventricle occurs separately from SHF under genetic control of Hand2, and from this genetic control comes the idea that there is no primary direct relationship between the two ventricles during cardiogenesis [2, 19, 20, 54]. To sum up, FHF is exhibiting Hand1, NKX2.5, TBX5 and supports the development of the left ventricle. On the other hand, SHF is exhibiting Hand2, NKX2.5, GATA4, Isl1 and TBX1, and supports right ventricle development.

Franco et al. showed on two different transgenic mouse lines trying to investigate the development of the muscular interventricular septum that the *Mlc1v-nlacZ-24* transgene is exhibited only by the OFT and the right ventricle myocardium [21]. Also, the *Mlc3f-nlacZ-2* transgene is exhibited only by the left ventricle myocardium and the atrial appendages. These results support that the development of the interventricular septum is initiated by a symmetric cooperation of both ventricles constituents [21]. Subsequently, Moorman et al. support that the left–right asymmetry doesn't express the morphological differences between both ventricles [17].

Regarding the initiation and development of the septation process there are two hypotheses, one active from the apex to the atrioventricular layer [22] and a passive one produced by the ballooning of the single ventricular cavity [23]. Moreover, Anderson et al. support the hypothesis of ballooning and proves that between the ascending and descending side of the primary tube, originates the interventricular septum (see Fig. 1.7) [24].

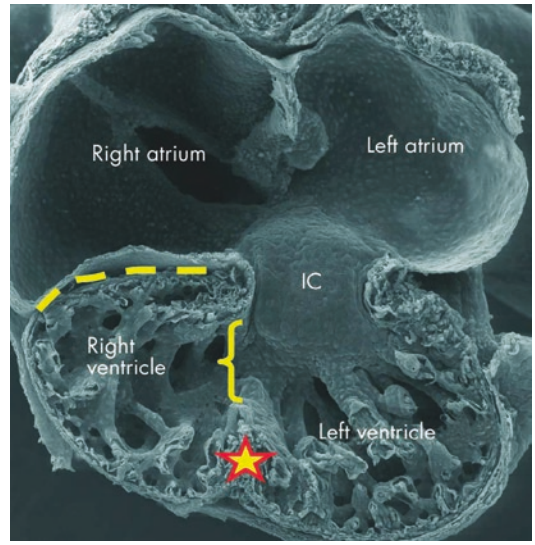

Fig. 1.7 This scanning electron micrograph, from a mouse embryo with 42 somites, shows the formation of the muscular ventricular septum. The specimen was prepared by transecting the heart through the atrioventricular canal, and the photograph is of the posterior segment. Note the inferior cushion (IC) occupying most of the posterior margin of the canal, but note also that the floor of the right atrium is in continuity with the roof of the developing right ventricle at the right margin of the atrioventricular canal, even though the atrioventricular groove interposes between the cavities of right atrium and right ventricle (yellow dashed line). Ballooning of the apical parts of the right and left ventricles from the ascending and descending parts of the ventricular component of the primary heart tube, respectively, has produced the primary muscular ventricular septum between them (star). The primary ventricular foramen (yellow bracket) provides the entrance at this stage to the developing right ventricle. From Anderson et al. [24] with permission.

1.8 Atrioventricular Junction Formation

The atrioventricular junction or atrioventricular canal (AVC) is an embryological structure that consists of the inferior component of the ventricular septum (inlet septum), the lowest area of

interatrial septum ("vestibular septum"), along with the primary structures of the mature atrioventricular valves [2]. To start with, the atrioventricular junction begins from the looping heart tube, particularly from the mesenchyme existent in endocardial cushions of the atrioventricular canal [2]. Initially, during the looping heart phase, the endocardial cushions of AVC join primitive atria with the embryonic left ventricle. Additionally, the embryonic right ventricle and the right part of the primitive atria have no interaction. Only that, during development of the right ventricle due to the migration of myocardial cells from the anterior SHF, the right AVC increases from the dorsal primary fold located among the right part of the AVC and the inner curvature of cardiac crescent [2].

Further, Gittenberger-de Groot et al. come up with their theory about AVC development (Fig. 1.8) [16]. Firstly, they sustain that "the primary heart tube after looping shows an atrioventricular canal, a primitive left ventricle, and a primitive right ventricle that are separated by the primary fold or ring" [16]. The primary interatrial septum (ostium primum) and membranous interventricular septum join in the atrioventricular canal by a progressive differential cellular multiplication process that is the initial stage of the atrioventricular junction. The atrioventricular endocardial cushion channel divides the upstream of atrioventricular junction into the right and left sides. The separation is initiated through a band (primary ring) (PR) (Fig. 1.8a) [16] and it is continued by its expansion to the muscular interventricular septum, thus achieving the initial separation of the atrioventricular canal into the two orifices that will be the future mitral and tricuspid valves (Fig. 1.8b) [16]. Concurrently with the valvular atrioventricular delimitation, a separation band is formed by modifying the primary ring, being a splitting band that begins the formation of the right ventricle (Fig. 1.8c) [16]. The ventriculo-arterial ring forms the separation between the unique ventricle, where the interventricular septum is initiated and the common arterial trunk which is separated by a band (ring) structurally similar with the atrioventricular canal to the initial aorta and the trunk of the pulmonary artery. This also delimits the spaces where the atrioventricular valves and semilunar valves will form (Fig. 1.8d) [16].

Wessel et al. studied fifteen human embryos and fetuses (at least two with same stage) starting with Carnegie Stage 14 forward [25]. They didn't solve the problem of atrioventricular junction genesis, but they stated two possible hypotheses as the mechanism of the atrioventricular junction genesis (Fig. 1.9) [25]. The first hypothesis assumes that the atrioventricular sulcus is the only structure responsible for the development of the fibrous annulus and the atrioventricular valves [26]. In addition, the second hypothesis considers that merging of sulcus tissue and cushion tissue of the ventricular side of the atrioventricular junctional myocardium triggers the division of atrial myocardium from ventricular myocardium (Fig. 1.9) [25].

Lockhart et al. studied the participation of epicardially-derived cells (EPDCs) and endocardially-derived mesenchymal cells (ENDCs) to the atrioventricular junction genesis [27]. According to them, the development of the AV sulcus and the annulus fibrosus is followed by the stage when a subtype of AV-EPDCs move in the components of AV cushions. In particular, the EPDCs populate only components of the lateral AV cushions [27]. On the other hand, the movement of AV-EPDCs to the AV junction and the annulus fibrosus development it is followed by subsequent movement of the AV-EPDCs to the parietal leaflets of atrioventricular valves. Therefore, AV-EPDCs have a significant function in the annulus fibrosus development and they combine with the existent AV-ENDCs being an important factor in the growth of the parietal leaflets of atrioventricular valves (Fig. 1.10) [27].

1.9 Atrioventricular Valves

The initiation of the atrioventricular valves genesis originates in endocardial tissue of AV cushions [28]. The cell population at this level is made up of AV-ENDCs with asymmetric and sequential multiplication forming two first subdivisions, the first one located upper and lower, and the

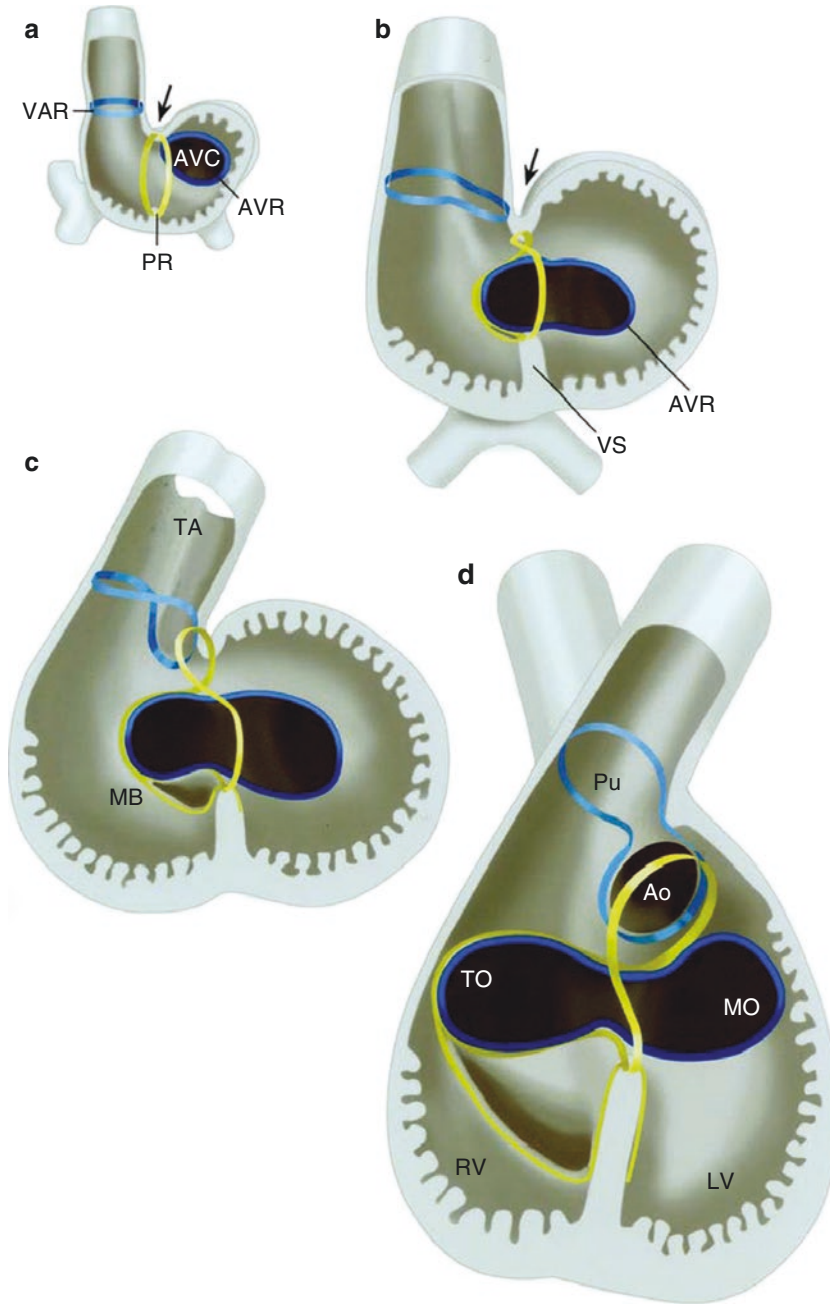

Fig. 1.8 Schematic representation of the remodeling of the cardiac chambers and the transitional zones at the ventricular level. (**a**) internal view of the looped heart tube. The transitional zones are, going from the venous to the arterial pole, the atrioventricular ring (AVR, dark blue), the primary ring (PR, yellow), and, at the distal end of the myocardial outflow tract, the ventriculoarterial ring (VAR, bright blue). (**b**) During looping, with tightening of the inner curvature (arrow), the right part of the AVR moves to the right of the ventricular septum (VS). (**c**) Start of formation of the inflow tract of the right ventricle by excavation of the PR. The lower border is formed by the moderator band (MB). (**d**) Completion of the process with formation of a tricuspid orifice (TO) above the right ventricle (RV) and the aortic orifice (Ao) and the mitral orifice (MO) above the left ventricle (LV). It is easily appreciated that there is aortic-mitral continuity, whereas the distance between the TO and the pulmonary orifice (Pu) is marked. From Gittenberger-de Groot et al. [16] with permission

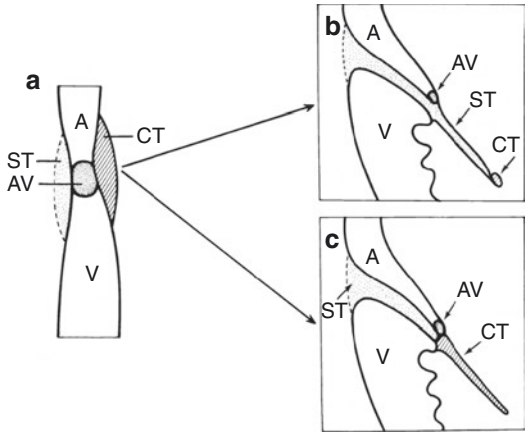

Fig. 1.9 Schematic diagram shows the two current hypotheses for the development of the atrioventricular junction in the human heart. (**a**) The situation at the atrioventricular junction at ~4 to 5 weeks of development. Myocardial continuity between atrium and ventricle is achieved through the myocardium of the atrioventricular canal. The atrioventricular junction is sandwiched between the tissues of the atrioventricular sulcus at the epicardial side and the atrioventricular cushion at the endocardial side. (**b**) The hypothesis in which the atrioventricular sulcus is held responsible for the insulation of atrium and ventricle and is supposed to be the only tissue contributing to the formation of the fibrous annulus and the leaflets of the atrioventricular valves (modified from information presented in Reference [26]). The presumed remnants of the atrioventricular cushions are located on the apical aspects of the leaflets. (**c**) The hypothesis supported by the data presented in this paper. The separation between the atrial and ventricular myocardium in this hypothesis is established by fusion of sulcus tissue and cushion tissue at the ventricular aspect of the atrioventricular junctional myocardium. (Note: The contribution of the myocardium to the formation of the leaflets is not illustrated in this schematic.) *A* indicates atrium, *CT* cushion tissue, *ST* sulcus tissue, *AV* myocardium of the atrioventricular canal, *V* ventricle. From Wessels et al. [25] with permission.

second one on the right and left side wall of AV cushion (Fig. 1.11) [29].

These two components progressively fuse accomplishing AV mesenchymal complex [30]. Process by which they will subsequently cause the primary atrial foramen enclosure (CS16) and accurate atrioventricular separation [7, 30].

Markwald et al. demonstrated how epicardial-derived cells (EPDCs) participate to genesis of the atrioventricular valves by their migration into AV cushion under the control of isoform 4 of morphogenetic bone protein (Bmp4) and TBx2 [28]. The formation of fibrous annulus is initiated by a subset of EPDCs migrated into the atrioventricular valves explaining the presence of these cells in the valvular cusps [29]. Remodeling of the cusps is done by the delamination process. Explicitly, it is separating the muscle tissue from the AV cushion from the mesenchymal tissue of the valvular leaflets that subsequently transform into fibrous tissue and collagen, mediated by fibroblast growth factors (FGF), PTPN11 (PTPN11 encodes the non-membranous protein tyrosine phosphatase), Wnt signaling and periostin [2].

Same mechanism, it is also involved in ENDCs, but the relationship between these cellular groups is not known [27]. Further, Lockhart et al. [29] suggest existence of evidence that derived cells AV-EPDCs may possible transform in various cell types such as interstitial fibroblasts, coronary smooth muscle cells, coronary endothelium, and myocytes [29].

However, there are few AV-EPDCs to the end of the valvulogenesis in the structure of the leaflet fibroblasts, this process being explained by their abundance in the atrioventricular annulus. Decreasing of the AV-EPDCs migration in the valvular tissue is controlled also by the isoform 2 of bone morphogenetic protein (Bmp2). Lockhart et al. showed in one study on mice that blocking the *Bmp receptor Alk3* from epicardial cells and their derivatives, results in reduction of AV sulcus, decrease of EPDCs migration to parietal atrioventricular valve cusps, and the absence of the annulus fibrosus development [29]. Also, this study proves the importance of Bmp signaling in AV valvulogenesis [29].

1.10 Atrioventricular Valvulogenesis

The mesenchyme of the endocardial cushions is common for all four heart valves [2]. Markwald et al. describe four steps in atrioventricular and semilunar valvulogenesis: (1) endocardial-to-mesenchyme conversion in junctional myocardium, (2) development of the mesenchyme as endocardial cushions, (3) remodeling process of

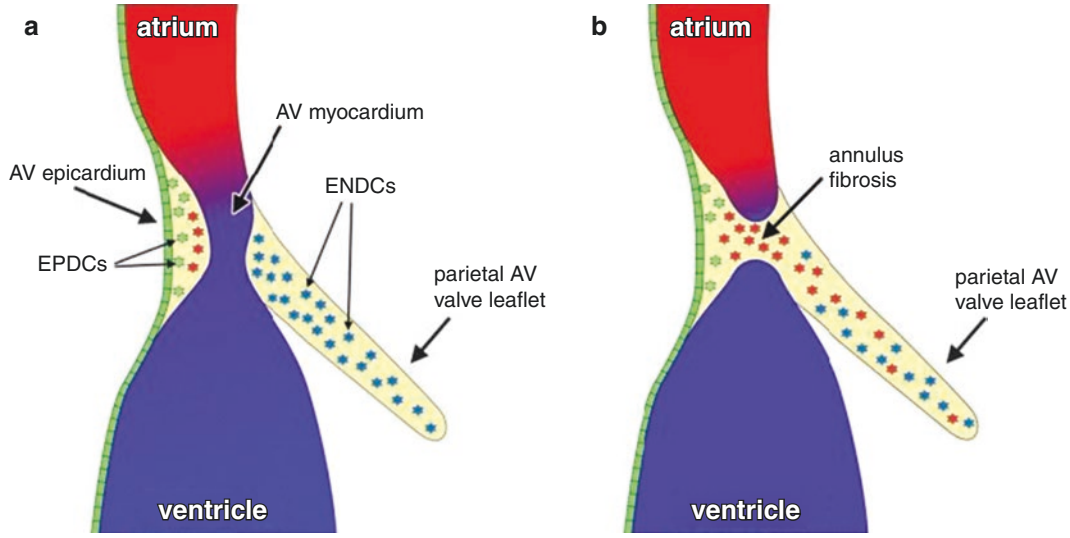

Fig. 1.10 Schematic representation of the contribution of the AV epicardium and the epicardially-derived cells to the development of the AV junction. After formation of the epicardial epithelium (green), epiEMT generates a population of AV-EPDCs (green cells in panel **a**) that, as far as their gene expression profile is concerned, are still very similar to the epicardium itself. However, when the AV-EPDCs migrate further into the AV sulcus and approach the AV myocardium (red cells), the molecular profile of the AV-EPDCs changes drastically as the expression of genes characteristically found in the mesenchyme of the annulus fibrosus (e.g., MMP2) and the AV cushions (e.g., Sox9) is upregulated. These "differentiated" AV-EPDCs (red cells in panel **a**) then penetrate the AV myocardium to form the annulus fibrosus (panel **b**) and migrate into the parietal AV valve leaflets where they intermingle with the endocardially-derived mesenchymal cells (ENDCs; blue cells in panels **a** and **b**). From Lockhart et al. [27]. It is an open access article.

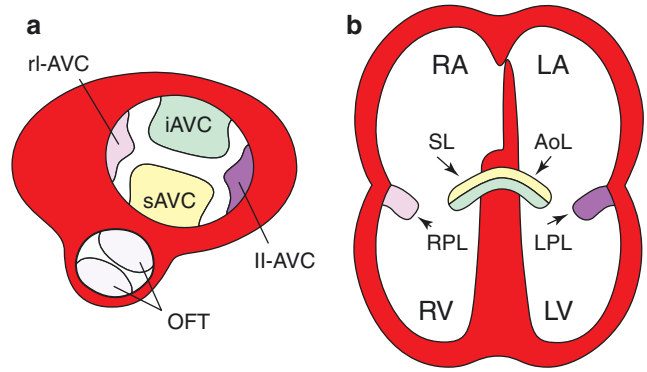

Fig. 1.11 This cartoon shows the fate of the individual AV cushions. The superior and inferior AV cushion (sAVC and iAVC) fuse at the midline and give rise to the septal leaflet of the right AV valve (SL) and the aortic leaflet (AoL) of the left AV valve. The right lateral AV cushion (rlAVC) forms the right parietal leaflet of the right AV valve (RPL), whereas the left lateral AV cushion forms the left parietal leaflet of the left AV valve (LPL). From Lockhart et al. [29] with permission.

mesenchyme into collagen-secreting interstitial valve fibroblasts, and (4) remodeling to the mature valve tissue by "leaflet compaction, attenuation, and formation of fibrous continuities" [31]. Furthermore, both atrioventricular valves have differences looking anatomical configuration and histology. It has to be underlined, that the mitral valve has insertion of the papillary muscles only in the free lateral wall of the left ventricle, and the septal tricuspid valve leaflet attaches directly to interventricular septum.

1.10.1 Mitral Valve

The mitral valve is composed from endocardium and connective tissue. Even if, the anterior and posterior mitral leaflets have same source from

the endocardial cushion of the AVC, their generation and forming are completely other [2].

Both mitral valve leaflets originate in the endocardial cell layer of the AV channel and their subsequent development is linked with septalisation process and aortic valve rotation [2]. Initially, the anterior mitral valve leaflet has only mesenchymal origin with no muscle component, and its papillary muscles are formed just from the free lateral wall of the left ventricle, explaining why the mature mitral valve does not have septal insertion [2, 32]. Also, de Lange et al. state that during formation of the aortic mitral valve leaflet this is connected to myocardium only at its cranial and caudal edges, therefore tendinous cords are forming and attaching to the papillary muscles at these sites [33]. However, there are no tendinous cordal connections of the mitral valve with the interventricular septum.

1.10.2 Tricuspid Valve

Initially, the tricuspid valve is a muscle structure with three developing points from the walls of right ventricle: septal (ventricular septum), anterior (anterior part of the right of the inferior AV cushion) and inferior (inferior right ventricle) [2]. The mesenchymal tissue of the endocardial AV cushions overlay inside all above three myocardial walls [2]. The anterior leaflet of tricuspid valve starts from anterior muscle wall of right ventricle, and this leaflet becomes functional by the process of myocardium apoptosis ("demyocardialization") [2]. Also, septal leaflet and posterior leaflet delaminate from myocardial walls of right ventricle [2]. On the other hand, the anterior leaflet keeps its connection with normal junctional part from the AV junction [2]. The papillary muscles start from the right ventricle walls and by compaction they develop in correlation with the cords of the tricuspid valve leaflets [33]. Finally, tendinous cords have their origin from the mesenchymal tissue of tricuspide valve, and they develop by the process of the remote component fragmentation of the ventricular side of the leaflets being transformed into fibrous structures [2].

1.11 Cardiac Outflow Formation

It also known as "conotruncus", "conus" and "infundibulum" [34]. The primitive OFT of the human heart is an endothelium-lined tube covered by an extracellular matrix layer named "endocardial jelly" that further it is coated by an outer muscular cuff [35].

The cells included within initial structure of OFT originate from anterior heart field (anterior component of the SHF) and cardiac neural crest (CNC) [2]. Therefore, CNC cells may be implied in the development of the smooth muscle cells from the walls of the two great vessels [2]. It seems that the remodelling of OFT into pulmonary and aortic arteries implies the cooperation of different cell types including neural crest cells, myocardium, and endocardium [36]. For instance, the cardiac neural crest signaling to SHF add together cardiomyocytes and smooth muscle cells in development of the OFT [34]. In humans, the OFT rotation has been accepted from Carnegie stage 15 [36]. Also, the myocardial wall rotation of the OFT is part of remodelling process of the OFT, directly correlated with the influx of neural crest [36].

Buckingham et al. believe that conotruncus—forming cells are derived from SHF only by excluding CNC participation in the distal portion of large vessels (truncus), theory unconfirmed by other studies [15]. In the initial stage (day 21), the OFT is found in the linear heart tube in the emerging portion of the single ventricle chamber, followed by the looping stage (day 28) when the differentiation begins in the conotruncus followed by the aortic sac (Fig. 1.12) [12, 37, 38]. As well, CNC cells do signaling process that form the OFT, the aortic arch, ventricular and atrial septae [12]. The ventricular myocardial structure is united with the vascular trunk by a fibrotic cell source called annulus, generated by endothelial derived mesenchyme (Fig. 1.12) [12, 37, 38].

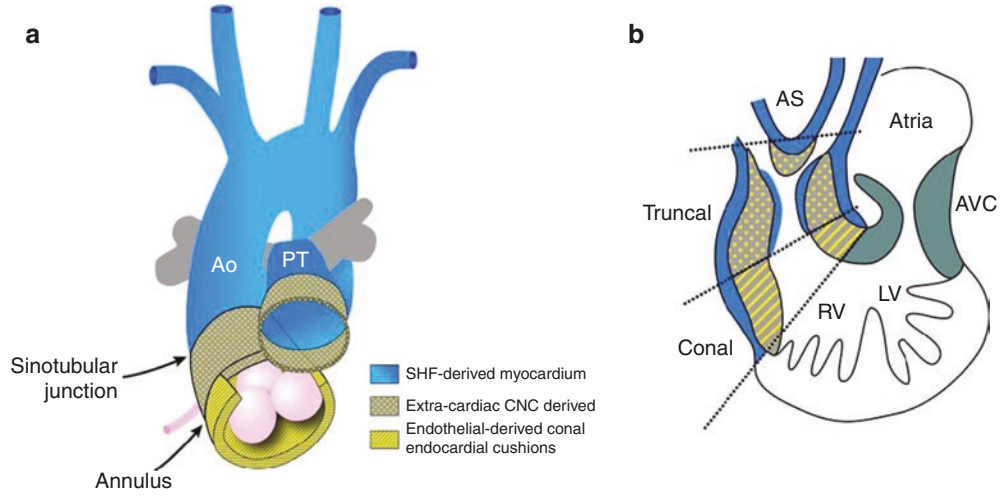

Fig. 1.12 Genesis and cellular contributions to the outflow tract. Schematic shows the locations of outflow tract (OFT) colonization by the extra-cardiac cardiac neural crest (blue), vascular smooth muscle derived from the second heart field (dotted yellow) and the location of myocardium from derived from the second heart field (striped yellow). The aortic annulus or hinge region is formed where myocardial cells meet the vascular smooth muscle cells of the media of the aorta and pulmonary trunk and endothelial derived mesenchyme is the source of the fibroblastic annular tissue. The media of the aorta and pulmonary trunk is derived from secondary heart field proximally (dotted yellow) and the cardiac neural crest distally (blue). The interface between these populations is at the sinotubular junction. Abbreviations: *Ao* aorta, *AS* aortic sac, *AVC* aorto-ventricular cushions, *LV* left ventricle, *PT* pulmonary trunk, *RV* right ventricle. Modified from [37, 38]. From Martin et al. [12]. It is an open access article

1.12 Outflow Separation

OFT septation begins between 23 and 25 days of human embryogenesis. Presently, the separation process mechanisms of OFT are still unclear, therefore there are many hypotheses. As well, there is still confusion looking plentiful terms used to explain "the endocardial ridges" or "cushions", structures implied in the septation of the OFT.

The hypothesis of Van Mierop et al. consider that three components split OFT, that is the aortopulmonary septum with distal and proximal ridges. Firstly, the ridges join and develop a septum that further joins with the aortopulmonary septum. Further, septation joins the proximal ridges developing the proximal conal septum that unifies with the distal septum finishing septation process [39].

The hypothesis of Icardo sustains the spiral septum development. He declares the existence of unconnected proximal and distal ridges. Spiralling is acquired by end-to-end joining of paired proximal ridges with the paired distal ridges, resulting in connected ridges unified lengthways, and intersected at their midpoints [40].

In same time, Bartelings on a human hearts study supposes that the endocardial ridges have no involvement in the OFT septation process [41].

Finally, Webb et al. consider that "it is the distal cushions that divide the distal outflow tract into the intrapericardial parts of the aorta and pulmonary trunk, with the proximal cushions separating both the arterial roots and their ventricular outflow tracts" [42].

Importantly, there is a counterclockwise direction in the rotation process of the junction of the OFT and great arteries align the aorta to the left ventricle and pulmonary artery to the right ventricle [38].

1.13 Aortic and Pulmonary Valves Formation

With development of OFT, its cushion tissue extend in the jelly and generates a spiral pattern around the lumen [35]. Further, the cushions of OFT join in the midline and separate the OFT into its aortic and pulmonary channels [35]. Shortly, the aorta and the pulmonary artery are developing from aortic sac [2]. Semilunar valves genesis begins on days 31–35 starting with the pre-existing endocardial cushions of the OFT and the atrioventricular junction of the primitive heart tube [43].

During the OFT septation process, in the proximal region an invasion of endothelial cells is produced in the contruncal region and fuse with endocardial cushions. This configuration is divided in two sides that contain inferior and posterior septal cushion and two sides of insertion of anterior pulmonary valve and aortic posterior valve. Therefore, from the right posterior side of interposed cushion forms the noncoronary aortic cusp and from the anterior left side forms the anterior pulmonary cusp. From the superior and inferior septal cushion form left and right cusps of the aortic and pulmonary valves (Fig. 1.13) [12].

Recently, based on serial and three-dimensional reconstructions of human embryos in the Shaner Collection at different stages, Milos et al. observed that "the pulmonary semilunar valve regions are more normal and uniform in structure supporting the concept that there is some independence of the development of the aortic and pulmonary semilunar valves from each other" [35].

1.14 Ventriculoarterial Junctions

Anatomic ventriculoarterial junctions represents the connection between a muscular component (infundibular) formed by the interventricular septum separation mechanisms, and the pulmonary

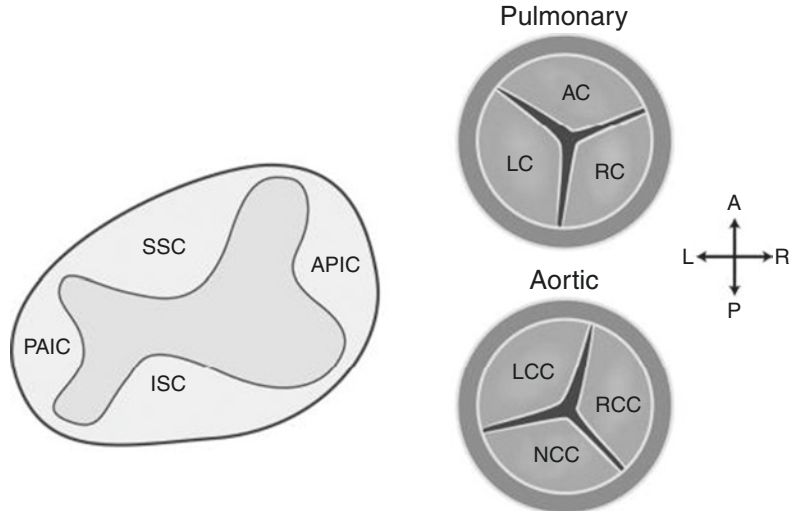

Fig. 1.13 Development of the leaflets of the aortic and pulmonary valves. The semilunar valves arise from the conotruncal and intercalated cushions of the outflow tract. The conotruncal (superior and inferior septal) cushions give rise to the right and left leaflets of each of the semilunar valves. In the aorta, these are the right and left coronary leaflets, while in the pulmonary valve, these are the right and left cusps. The right-posterior and the left-anterior intercalated cushions develop respectively into the posterior aortic (non-coronary cusp of the aortic valve) and the anterior pulmonic (anterior cusp of the pulmonic valve) leaflets. Abbreviations: *AL* anterior leaflet, *APIC* anterior pulmonary intercalated cushion, *CA* coronary artery, *ISC* inferior septal cushion, *LL* left leaflet, *LCL* left coronary leaflet, *NCL* non-coronary leaflet, *PAIC* posterior aortic intercalated cushion, *RCL* right coronary leaflet, *RL* right leaflet. From Martin et al. [12]. It is an open access article.

and aortic valves generated in proximal portion of the arterial trunk. When OFT septation process undergoes, the aortic orifice attaches to the left ventricular outflow tract, meanwhile the pulmonary orifice lies over the right ventricle [16]. Moreover, the team of Gittenberger-de Groot et al. showed by reconstruction the OFT of two human embryos that the condensed mesenchyme is located corresponding to the mesenchymal vessel wall, the arterial orifice level, the cushion tissue and the myocardium (Fig. 1.14) [16].

1.15 The Cardiac Vascular Genesis

1.15.1 Coronary Arteries

There is still a lot of uncertainty about the genesis of the coronary arteries. However, it is clear that the coronary artery connection is the last stage of cardiogenesis being done after the separation of the cardiac cavities, and the inlet and outlet pathways from atria and ventricles. Ventricular endocardial cells represent the main origin of the coronary arter-

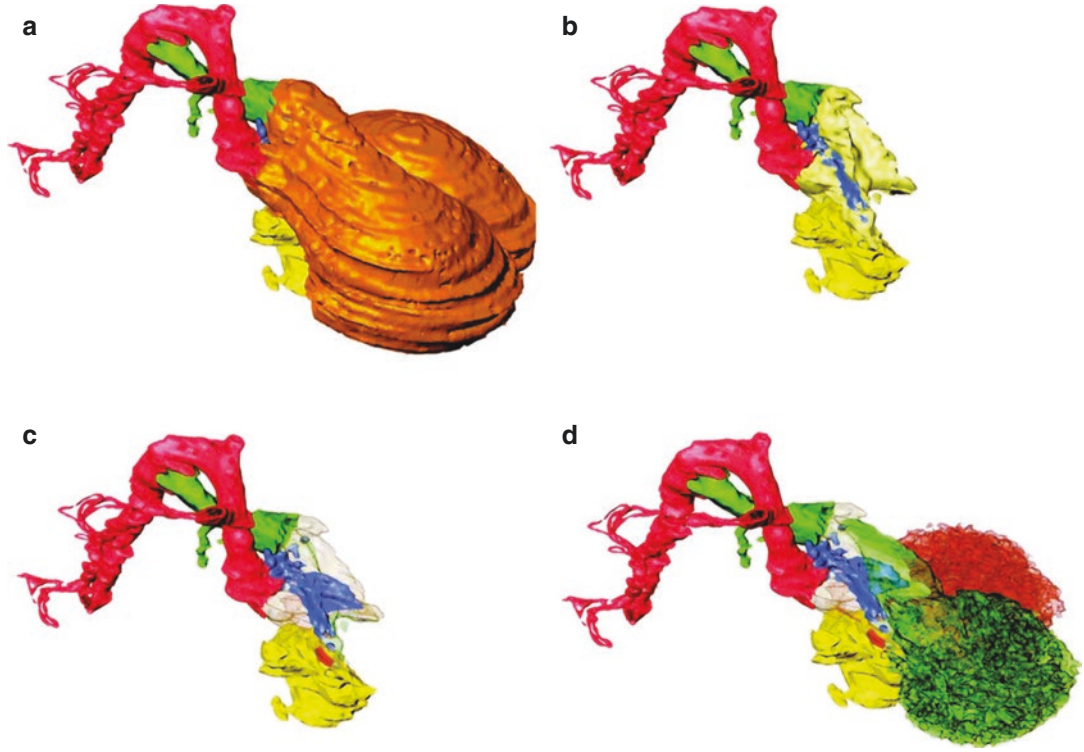

Fig. 1.14 Reconstruction of the heart of a *human embryo* of 5 week development. (**a**) The myocardium (brown) of the ventricles reaches up to the arterial orifice level. The pulmonary trunk (green) arises anteriorly from the right ventricle and the aorta (red) originates at a more caudal and posterior level. (**b**) The myocardium has been removed and the endocardial outflow tract cushions (light yellow) and the atrioventricular cushions (dark yellow) become visible. The condensed mesenchyme (blue), consisting mainly of neural crest cells, is incorporated within the outflow tract cushion mass. It is visible, however, at the entrance site between the arterial orifices (see also a) and as a lateral streak (right side visible, left side not) where the condensed mesenchyme connects to the outflow tract myocardium (removed, see a) At these sites, the myocardialization of the outflow tract septum will take place. The right lateral outflow tract cushion is connected to the atrioventricular cushion mass, whereas the left lateral cushion is not connected to this mass. (**c**) By making the outflow tract cushions translucent, the complete condensed mesenchyme becomes visible extending way out into the cardiac outflow tract. (**d**) Insertion of the right (green) and left (red) ventricular lumen shows how the condensed mesenchyme and thus the outflow tract septum mainly borders the right ventricular pulmonary infundibulum. From Gittenberger-de Groot et al. [16] with permission.

ies and by angiogenesis produce coronary arteries [44]. It seems that myocardial Vegf-a to endocardial Vegfr-2 signaling controls coronary angiogenesis. On contrary, the coronary arteries and veins come up mostly by various origins and mechanisms [44].

Some studies prove that the origin of coronary arteries is in epicardial cells [45]. In fact, Reese et al. state further that "cell lineage commitment and diversification, directed cell migration, control of epithelial/mesenchymal transition, and cell differentiation are some of the hallmarks in the development of coronary arteries" [45].

Also, Red Horse et al. studied based on anatomical and histological analysis the coronary vessel development during mouse embryogenesis using endothelial markers [46]. They concluded that developed and differentiated venous endothelial cells from sinus venosus emerge into myocardium where transform into arteries and capillaries [46]. Therefore, these differentiated venous endothelial cells from sinus venosus extend to develop the coronary plexus, and coronary arteries, capillaries, and veins. Only minor number of the endocardium cells detach to develop blood islands and then join to the coronary plexus nearby the interventricular septum [44, 46].

As a result coronary vessels are generated by complex processes such as: vasculogenesis, angiogenesis, arteriogenesis and remodelling specific to each arterial, venous or capillary vessel [47]. The origin of angiogenesis can be initiated including by proepicardium, sinus venous or endocardium [48]. Of note, Tian et al. consider that complete heart vasculogenesis include all cardiac structures from the epicardium to endocardium, which begins by migration of the subepicardial ECs into myocardial cells of the embryonic ventricle free walls, and finalized with coronary veins and intramyocardial coronary arteries/capillaries (Fig. 1.15) [48].

To sum up, Kloesel et al. synthesize coronarogenesis in the most simplified way [1]. Newly, his team sustains that "the coronary vasculature is derived from proepicardial progenitor cells and venous endothelial angioblasts originating from the sinus venosus". The epithelial progenitors undergo epithelial-to-mesenchymal transformation. After formation of the main coronary vessels, the coronary system connects to aorta by invasion of arterial endothelial cells into the aorta. By day 50, the heart has developed to its mature form [1].

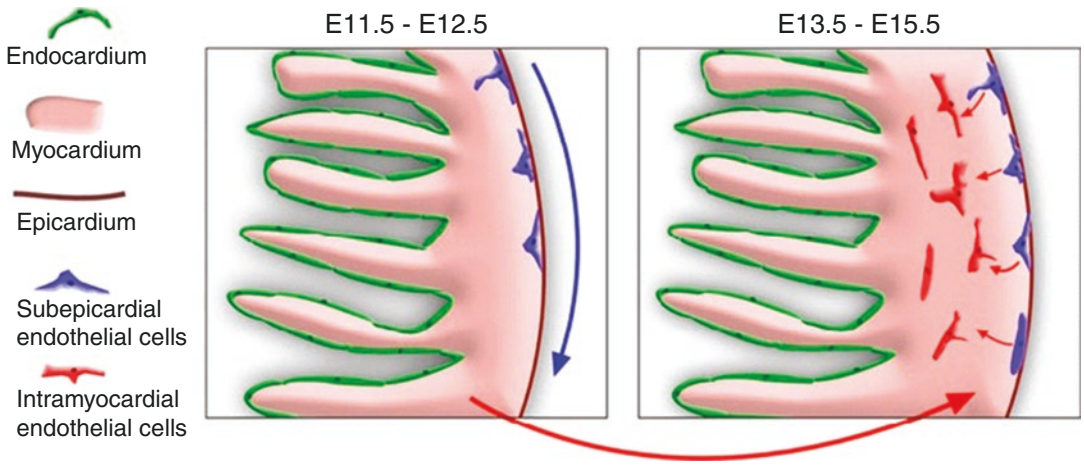

Fig. 1.15 Schematic showing subepicardial ECs as a major source for intramyocardial coronary vessels. During embryogenesis, subepicardial endothelial cells ECs (blue) located beneath the epicardium (brown) migrate along the surface of the heart between E11.5-E12.5 (blue arrow). Subepicardial ECs then migrate into the compact myocardium to become intramyocardial coronary arteries and capillaries at E13.0-E15.5 (red arrows). From Tian et al. [48] with permission.

1.15.2 Aortic Arches

The origin of the aortic arches is the mesoderm of the pharyngeal arches [2]. Further, they join with distal part of aortic sac. Firstly, a part of aortic branches, especially the third, fourth and sixth remodels in the presence of CNC cells to asymmetric great arteries. The third aortic arch developes into the common carotid arteries and the proximal segment of the internal carotid arteries. Further, the fourth aortic arch develops the horizontal aorta. Usually, the fifth aortic arch is not constant. However, the sixth arch develops the arterial duct and first component of the central pulmonary arteries [2].

1.15.3 Sinus Venous

The dorsal mesocardium joins the primitive atria to the dorsal body wall, where the sinus venosus and its contributory veins are blocked [16]. When heart tube is looping, the main veins supplying the sinus venosus (the right anterior and posterior cardinal veins as well as the left anterior cardinal vein) will incorporate into the posterior wall of the right atrium [16]. Also, during this process, a right and a left sinus venosus valve develop, in which blood access into the atrium through a type of channel [16]. Moreover, the left and right venous valves join and develop the septum spurium that is connected with anterior part of the AVC [16].

1.16 Cardiac Conduction System

As cardiogenesis advances with heart remodelling into a four-chambered structure, the myocardium undergo a transformation as "working myocardium" and "conduction system myocardium" [16]. Gittenberger-de Groot et al. [16] stated that the integration of the sinus venosus into the atrium demonstrates existence of the embryonic structures represented by three internodal pathways among the sinoatrial node, the atrioventricular node and the relationship of the pulmonary venous system from the dorsal left atrial wall with the primitive conduction system [16].

In fact, the heart is working with the onset of its development [1]. The primitive heart tube starts to beat about day 21 with pumping blood by day 24 or 25 [1], and the sinoatrial node (the pacemaker of the heart) develops and becomes noticeable in CS17 [7]. In mammalian embryonic ventricles, the contraction signal begins in the inflow part of the heart tube and spread to the ventricles and then to the OFT from base-to-apex [1]. It seems that advanced vertebrates form a "compact myocardium" need to respond to higher heart rhythm and pressure. Of note, this compact myocardium favours developing of the conduction system, with a specific activation from base-to-apex in the trabecular part of the ventricles, and with a specific activation in the subepicardial compact myocardium from apex-to-base, correlated to the His-Purkinje system formation [49].

Wenink et al. studied eight human embryos and the heart of a 90 mm human fetus selected from the collection of the Leiden University and released the "four ring theory" in which tries to explain the developing of cardiac conduction system [50]:

- The conducting rings are inserted between sinus venosus, atrium, ventricle, bulbus and truncus;
- The sinoatrial node develop only from the sinoatrial ring;
- The sinoatrial ring participates to the atrioventricular (AV) node formation;
- Atrioventricular ring develops AV node;
- Ventriculoventricular (primary ring) will be in time bundle His and bundle branches [50]. Although initially controversial, this hypothesis is partially confirmed by studies with immunohistochemical markers [51].

Importantly, the mammalian ventricular conduction system is characterized by biphasic growth and development, but lineage restriction is followed by restricted outgrowth [52].

The spongy myocardium of embryonic mammals allows high ejection fractions and also assists to conduct the ventricular depolarization [53]. Nonetheless, increase of pressure and heart rate cause an evolution to compact myocardium, that further, turn into the early trabecules secondary to force generation, but available to differentiate into fibres of poor contractility and high propagation speeds. In addition, mammals increase compact myocardium ventricular septum while the early trabecules form the septal surfaces with the findings of bundle branches of the His bundle (Fig. 1.16) [53].

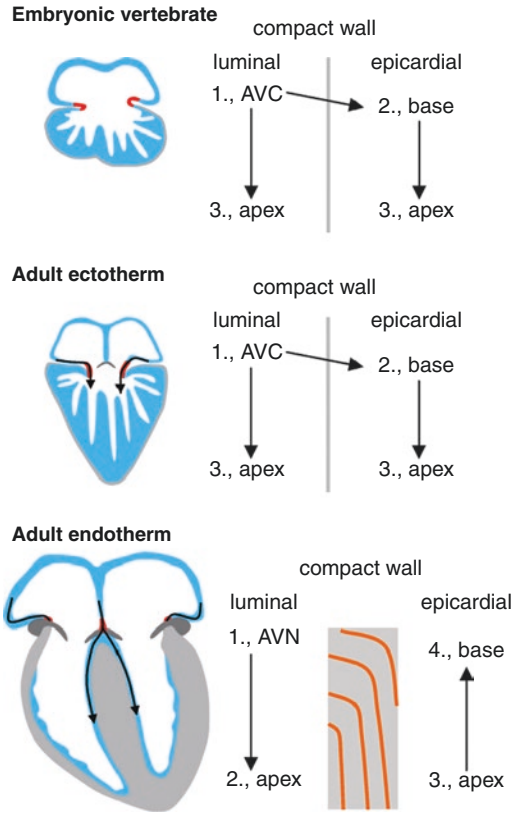

Fig. 1.16 The trabecular myocardium is activated from base to apex in all vertebrates. (**a**–**c**) The trabecular myocardium gives rise to the His-Purkinje system in mammals and birds and remains activated from base to apex. (**c**) On the epicardial surface of septated and thick-walled ventricles, as in the formed hearts of mammals and birds, activation is seen to occur from apex to base and the luminal base-to-apex activation is obscured [53]. It is an open access article.

Conclusions

It is considered that intrauterine life begins with cardiac contraction and heart development is a complex process. Mechanisms of cardiogenesis are sequential, starting from the primary cell differentiation stages to the final processes of cardiogenesis.

Increase in knowledge of genetics, embryology, and molecular medicine offer understanding into the mechanisms of congenital heart disease [1]. For physicians, clear knowledge of cardiac development, including, embryology, genetics, molecular cell biology, and anatomy, provide a better diagnosis of congenital heart diseases [1]. In last years, recent results in cardiac development have proven to improve our knowledge in prenatal diagnosis. Nonetheless, more data are compulsory looking the cardiogenesis in human embryo for an early and accurate diagnosis of congenital heart diseases.

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Right Heart Anatomy: A Short Uptodate

2

Mircea Ifrim, Ecaterina Bontaş, Daniel Cochior, and Ion C. Ţintoiu

Abstract

Despite of the first description of Sir William Harvey in 1616 looking the significance of right ventricle function for human heart and lungs, its importance was disregarded in clinical practice. Starting with 1950s until the 1970s, cardiovascular surgeons assessed techniques to treat right-heart hypoplasia and as a result they accepted the significance of right heart function. During last decade, the impact of right heart evaluation has been established for the treatment of cardiopulmonary disorders. Knowledge of the right heart anatomy, imaging pathology and related clinical manifestations is essential to prevent neglected features of cardiovascular diseases and false-positive diagnoses. Understanding image features of the human heart acquired by histological studies, echocardiography, computed tomography (CT), micro-CT studies, or diffusion tensor magnetic resonance imaging (DT-MRI) has a very important role in the correctness of anatomically outlining of the cardiac features, especially those associated to the conduction system. Studying classic anatomy of the heart on cadaveric samplings is a requirement to know what imaging investigations brings for the study of RV anatomy and physiology. Considering that, it has to be underlined important anatomical features of the human right heart.

Keywords

Right heart anatomy · Right atrium · Right ventricle · Interatrial septum · Interventricular septum · Conduction system · Right heart vessels · Myoarchitecture of right heart Computational cardiac modelling and anatomy

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2.1 Background

It has to be underlined that Sir William Harvey was the first who depicted in 1616 the significance of right ventricular (RV) function in his seminal treatise, De Motu Cordis: "Thus the right ventri-

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