Right Ventricular Physiology, Adaptation and Failure in Congenital and Acquired Heart Disease

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Preface

The inspiration for 'Right Ventricular Physiology, Adaptation and Failure in Congenital and Acquired Heart Disease' stemmed from the 3rd International RV Symposium held in Toronto. Many of its authors were invited speakers in that symposium, and all are leaders in their areas of expertise.

Paediatric cardiologists and cardiovascular surgeons have been well aware of the importance of the right ventricle (RV) for many years, yet the RV is still sometimes characterised as the 'forgotten ventricle'. However, it is evident from the explosion of research in the past decade or two that the RV is 'coming of age' and its importance increasingly recognised. Indeed, there have been substantial advances in basic research, diagnosis and management of a diverse array of conditions that affect the RV, and although our understanding of the RV is far from complete, it is considerably more comprehensive than just a few years ago.

Despite these advances in knowledge, to date, there has not been a written framework that provides a comprehensive review of RV embryology, physiology, function, failure and disease. This text aims to fill that gap, with state-of-the-art contributions from thought leaders in the field. The book incorporates a wide variety of topics including chapters that relate to early development, molecular adaptation to stress, interactions between the right and left ventricles, imaging, RV failure, neonatal conditions, congenital heart disease, interventional management and surgery. We hope these will be of interest to a wide audience of professionals including basic scientists, neonatologists, intensive care physicians, paediatric cardiologists, surgeons, heart failure specialists and specialists in adult congenital heart disease.

It is our hope that this 'translational' approach will not only be new and informative but will place the RV at the centre of discussion and research across disciplines that will bridge between scientists and clinicians to enrich and advance our field for the betterment of our patients.

The saying 'it takes a village' is particularly appropriate when producing a book such as this. Many people deserve our gratitude in helping this book come to fruition, including colleagues at the Hospital for Sick Children in Toronto; family, friends and colleagues from across the globe; and Noreen Adatia and Elektra McDermott for their administrative support.

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Embryological Origins: How Does the Right Ventricle Form

1

Paul Delgado-Olguin

Abstract

The heart originates from a group of cardiac progenitor cells that form the cardiac tube, which develops into a complex four-chambered beating organ. Several tissues signal to stimulate cardiac progenitors to acquire cell fate and differentiate. The timing of differentiation of cardiac progenitors defines the first and second heart fields. The first heart field gives rise to the left ventricle. The second heart field, located anterior to the first heart field, is added to the cardiac tube to give rise mainly to the outflow tract and the right ventricle. Several epigenetic mechanisms including histone and DNA methylation stabilize the transcriptional programs controlling cardiac development.

Keywords

Cardiac development • Second heart field • Cardiac progenitors • Right ventricle • Cardiomyocyte differentiation • Transcriptional regulation

Introduction

The heart develops from cardiac progenitor cells that originate during gastrulation and which move through the primitive streak and emerge as a bilateral cardiac field that fuses in the embryonic midline to form the cardiac crescent and the heart tube later on. The cardiac tube, in which cardiac progenitors start differentiating into cardiomyocytes, serves as a scaffold for addition of cardiac progenitors through the arterial and venous poles. The cardiac tube undergoes complex morphogenetic movements including looping and septation that result in the division of the heart into chambers [1, 2]. Understanding how these processes occur has been the goal of very active research. Early experiments aimed at identifying the cells acting as the building blocks that form the heart identified the population of progenitors cells that are added to the cardiac tube

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[3]. These observations fueled further research that confirmed the existence of two groups of cardiac progenitors, known as the first and second heart fields. The first heart field forms the cardiac crescent and the cardiac tube, and gives rise mainly to the left ventricle. The second heart field, added to the cardiac tube, contributes the totality of outflow tract and the right ventricle [4]. A recent finding of a group of progenitors regulated by canonical Wnt signaling that gives rise to pacemaker cells in chicken led to proposing the existence of a "tertiary" heart field [5]. The exact nature of the molecular cues that induce segregation of these progenitors is not clear, however extensive research using mainly animal and cellular model systems has made significant progress in uncovering the transcriptional pathways that regulate differentiation of cardiac progenitors and cardiogenesis.

This chapter provides an overview of the process of cardiac development, starting with a concise explanation of the morphogenetic events that transform the cardiac crescent into the four-chambered heart. Then, the events that led to the identification of the cardiac fields are discussed, emphasizing the discovery of the second heart field and its contribution to cardiogenesis. The transition from proliferating to differentiating cardiac progenitors and its relevance for development of the second heart field and right ventricle is discussed. Finally, recent findings on the molecular mechanisms controlling differentiation and maturation of cardiac myocytes are summarized.

Overview of Cardiac Development

Early Cardiac Development

The heart is the first organ to function during embryogenesis. The formation of the heart is a complex process that starts very early during development. The earliest cardiac progenitors arise during gastrulation [6, 7], during which the three embryonic layers ectoderm, mesoderm and endoderm are patterned. Multipotent cardiac progenitors arise from a cell population expressing mesoderm posterior 1 homolog, or Mesp1. Mesp1-expressing progenitors give rise first to the first heart field, and then to the second heart field at E6.75 in the gastrulating mouse embryo. Progenitors of the first heart field give rise to either cardiomyocytes or endothelial cells. Progenitors of the second heart field give rise to cardiomyocytes, endothelial cells, and smooth muscle cells [7]. Thus, cardiac progenitors are hierarchically segregated early during gastrulation. Studies using stem cell models of cardiac differentiation, as well as cell lineage tracing in animal models have shed light on some of the intermediate stages in the progression from stem cells to specialized differentiated cardiac lineages (Fig. 1.1) [8].

The cardiac progenitors emerge through the primitive streak and they take position cranially to the forming neural tube and surrounding the neural plate at approximately 18 days of human development. The cardiac progenitors aggregate to form two bilateral primitive heart fields, which fuse in the midline to form a horse shoe-shaped tube from splanchnic mesoderm known as the cardiac crescent. The cardiac crescent harbors a population of cardiac progenitors known as the first heart field, which contributes to the formation of the left ventricle and portions of the atria. As a result of ventral folding of the embryo in a cranial to caudal direction, the limbs of the cardiac crescent coalesce and fuse in the midline to form the linear heart tube (Fig. 1.2). Co-migration of cardiac and vascular progenitors allows for the formation of the endothelial heart tube, which is separated from the primitive myocardium by cardiac jelly, and which will form the endocardium. At this stage, day 22 of development, dilations and constrictions of the heart tube define the *truncus arteriosus*, *bulbus cordis*, primitive ventricle and atrium, and the *sinus venosus* (Fig. 1.3). The transition from cardiac progenitors into differentiating cardiomyocytes results in coordinated contraction of the linear heart tube and blood flow from the *sinus venosus* towards the cranial portion of the embryo. The linear heart tube is then extended by proliferation of resident differentiating cardiac progenitors and by contribution of additional ones

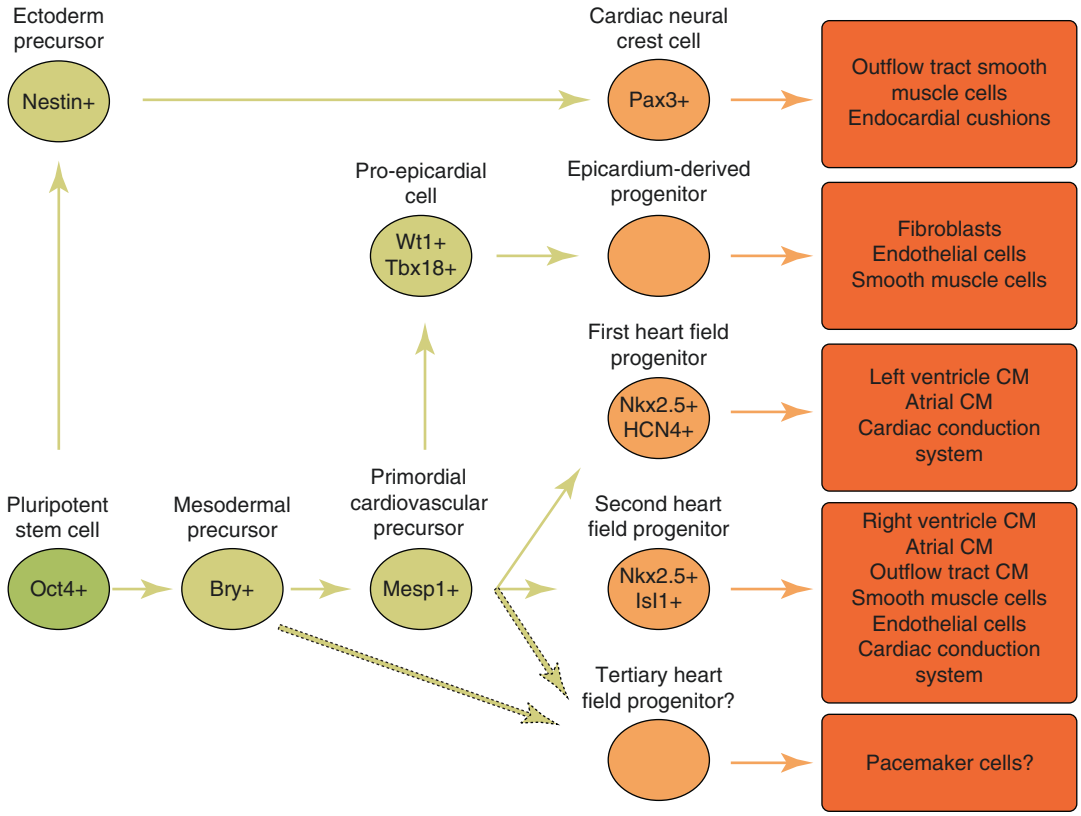

Fig. 1.1 Cardiac cell lineage progression. Intermediate stages generated from pluripotent stem cells towards differentiated cardiac lineages. Markers expressed in the intermediate progenitors are indicated. *CM* cardiomyocytes. Progression towards tertiary heart progenitors is speculative and is indicated with *dotted arrows*. Modified from [8]

originated from splanchnic and pharyngeal mesoderm, which migrate into the linear heart through the arterial and venous poles. This population of cardiac progenitors added to the linear heart is known as the second heart field. Cardiac progenitors of the second heart field give rise to the totality of the right ventricular myocardium, the outflow tract and an important proportion of the atria (Fig. 1.2) [4, 9, 10].

Cardiac Looping

Looping of the heart tube is the first visual evidence of embryonic asymmetry. Progenitors of the second heart field continue to be added during the process of looping, in which torsion forces cause the elongating heart tube to simultaneously twist and rotate rightwards, resulting in the formation of a C-shaped cardiac tube at embryonic day 23 (Fig. 1.3). These morphogenetic movements push the ventral portion of the linear tube towards the right outer curvature of the C-shaped tube, while the dorsal portion of the linear heart separates from the dorsal pericardial wall and forms the inner left curvature. Elongation continues at the arterial and venous poles, and the cardiac tube arranges into and S-shape structure, in which the outflow and inflow tracts come closer together cranially. Displacement of the *bulbus cordis* caudally, ventrally and rightwards, leftwards displacement of the primitive ventricle, and dorsal and cranial displacement of the primitive atrium by embryonic day 28, results in the proper spatial arrangement of the future cardiac chambers (Fig. 1.3). The rightwards movement

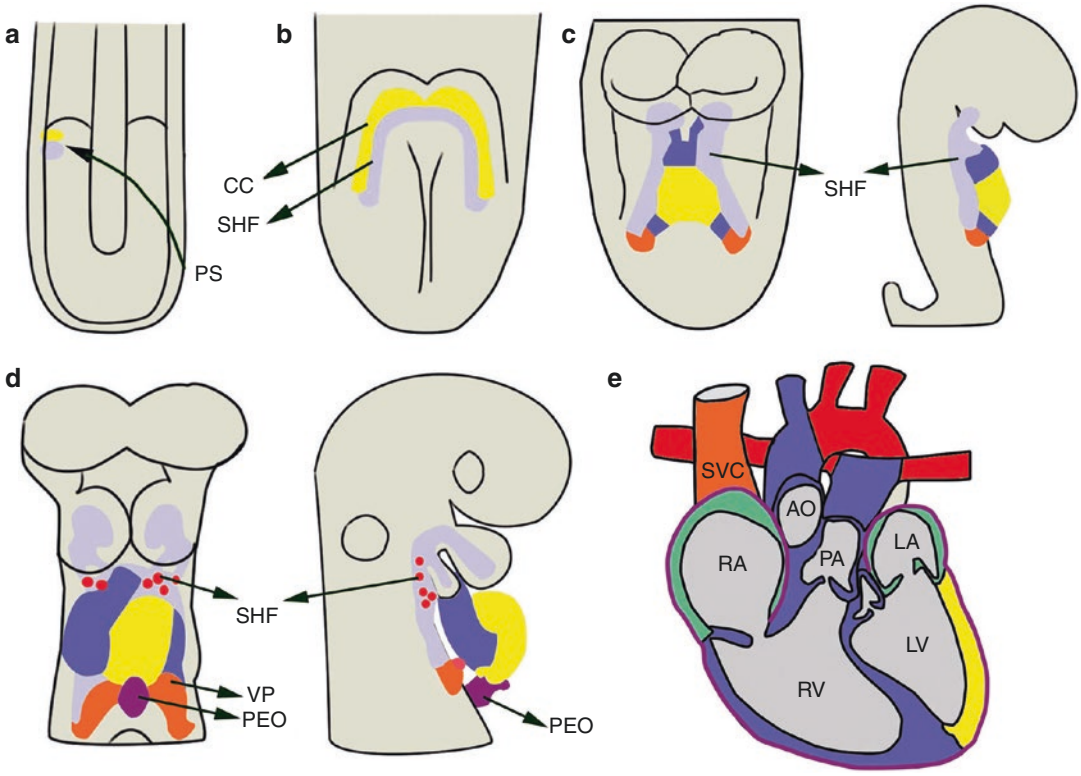

Fig. 1.2 Cardiac development. (**a**) Cardiac progenitors migrate anteriorly from the primitive streak (PS) to form two bilateral cardiac fields that (**b**) fuse in the midline to form the cardiac crescent (*yellow*) with the second heart field (*purple*) located medially. (**c**, **d**) Front (*left*) and lateral (*right*) views of the (**c**) linear, and (**d**) looping heart tube. Progenitors of the second heart field and the neural crest (*red*) migrate into the looping heart. (**e**) Fully developed heart. *Green colored atria* represent contribution of first and second heart field progenitors. The proepicardial organ gives rise to the epicardium. *AO* aorta, *CC* cardiac crescent, *LA* left atrium, *LV* left ventricle, *PEO* proepicardial organ, *PA* pulmonary artery, *SHF* second heart field, *RA* right atrium, *RV* right ventricle, *SVC* superior vena cava, *VP* venous pole. (**a**–**d**) modified from [10]. (**e**) Modified from [126]

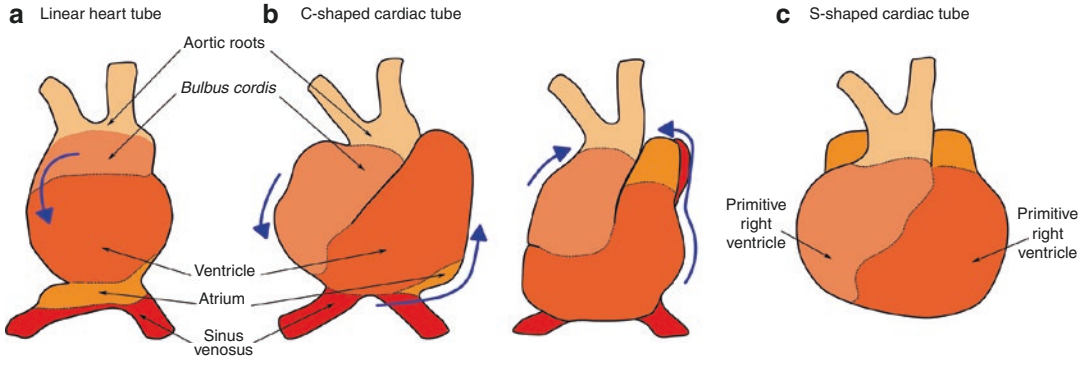

Fig. 1.3 Cardiac looping. The linear heart tube (**a**) twists and rotates rightwards resulting in the formation of the C-shaped tube (**b**). Elongation at the arterial and venous poles force arrangement into the S-shape tube (**c**), in which the outflow and inflow tracts come closer together cranially. Displacement of the *bulbus cordis* caudally, ventrally and rightwards, leftwards displacement of the primitive ventricle, and dorsal and cranial displacement of the primitive atrium, results in the proper spatial arrangement of the future cardiac chambers. Modified from [127]

of the heart tube and the establishment of asymmetry is regulated by leftwards flow in the node, which is a structure formed at the distal tip of the primitive streak containing motile cilia. The leftwards flow in the node elicits asymmetrical activation of diverse signaling pathways controlling left-right asymmetry, and include Ssh, Notch, Wnt, and FGF signaling. Nodal signaling activates expression of *FoxH1*, resulting in downstream asymmetric activation of left-right determinants *Nodal*, *Lefty* and *Pitx2c* [11].

After looping is complete, cells from the pro-epicardial organ (Fig. 1.2), which is a transient group of cells originated from lateral plate mesoderm and located ventro-caudally to the base of the heart [12], migrate towards the surface of the heart to form the epicardium and later contribute to formation of the coronary vasculature, early *sinus venosus*, and endocardium [13].

Cardiac Septation

The process of cardiac septation has been extensively reviewed [1, 14, 15]. Cardiac septation occurs during the fourth to the seventh week of embryogenesis and completely defines the cardiac chambers, separating the left from the right side and establishing the pulmonary and systemic circulatory systems. Studies on animal models have identified numerous molecular pathways that regulate cardiac septation and valve development, highlighting the complexity of the process. TFG, BMP, SMAD, Notch, Wnt, EGF, calcineurin/NFAT and VEGF signaling pathways are important regulators of cardiac septation. Transcription factors also required for the process are Pax3, Pbx and Meis, GATA, and T-box factors. In addition, epigenetic mechanisms controlling the expression of genes, including microRNAs and chromatin regulators also play central roles [16].

Ventricular Septation

Septation of the common ventricle occurs during the fifth week of development, and is completed by the ninth week. The muscular projection that will separate the ventricle starts forming during the looping process, when the walls of the future right and left ventricles grow concomitantly and coalesce resulting in the formation of the primitive interventricular septum, or interventricular ridge, at the base of the common ventricle [17]. The interventricular septum grows and extends posteriorly towards the endocardial atrioventricular cushions, leaving a space known as interventricular foramen. The interventricular foramen is closed when the interventricular septum fuses with the conotruncal septum, which forms from the fusion of conotruncal ridges derived from the endocardial cushions [18, 19].

The molecular processes patterning the ventricles are poorly understood. Comparative studies of the expression of the developmental regulator *Tbx5*, which is a key transcription factor regulating cardiac differentiation, have provided interesting insight. While *Tbx5* is homogenously expressed in the early developing single ventricle of turtle and lizard, it is restricted to precursors of the left ventricle in chicken and mouse. In later stages of development, *Tbx5* is preferentially expressed in a left to right gradient in the turtle ventricle, which by then develops an interventricular primary septum-like structure. Consistent with a key function for *Tbx5* in cardiac septation, genetically modified mice that mimic the reptilian *Tbx5* expression pattern develop a single ventricle. Thus, expression of *Tbx5* may constitute a patterning cue for ventricular septation [20].

Atrial Septation

The process of atrial septation has also been extensively reviewed [1, 14, 21]. Cardiac septation starts in the atrioventricular (AV) canal, a constriction of the looped cardiac tube that defines the primitive ventricle and atria. A subset of endothelial cells on the ventral and dorsal surface of the AV canal undergo endothelial to mesenchymal transition and migrate into the underlying cardiac jelly to form the endocardial cushions, which grow and fuse separating the right and left sides of the AV canal and partially separating the primitive atria from the ventricle. Then, the primitive atrium starts septation through the growth of the *septum primum*, which is a muscular appendage arising from the roof of

the left side of the chamber that grows towards, but does not reach the endocardial cushion [21], leaving an orifice known as the *ostium primum* or atrial foramen (Fig. 1.4). Apoptosis in the elongating *septum primum* creates a perforation known as the *ostium secundum*. The mesenchymal cap at the end of the growing *septum primum* fuses with the endocardial cushion in the AV canal. Before fusion of the *septum primum* with the endocardial cushion, another muscular appendage grows from the roof of the atrial chamber in the right side of the *septum primum* [21], known as *septum secundum*, which grows downwards overlapping the *ostium secundum* but does not reach the endocardial cushion. The partial overlap of the *septum secundum* with the *septum primum* and *ostium secundum* results in incomplete septation of the embryonic atria, which communicate through the *foramen ovale* (Fig. 1.4). This communication allows oxygenated blood coming from the placenta to reach the fetal circulation. Atrial septation is completed after birth, when increased pressure in the left atrium pushes the *septum primum* laterally towards the *septum secundum* closing the *foramen ovale*.

Outflow Tract Septation

Given the relevant function of the outflow tract in development of the right ventricle, its early stages of development will be discussed in more detail later in the "Development of the second heart field" section.

The process of septation of the outflow tract has been extensively reviewed [15, 16]. Septation of the outflow tract starts during the fifth week of development, and consists in the division of the common outflow chamber and *truncus arteriosus* to form the outlets and valves of the right and left ventricles, the pulmonary trunk and the aorta, respectively (Fig. 1.4). At the fifth week of human development, the outflow tract myocardium extends from the aortic sac [22]. At this stage, the proximal (conal) and distal (truncal) portions of the outflow tract can be distinguished by the presence of the conotruncal curvature, also known as the "dog-leg bend" [23]. Two pairs of endocardial ridges, the conotruncal and intercalated ridges, follow a spiral path and give rise to cushions that develop along the proximal and distal outflow tract. The spiral arrangement of the endocardial ridges positions the pulmonary trunk around the aorta. These cushions are formed in part with migrating mesenchyme derived from the neural crest. Septation starts with the fusion of the distal cushions, located towards the aortic sac, followed by fusion of the proximal cushions. Fusion of the distal portion of the proximal cushions with distal intercalated cushions will generate the aortic and pulmonary valves [15]. Around the 50th day of gestation, fusion of the proximal part of the outflow tract cushions results in formation of an embryonic outlet septum within the right ventricle. This septum is muscularized by invasion of parietal cardiac myocytes [24]. The septum then fuses with the muscular ventricular septum, confining the outlet of the aorta to the left ventricle and separating the ventricles. Further muscularization of the endocardial cushions [25], contribution of progenitor cells originated in the neural crest, and apoptosis [26] are required for complete separation of the outflow tract into the pulmonary artery and aorta.

Trabeculation

Trabeculae are projections of cardiac myoctes covered by endocardium that extend into the ventricle. Trabeculae are very important in the developing heart, as they extend the surface area favoring cardiac oxygenation and nutrient uptake before development of the coronary vasculature [27]. Trabeculae begin to form after looping of the cardiac tube by delamination of myocytes from the ventricular wall into the cardiac jelly [28]. Coordinated myocardial proliferation and differentiation results in the definition of two myocardial layers, the compact and trabecular myocardium. This process requires reciprocal communication between myocardium and endocardium via NOTCH and bone morphogenetic protein (BMP) signaling. NOTCH is activated exclusively in endocardial