Seminars in Fetal & Neonatal Medicine 18 (2013) 237–244

Contents lists available at SciVerse ScienceDirect

Seminars in Fetal & Neonatal Medicine

journal homepage: www.elsevier.com/locate/siny

Embryology of the heart and its impact on understanding fetal and neonatal heart disease

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Keywords:
Cardiac development
Congenital heart malformation
Epicardium
First heart field
Neural crest cells
Nuchal translucency
Second heart field

SUMMARY

Heart development is a complex process during which the heart needs to transform from a single tube towards a fully septated heart with four chambers and a separated outflow tract. Several major events contribute to this process, that largely overlap in time. Abnormal heart development results in congenital heart disease, which has an estimated incidence of 1% of liveborn children. Eighty percent of cases of congenital heart disease are considered to have a multifactoral developmental background, whereas knowledge of monogenetic causes for congenital heart disease is still limited. This review focuses on several novel findings in cardiac development that might enhance our knowledge of aetiology and support refinement of prenatal diagnosis of congenital heart disease.

1. Introduction

In recent years novel findings in cardiac development have had an impact on perinatal clinical diagnosis. A better understanding of the still limited number of monogenetic causes for congenital heart disease (CHD) opens up new avenues for research in the developmental background of the approximately 80% of cases with a multifactorial origin of fetal and neonatal CHD. This review focuses on several new findings in the development of cardiac structures that might further enhance our knowledge of aetiology and support refinement of prenatal diagnosis. As there are marked homologies in avian and mammal, including human, cardiac development, research results from the various species will be integrated in this review.

2. Origin of the embryonic cardiac tube and looping

The bilateral cardiogenic fields in the embryonic mesoderm merge in the midline and form a primary cardiac tube, lined on the inside by endocardium and on the outside by myocardium consisting of about two cell layers. A thick basement membrane is sandwiched in between referred to as cardiac jelly, containing water-binding extracellular matrix molecules including hyaluronic acid. At a later stage the cardiac jelly is restricted to endocardial cushions lining the myocardial outflow tract (OFT) and the atrioventricular (AV) canal. The primary cardiac tube is genetically primed to have a dextral looping. During looping the connection to the dorsal body wall mesoderm is disrupted except at the venous and arterial poles where vessels enter and leave the heart tube. At the venous pole the cardinal veins become confluent in the sinus venosus supplying venous blood (oxygen rich in the embryo) to the heart, while at the arterial pole the blood is pumped into the aortic sac connecting to the bilateral pharyngeal arch arteries and the dorsal aortae.

By contrast with the general view in the 1990s, the primary heart tube does not contain in miniature all elements of the mature heart. The myocardium-lined primary heart tube initially consists of a small atrial component (connected to the sinus venosus), an atrioventricular canal, a ventricular inflow tract (VIT) and a small OFT (connecting to the aortic sac). On the borderline of VIT and OFT a bulboventricular or primary fold is present (Fig. 1a). These cardiac components are derived from the mesoderm of the first heart field. The addition of dorsal cardiac mesoderm positioned between the primary heart tube and the primitive gut, the so-called second heart field (SHF) mesoderm,[1] is essential for the subsequent development of all cardiac components (Fig. 2). It may be argued that first and second heart fields are continuous in time and space,

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1744-165X/$ – see front matter © 2013 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.siny.2013.04.008

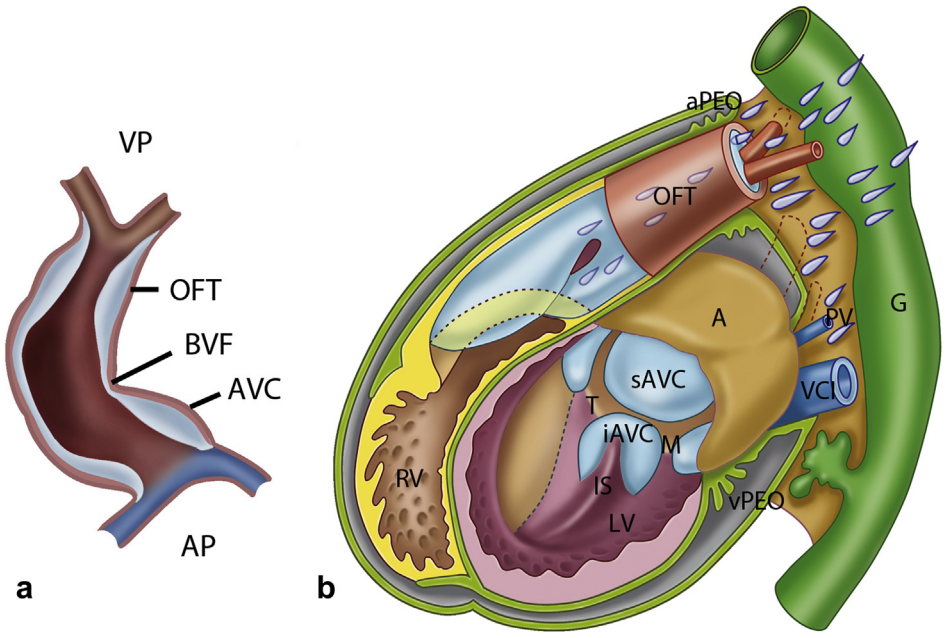

Fig. 1. Schematic representation of the developing heart. (a) A primitive heart tube consisting of myocardium (brown) enclosing cardiac jelly (blue). The bloodstream runs from the venous pole (VP) to the arterial pole (AP) with the first two pharyngeal arch arteries attached. (b) A simplified model of a heart prior to ventricular septation. The roof of the atrium (A, light brown) is closed; therefore, atrial septation is not shown here. The anterior walls of the left ventricle (LV) and right ventricle (RV) are opened to reveal the inside. The interventricular foramen is present. The inlet septum (IS) is connected to the inferior AV cushion (iAVC). The second heart field-derived part of the RV is illustrated in a contrasting colour (yellow). The epicardium (olive green) covers most of the surface of the heart, but the venous pro-epicardial organ (vPEO; between liver and venous pole) and the arterial PEO (aPEO) surrounding the arterial pole are still present. The endocardial cushions are shown in light blue, neural crest cells in lavender and the gut (G) including liver in green. The tricuspid (T) and mitral (M) ostia are indicated. AVC, atrioventricular canal; sAVC, superior AV cushion; BVF, bulboventricular fold; OFT, outflow tract; PV, pulmonary vein; VCI, inferior cardinal vein.

but for simplicity's sake these are dealt with as separate components. This SHF mesoderm can reach the heart tube at both the arterial (anterior SHF) and venous poles (posterior SHF) (Fig. 1b). At the latter site, the sinus venosus, which becomes covered by posterior SHF-derived myocardium, is incorporated, forming the smooth-walled surfaces of the dorsal wall of both the right and left atrium including the primary atrial septum. At the arterial pole the anterior SHF-derived mesoderm supplies the myocardium of the right ventricle (RV) up to the right side of the ventricular septum. The SHF also contributes to the semilunar valves and the walls of the great arteries.

For subsequent remodelling, septation, valve formation and coronary vascular development (Fig. 2) two other cell populations are added to the heart, being the neural crest cells and the epicardium (Fig. 1b). Both cell types have important structural and instructive functions that are discussed below.

2.1. Clinical relevance

The discovery of the sequel of first and second heart field contributions to heart development enhances our understanding that disturbances in early heart tube formation can lead to spontaneous

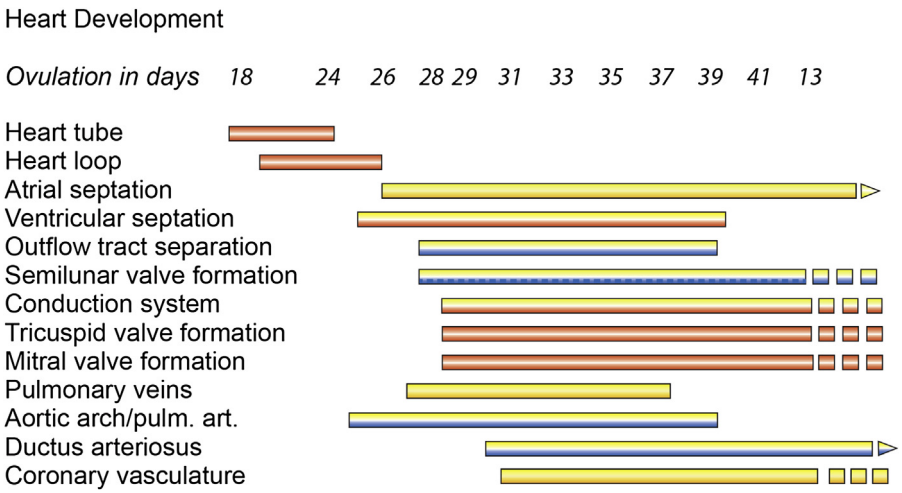

Fig. 2. Timeline of cardiac development according to age (days) and the most important cardiac structures reviewed in this article. The colours reflect contributions of various cell populations including first (red) and second heart field (yellow), and neural crest (blue). Note that several elements of the heart receive contributions from more than one source.