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Review

Normal and abnormal development of pulmonary veins: State of the art and correlation with clinical entities

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ABSTRACT

Interest for the pulmonary veins has increased in the past decade after the potential arrhythmogenicity of the myocardial sleeve surrounding these structures has been recognized. Furthermore, there are several clinical entities, such as anomalous connection pattern and pulmonary vein stenosis, that are related to abnormal pulmonary vein development.

In this review, we will describe current literature and aim to elucidate and reorganize current opinions on normal and abnormal pulmonary vein development in relation to clinical (management of) diseases. Several unresolved questions will be addressed, as well as current conceptual controversies. First, a general overview of development of structures at the venous pole of the heart, including normal development of the pulmonary vein from a primitive Anlage, will be provided. Recent insights indicate an important contributory role of the mesoderm behind the heart, the so-called second heart field, to this area. Subsequently, the formation of a myocardial and smooth muscle vascular wall of the pulmonary veins and the left atrium is described, as well as current insights in the mechanisms involved in the differentiation of these different cell types in this area. Next, developmental concepts of normal pulmonary venous drainage patterns are reviewed, and an overview is provided of clinical entities related to abnormal development at several anatomical levels. Lastly, attention is paid to arrhythmogenesis in relation to pulmonary vein development, as well the consequences for clinical management.

1. Introduction

In recent years, the involvement of the pulmonary veins (PVs) in several pathogenetic processes, has increasingly been recognized. The PVs play a role in the onset of atrial arrhythmias, such as atrial fibrillation [1]. Furthermore, congenital malformations, including abnormal pulmonary venous drainage patterns and PV stenosis, may warrant surgical or percutaneous interventions. Also the structure of specific components of the PVs may be involved in pathogenesis, e.g. vulnerability of the smooth muscle and myocardial wall for acquired PV stenosis.

In the light of these clinical considerations, understanding of both normal and abnormal PV development is mandatory. PV development is narrowly related to development of the venous pole of the heart, that includes the sinus venosus and atrial segment. Recent new insights have demonstrated that during cardiac development large compartments of the heart are developed in and subsequently incorporated from the mesocardium behind the heart, the so-called second heart field [2,3].

Current concepts of PV development result in several questions that seem to recirculate and ask for clarification. We should in this regard also take notice of the fact that differences in semantics, definitions and interpretations of findings might be of great influence. After giving a general overview of development, in this review we will focus on the following questions:

1. How are the different components of the venous pole defined and what are current controversies?
2. Which role does the second heart field play in the development of the venous pole, myocardialization and smooth muscle cell (SMC) formation of the PVs?
3. What, in the view of previous points, are the current developmental concepts on the origin of normal and abnormal PV connection?
4. How is PV development related to arrhythmogenesis?
5. What are the consequences of the various concepts of PV development on clinical management?

We will try to clarify these topics by describing normal and abnormal PV development, as well as the relation to clinical entities, based on our own research and current literature.

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With regard to abnormal PV development, in literature different terms are used to describe the same condition. While “anomalous PV drainage or return” mainly focuses on the physiological condition, “anomalous PV connection”, in our opinion, describes most accurately the anatomic condition.

2. General overview of early cardiac development

The embryo starts as an embryonic plate, in which a primitive streak area develops [4]. The primitive streak is formed as an invagination in the midline of the embryonic plate, at the initiation of gastrulation (the formation of the three embryonic germ layers). From the primitive streak, two large lateral plate mesodermal compartments are derived on both sides of the embryonic axis [4] (Fig. 1a, upper panel). In each compartment a coelomic cavity develops that splits the mesoderm into a somatic layer, lining the ectoderm, and a splanchnic layer, lining the endoderm [5]. The bilateral splanchnic mesoderm contains the cardiac precursor cells. Anterior to the embryonic axis (notochord), these mesodermal compartments fuse to form a primitive myocardial heart tube (primary heart tube) that is lined on the inside with endocardium and separated from the myocardial layer by cardiac jelly [4,5]. After a complicated bending of the head region of the embryo, this heart tube obtains an arterial (anterior/cranial) pole and a venous (posterior/caudal) pole (Fig. 1a, lower panel).

During further development of the heart, splanchnic mesodermal cells from the so-called second heart field will continue to be added to the heart [2,3]. The second heart field is defined as an anteroposterior extension of mesoderm, located behind the heart, from which myocardium is incorporated to the heart during further development. The contribution to the venous pole of the heart is referred to as derived from the posterior heart field [6,7], whereas the contribution at the arterial pole is referred to as derived from the anterior or secondary heart field [8,9] (Fig. 1b–d). The second heart field in relation to PV development is discussed in detail in Section 4 of this paper. The splanchnic mesoderm also differentiates into a vascular plexus of endothelial cells. This plexus is the source of the lining of the vitelline veins, the pharyngeal arch arteries and the initially bilateral dorsal aortae [4,5]. The splanchnic plexus is connected to the sinus venosus, being itself in connection with the common atrium, by means of a small strand of endothelial cells, the so-called midpharyngeal endothelial strand, which runs from the arterial to the venous pole of the heart [10]. This structure is the Anlage of the primitive PV (see Section 5), that is situated in the mesocardium behind the heart (the dorsal mesocardium). We will focus on structures that will develop on the venous pole of the heart, being the area in which the PV develops.

3. How are the different components of the venous pole defined?

The inflow part or venous pole of the heart includes the embryological sinus venosus segment and the atrial segment. These compartments constitute the most caudal parts of the primary heart tube (Fig. 1a). In this paragraph we will clarify nomenclature of embryological structures at this site, as well as their counterparts in the adult. As will become clear, definitions and descriptions of some structures have been the subject of vivid discussions over the past decades. We will also address these controversies where appropriate.

After development from the second heart field (see Section 4), the sinus venosus is connected to the common atrium and consists during the 4th week of development of a left and right part, each receiving blood from the vitelline/omphalomesenteric vein, the umbilical vein and the common cardinal vein. During early stages of development, the border between the sinus venosus and the still unseptated common atrium, can be distinguished as a fold of myocardium, the sino-atrial fold. Asymmetrical growth of the right part of the common atrium causes a rightward shift of the site of connection of the sinus venosus to the common atrium. The right part of the sinus venosus and corresponding veins also enlarge and form the caval veins that are incorporated into the future right atrium. The left part of the sinus venosus obliterates to a large extent in human development. The left common cardinal vein will form the coronary sinus. In mice, the left anterior cardinal vein (the cranial branch of the common cardinal vein) will persist as the left superior caval vein, while in human the left caval vein usually obliterates, forming the ligament of Marshall (oblique vein of Marshall in case of incomplete obliteration). After septation, the right atrium consists of 2 parts: the smooth-walled main body derived from the sinus venosus and the right trabeculated atrial appendage. The sinus venosus part of the right atrium, receiving the caval veins and the coronary sinus (in the adult called sinus

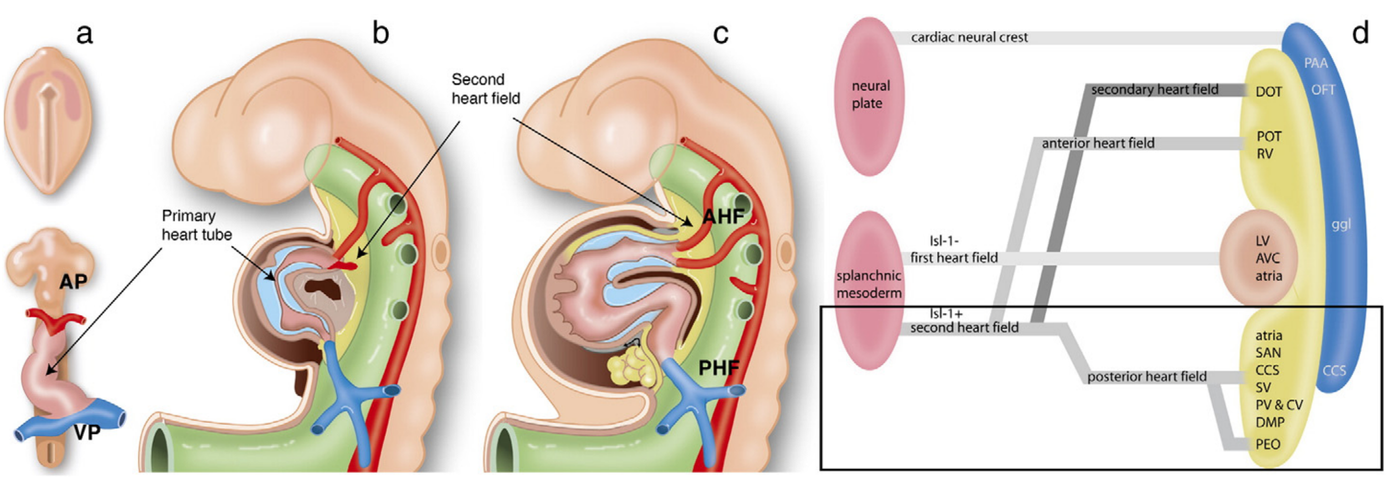

Fig. 1. Schematic representation of sequential stages of cardiac development and the contribution from first and second heart field. The primary heart tube is depicted in brown and the myocardium that is derived from the second heart field (and incorporated later in the heart) in yellow. a. The primary heart tube is formed after fusion of bilateral plates of splanchnic mesoderm in the primitive plate. This tube already has a venous pole (VP), and an arterial pole (AP) b. Lateral view of embryo (approximately 23 days in human), showing the primary heart tube, surrounded by cardiac jelly (blue), and the second heart field situated dorsally to the heart. c. Human embryo at 25 days. The primary heart tube has expanded both at the venous and at the arterial pole with myocardium derived from the second heart field (depicted in yellow). d. Scheme of the nomenclature the primary and second heart field. At the venous pole of the heart, myocardium is derived from the *posterior heart field*, that contributes to the posterior wall of the atria, the sino-atrial node (SAN), the myocardium of the sinus venosus (SV), pulmonary veins (PV) and cardinal veins (CV) including the coronary sinus, part of the central conduction system (CCS) and the dorsal mesenchymal protrusion (DMP). The second heart field contribution to the venous pole is discussed in more detail later on in this review. Modified after: Crawford and DiMarco, third edition 2009 [125].