Origin and Development of the Coronary Arteries

Origen y Desarrollo de las Arterias Coronarias

Geraldo de Oliveira Silva-Junior; Sandro Wilson da Silva Miranda & Carlos Alberto Mandarim-de-Lacerda

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SUMMARY: The formation of the coronary vasculature is a fundamental event in heart development and involves a series of carefully regulated temporal events that include vasculogenesis and angiogenesis. This review focuses the knowledge concerning the formation of the coronary arteries available so far and some molecular mechanisms involved in this process. Understanding coronary embryogenesis is important for interventions regarding adult cardiovascular diseases as well as those necessary to correct heart congenital defects. The insight of the coronary artery development as a result of ingrowth changed the understanding of several congenital coronary artery variations and anomalies described in gross anatomy.

KEY WORDS: Coronary artery; Embryology; Heart; Angiogenesis; Vasculogenesis.

INTRODUCTION

The development of the coronary vascular system is an interesting model in developmental biology with major implications for the clinical setting. Although coronary vessel development is a form of vasculogenesis followed by angiogenesis, this system uses several unique developmental processes not observed in the formation of other blood vessels (Wada *et al.*, 2003). In embryos at the stages in which identification of the coronary orifices was variable, the proximal epicardial segments of the left and right coronary arteries are usually already identified, in human as well as in rat embryos. On the other hand, a coronary orifice is never seen in the absence of a proximal coronary artery. At all stages studied (in human embryos from 10 mm crown-rump length and in rat embryos from 11 mm crown-rump length) vascular structures are identified in the epicardial covering of the heart. Thus, the theories on proximal coronary artery development are inadequate to explain either these data or the known possible congenital abnormalities of the coronary arteries (Bogers *et al.*, 1988). At the earliest embryonic stages, nonetheless, a coronary circulation does not exist, with the blood flowing through the lumen of the heart tube serving to nourish the endocardium and myocardium. By the beginning of the post-somitic period (third week in humans), as the walls of the developing heart increase in thickness, a dedicated vascular system begins to form over the epicardial

surface of the myocardium (Bernanke & Velkey, 2002) but still not connected to the aorta.

There are two models regarding the physiological development of the embryonic coronary arteries. Some authors mentioned that the coronary arteries develop as a budding or outgrowth of the endothelial aortic sinus running towards the adjacent tissue (outgrowth interpretation of the coronary development) (Dbaly *et al.*, 1968; Rychter & Ostádal, 1971; Virágh & Challice, 1981). However, the long-held supposition that coronary veins and arteries were formed by outgrowths from the systemic venous sinus and the aorta, respectively, was argued 20 years ago (Bogers *et al.*, 1989). In their study, Bogers and coworkers demonstrated that the major coronary arteries could be identified in the walls of the aortic sinuses before the emergence of coronary arterial orifices, thus suggesting ingrowth rather than outgrowth of the arterial channels. The roots of the right and left coronary arteries are formed when strands from a peritruncal ring of vascular structures penetrate the aorta at the right and left aortic sinuses of Valsalva (Ando *et al.*, 2004).

Thus, at the end of the vasculogenic period without blood flow, the general pattern of the coronary system is set,

but significant remodeling of the major vessels and capillary system will take place after connection to the aorta. The joining of the coronary system to the general circulatory system is a complex and understudied developmental process, and whether this movement is directed by a chemotactic event or simply represents the “path of least resistance” is unclear thus far (Wada *et al.*).

It is fascinating to realize the precision with which the coronary arteries connect to the aorta because they are located at the centre of the aortic valve leaflets. Still, it is interesting to note that when anomalies do occur, they are invariably circumferential and not longitudinal. Elucidating the cellular and molecular regulation of this process is imperative for an understanding of coronary arteries formation (Wada *et al.*). Thus, the goal of this short review is to examine the latest studies that are providing new insights to the complex process of development of the coronary arteries.

The development of the coronary vessels. The formation of the coronary vasculature involves a series of carefully regulated temporal events that include vasculogenesis, angiogenesis and remodeling (Tomanek, 2005). The need for a coronary circulation first occurs in the embryo when the compact portions of the ventricles thicken,

increasing the diffusion distance for oxygen from the ventricular lumen. This myocardial growth triggers events that dictate the differentiation and migration of precursor cells of the epicardium (Tomanek & Zheng, 2002). Vasculogenesis has been described as the *de novo* generation of blood vessels, whereas angiogenesis can be thought of as the generation of capillaries, veins and arteries from preexisting vessels. The process starts with the delivery of vasculogenic cell types to the surface of the heart after beating has begun (Munoz-Chapuli *et al.*, 2002).

Delivery of a population of cells to an existing organ requires dynamic cellular events, and coordination of cell movement with the precise timing of delivery. Moreover, commitment and differentiation is critical for proper vessel formation and organ development. The mesenchymal precursors of the vascular smooth muscle cells and the adventitial fibroblasts originate from an epithelial-mesenchymal transformation of the epicardial mesothelium. Precursors of the coronary endothelium are also epicardium-derived cells (EPDCs); the early EPDCs might be found to have a similar competence to that shown by the recently discovered bipotential vascular progenitor cells, which are able to differentiate into endothelium or smooth muscle depending on their exposure to the vascular endothelial growth factor (VEGF) or the platelet-derived growth

Fig. 1. Angiogenesis and vasculogenesis forming vessels: (A) angiogenesis: it occurs initially with the formation of the budding (1) or endothelial cell outgrowth followed by stretching (2) of small vessels and branching by proliferation (3) of existing endothelial cells and remodeling (4); (B) vasculogenesis: it is the growth of capillaries from pre-existing vessels (1 and 2), after formation of vascular (capillary) tubes, these undifferentiated vessels fuse forming a continuous vascular structure (3 and 4).

Fig. 2. Photomicrographs of longitudinal histological sections of the aortic valves and ascending aortas of C57BL/6 mice embryos at post somitic period stained with hematoxylin and eosin. (A) Embryo at stage 16 -- staging based on the Carnegie Institute of Washington system (O'Rahilly, 1972), section through the outflow tract and aortic bulb, the subepicardial layer does not show already evident capillaries (scale bar = 100µm). (B) Embryo at stage 19, subepicardial capillaries are observed around the aortic bulb (arrows) (scale bar = 75µm). (C) Embryo at stage 23, section through the outflow tract and aortic bulb shows the connection between the subepicardial coronary artery (arrows, vessel containing blood cells) and the aortic sinus (of Valsalva, asterisk) through the coronary ostium (open arrow, v = semilunar valve) (scale bars = 75µm).

factor(PDGF)-beta. It is conceivable that the earliest EPDCs differentiate into endothelial cells in response to myocardially secreted VEGF, while subsequent EPDCs, recruited by the nascent capillaries via PDGF-beta signaling, differentiate into pericytes and smooth muscle cells (Munoz-Chapuli *et al.*, 2002). On the other hand, experimental techniques demonstrated the coronary vessel development from its origins in the proepicardium to the final assembled network of arteries, veins, and capillaries present in the mature heart (Dong *et al.*, 2008). The older conception about the origin of the coronary vascular progenitors was derived from the cardiac mesoderm, like the other cell types in the myocardium and endocardium (Patten, 1949; Haan, 1965).

Endothelial cells form vascular (capillary) tubes that fuse and grow in a branching pattern. A capillary plexus makes contact with the coronary sinus and fuses to form a venous connection. Later, the venous system acquires smooth

muscle (van den Hoff *et al.*, 2001; Bernanke & Velkey). As noted in many species, the appearance of capillaries is followed by the development of a venous system prior to the appearance of arterial components of the coronary circulation (Licata, 1954; Hirakow, 1983; Hutchins *et al.*, 1988). The arterial system develops as smooth muscle cells differentiate around the endothelial cells that formed vascular channels (Hood & Rosenquist, 1992; Mikawa & Fischman, 1992). The main coronary vessels are formed by a coalescence of small endothelial channels which penetrate the aorta (Bogers *et al.*, 1989; Waldo *et al.*, 1990). Vascular growth is proportional to myocardial growth in the embryonic, overloaded heart, but the persistence of the pressure overload results in a failure or severe limitations in coronary artery development suggesting that vascular growth during this period of development is regulated, at least in part, by the rate and magnitude of myocardial growth (Tomanek *et al.*, 1999).

Formation of the coronary arteries. The coronary arteries were considered for a long time as mere outgrowths of the aortic root (Dbaly *et al.*; Rychter & Ostádal; Virágh & Challice). In 1989, Bogers and colleagues showed that the major coronary arteries could be seen in the aortic wall prior to the emergence of coronary ostia, thus suggesting an ingrowth rather than outgrowth of these vessels (Bogers *et al.*, 1989). Definitive evidence of this pattern was provided in chick-quail chimeras (Poelmann *et al.*, 1993) and in serially sectioned chick (Waldo *et al.*, 1990) and rat (Tomanek *et al.*, 1996) hearts. The roots of the two main coronary arteries are formed when strands from the peritruncal ring of vascular tubes penetrate the aorta at the left and right cusps (Ando *et al.*).

Initially, the proximal ends of the coronary arteries migrate toward the proximal aorta. The tips of the advancing coronary vessels must penetrate the tunica media of the aorta, pierce the endothelial lining, and establish continuity with the lumen. Primarily, several coronary vessels approach the left and right aortic sinuses, but only one of these arteries will establish firm contact with each sinus and become the right and left coronary arteries. The mesenchyme of the approaching epicardial vessels meshes with that of the great vessels (Vrancken Peeters *et al.*, 1997; Velkey & Bernanke, 2001). When connecting coronary vessels approach the endothelium of the aorta, apoptotic cells are found along the

aspects of these vessels and their attachment to the aorta (Velkey & Bernanke).

The formation of the coronary arteries in humans follows a similar pattern to that observed in other mammals and birds. Table I compares the chronological development of the coronary arteries in staged embryos of different species. Penetration of the aorta by the tubular network at the aorta's base is precisely orchestrated so that normally only two major coronary arteries are formed. However, establishment of the coronary ostia is not only spatially, but also temporally, regulated since the left coronary ostium forms prior to the right in both humans and rats (Hirakow; Bogers *et al.*, 1989; Mandarin-de-Lacerda, 1990).

The reasons for confinement of the coronary ostia on two of the three aortic sinuses are still unclear. Microscopic examination of serial sections of human embryos from 5.0 to 17.5 mm CR length (Carnegie stages 13-19) confirmed that the earliest vessels in the heart wall develop subepicardially near the apex at stage 15. The network extends centripetally and only at stage 17 could coronary arterial stems, communicating with the aortic lumen, be identified. The sequence suggests that confinement of the coronary ostia to the interior of both the right and left posterior sinuses probably occurs because these represent the most accessible contact points for the centripetally growing vascular plexus (Turner & Navaratnam, 1996).

Table I. Chronology of coronary artery (CA) development in staged embryos – to mammals, Carnegie Institution of Washington classification (O'Rahilly, 1972); to quail, Hamburger and Hamilton (1992).

Author(s)	Species	Epicardial Plexus	Left CA	Right CA	Both CA
Hirakow, 1983	Human		Stage 18 (25% of the cases)	Stage 19	Stage 19 (40% of the cases)
Hutchins <i>et al.</i> , 1988	Human	Stages 14 and 15			Stage 19 (50% of the cases)
Bogers <i>et al.</i> , 1988	Rat	Stage 16	Variable, Stage 18-21	Variable, Stages 18-21	Stage 22, with coronary orifice
Bogers <i>et al.</i> , 1988	Human	Stage 14	Stage 16 (75% of the cases)	Stage 16 (25% of the cases)	Stage 17, with coronary orifice
Bogers <i>et al.</i> , 1989	Quail		Variable, Stage 19-22	Variable, Stages 19-22	Stage 23, with coronary orifice.
Mandarin-de-Lacerda, 1990	Human	Stage 15	Stage 18 (66.7% of the cases)	Stage 19	Stage 19 (100% of the cases)
Tomanek <i>et al.</i> , 1995	Rat	Stage 15			Stage 17, with coronary orifice

Fig. 3. The apoptosis in the coronary artery ostia formation: (A) transverse section of the peritruncal region and the developing valves in chicken embryo at stage 30 -- staging based on Hamburger and Hamilton (1992). Peritruncal capillary plexus (PCP) is observed around the aorta (Ao) and pulmonary artery (PA); (B) blind-ended vessels (B-eV) from the PCP penetrate the aortic tissue, apoptotic cells (Apo) are found in association with proliferating vessels of the PCP; (C) once the penetrating vessel reaches the aortic endothelium, the interface between the aortic endothelium and the B-eV is transformed into a patent orifice via apoptosis, creating a connection; (D) after connecting the aorta (Ao), some of the penetrating vessels are selected (unknown mechanism) and develop into the definitive proximal coronary arteries (CA).

The developmental proximal part of coronary artery undergoes extensive remodeling as its luminal diameter increases 4-fold between stages 18 and 21 (Ratajska & Fiejka, 1999). Moreover, experimental evidences suggest that coronary arteriogenesis in the chick provides a structural framework, or conduits, for the differentiation of myocardial cells into Purkinje fibers (Harris *et al.*, 2002).

Some mechanisms are considered reinforcing the theory of "ingrowth" to the development of the coronary arteries. The role of the neural crest cells in the establishment of the main coronary artery stems was indicated (Waldo *et al.*, 1990; Hood & Rosenquist) as well as transcription factors in the epicardium, eg, Fog-2 (Tevosian *et al.*, 2000) and Ets-1 and Ets-2 (Lie-Venema *et al.*, 2003). The need of VEGF family members for capillary plexus penetration of the aortic root and formation of coronary arteries is also accepted (Tomanek *et al.*, 2006). The unilateral neural crest

ablation in the chick resulted in only one contralateral coronary artery main stem which branched to form the right and left. Ectopic origins of a second coronary artery were found in all embryos with neural crest ablation. In the chicken, neural crest cells have been found to disrupt the media of the base of the coronary artery (Waldo *et al.*, 1994) and contribute to parasympathetic ganglia and nerves, present prior to the establishment of coronary arteries (Tomanek).

Role of growth factors in coronary morphogenesis. The mechanisms underlying the specification of this key event are still unknown. One morphological clue noted in the quail is the intense density of transcripts for receptors VEGF receptor-2 (R2) and VEGF receptor-3 (R3) at the sites where the coronaries originate. This is a region where epicardial and subepicardial cells stain more intensely for VEGF (Tomanek *et al.*, 2002). Thus, VEGF and its receptors are critical for the formation of the coronary artery stems (Munoz-Chapuli *et al.*).

The hypothesis that this family of growth factors provides the key signaling mechanism for coronary ostia and artery formation were based on the observation of high expression of VEGF in epicardial and subepicardial cells at the aortic root and the high density of VEGF-R2 and -R3 transcripts at the aortic sites of coronary artery roots. VEGF family members are required for the formation of the main coronary arteries via endothelial cell penetration in the aorta because VEGF-Trap prevented this event (Tomanek *et al.*, 2002; Tomanek *et al.*, 2006).

Apoptosis during development of the coronary artery.

During the formation of the proximal coronary artery, endothelial strands from the peritruncal ring penetrate the facing sinuses and then fuse, whereas those strands penetrating the noncoronary sinus disappear. Thereafter, the tunica media of the coronary artery demarcates the definitive proximal coronary artery from the aortic tunica media (Ando *et al.*). A relationship between apoptosis and coronary ingrowth was first reported by Velkey and Bernanke (Velkey & Bernanke). These authors did not clearly indicate any specific regulatory mechanism acting during coronary artery development. In the absence of any characterization of the apoptotic cells or any experimental manipulation of aortic and coronary vascular tissue, it is difficult to offer a molecular explanation for the complex events involved in coronary artery development. The results only confirm that apoptosis is involved in the formation of the proximal coronary arteries and their orifices. Thus, these findings generate avenues for future research and suggest that factors involved in regulating apoptosis should be included in future models of coronary artery development (Bernanke & Velkey).

The process of apoptosis in the development of the coronary artery can be didactically divided into three stages: a) invasion, during the process of vascular invasion of the aorta, blind-ended vessels from the peritruncal capillary plexus invade the aortic tissue. Apoptotic cells are found in association with the proliferating vessels of the peritruncal capillary plexus, but not within the aortic endothelium; b) connection, when the invading vessel contacts the aortic endothelium, the interface between the aortic endothelium and the blind end of the vessel is transformed into a patent orifice via apoptosis; c) remodeling, after connecting to the aorta, some of the penetrating vessels are selected by an yet unknown mechanism that develops into the definitive proximal coronary arteries. These vessels begin to acquire a vascular smooth muscle coat and increase in diameter. The coronary orifice and the surrounding aortic tissue must accommodate the expansion of the coronary arteries, and it is presumed that apoptosis plays a vital role in this remodeling process (Velkey & Bernanke, 2001; Rothenberg *et al.*, 2002).

Final remarks. The insight of the coronary artery development as a result of ingrowth changed the understanding of several congenital coronary artery variations and anomalies classically described in gross anatomy. The origin of the coronary arteries outside of the aortic sinuses, e. g. the pulmonary trunk or the pulmonary arteries (Castorina *et al.*, 2008; Farouk *et al.*, 2009), or the extremely high position of the coronary orifices from the ascending aorta (Piegger *et al.*, 2001), are better explained by the ingrowth theory of the origin of the coronary artery. The existence and high prevalence of myocardial bridges on the main branches of the coronary arteries (Mandarim-de-Lacerda *et al.*, 1987; Belov Iu & Bogopol'skaia, 2004) is also comprehensible in view of the ingrowth theory.

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RESUMEN: La formación de la vascularización coronaria es un acontecimiento fundamental en el desarrollo del corazón e implica una serie de eventos temporales cuidadosamente regulados que incluyen vasculogénesis y angiogénesis. Esta revisión se focaliza en el conocimiento sobre la formación de las arterias coronarias y algunos mecanismos moleculares implicados en este proceso. Entender la embriogénesis coronaria es importante para las intervenciones relacionadas con las enfermedades cardiovasculares en los adultos, así como también, para corregir defectos congénitos del corazón. La idea del desarrollo de la arteria coronaria, como resultado del crecimiento interno, cambió la comprensión de diversas variaciones y anomalías congénitas de estas arterias descritas en la anatomía macroscópica.

PALABRAS CLAVE: Arteria coronaria; Embriología; Corazón; Angiogénesis; Vasculogénesis.

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Correspondence to:

Prof. Dr. Carlos Alberto Mandarin-de-Lacerda
Laboratório de Morfometria e Morfologia Cardiovascular,
Centro Biomédico, Instituto de Biologia,
Universidade do Estado do Rio de Janeiro.
Av 28 de Setembro, 87 (fds) - 20551-030
Rio de Janeiro, RJ,
BRASIL

Phone/Fax: (+55. 21) 2587-6416

E-mail: mandarim@pq.cnpq.br

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