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Embryology of coronary arteries and anatomy/pathophysiology of coronary anomalies. A comprehensive update☆

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ABSTRACT

Objectives: This paper reviews new findings in both embryology of coronary arteries and in clinical observations of coronary artery anomalies.
Focus: Our presentation emphasizes studies based on: 1) newer methods of coronary development in animals and humans, and 2) intravascular ultrasonography to interpret pathophysiology and guide treatment of coronary anomalies.
Conclusions: New data reveal the roles of many cellular interactions and signaling pathways involved in the normal and abnormal formation of the coronary arterial system and the consequences of their defective formation. Pathogenetic developmental mechanisms include dysfunction of the Notch and Hypo signaling pathways, angiogenic and arteriogenic molecules, and neural crest cells. We addressed numerous clinically significant coronary anomalies and their prevalence in a general population (especially those characterized by an ectopic origin with aortic intramural course), and point out the critical relevance of understanding the variable mechanisms of coronary dysfunction, especially, fixed versus phasic stenoses or intermittent spasm, and individual severity of clinical presentations.

1. Introduction

The need to update our knowledge regarding the development of the coronary arteries, as well as to improve our understanding of the basic concepts of the complex field of coronary anomalies was recently recognized by a consensus document from the *Development, Anatomy and Pathology Working Group of the European Society of* Cardiology [1]. Our paper discusses recent discoveries in the fields of molecular biology and experimental embryology with those from recent clinical studies on the spectrum of coronary anomalies. The relevance of coronary anomalies is indicated by the recent MRI-based survey, suggesting that important coronary anomalies are present in 1,300,000 of the US population and are one of the main causes of sudden cardiac death in sportsmen and military recruits [2,3].

The coronary ostial and artery stem formation is initiated by ingrowth of a capillary plexus into the aortic sinuses[S.1], a complex process that requires the proliferation and migration of cells that originate outside the heart and then differentiate into endothelial (EC) cells, vascular smooth muscle cells (VSMCs) and fibroblasts [4].[S.2–S.5] The acquisition of an epicardial layer by the embryo is critical for the events that lead to the formation of an endothelium-lined network (vasculogenesis), the sprouting of these vascular channels (angiogenesis), and the addition of vascular smooth muscle cells (VSMCs) to form coronary arteries and arterioles (arteriogenesis). A major source of precursor coronary cells is the proepicardium at the dorsal aspect of the atrioventricular groove near the sinus venosus.[S.4,S.5] Coronary endothelial cells (ECs) are primarily derived from the sinus venosus and the endocardium [5],[S.6] and their role in coronary vasculogenesis requires Tbx5[S.7] and Tbx18 [6].

2. Normal coronary embryologic development

2.1. Primary capillary plexus

EC precursors assemble into primitive tubular structures in response to increased metabolic rate and thickening of the compact portion of the myocardium, a coronary event triggered by hypoxia inducing hypoxic factors 1α (HIF-1α) and HIF-1β[S.8] and leading to increased levels of VEGF mRNA.[S.9,S.10] HIF-1α also induces FGF-2 and PDGF, two additional important pro-angiogenic factors [7].[S.11] Sonic hedgehog (Shh)

☆ Subject terms: developmental biology, pediatrics, pathophysiology, vascular biology, coronary circulation, coronary artery anomalies.

Note: The references included in the text contain both customary digital reference number and some with the format S.# implying that the interested reader will find such additional references in the supplement material that is available online.

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signaling from the epicardium stimulates production of VEGF-A, VEGF-B, and angiopoietin-2 in the myocardium[S.12] and regulates the expression of VEGF-C in perivascular cells. VEGF and FGF signaling promote several critical events, necessary for the formation of the EC-lined tubular plexus.

2.2. Formation of the coronary ostia and proximal stems (Fig. 1)

As the common truncus subdivides into the aorta and pulmonary artery (at 42 days in the human embryo), ECs from a capillary ring encircling the aortic root strands penetrate the aortic wall, aided by local apoptosis [8].[S.13,S.14] Thus, the coronary ostia establish connections with the capillary plexus, and coronary circulation immediately commences, triggering recruitment of VSMCs, first at the coronary ostia and then, progressively, more distally in avian[S.2,S.5,S.13–S.15] and rodent[S.16,S.17] models, and in humans [9]. Such studies documented the similar invasion by capillaries, spindle cells and erythroblasts into the aortic root in animal models and in humans, validating the concept of studying coronary ectopia in animals. Fig. 2 provides histological sections from human embryos that illustrate progressive changes in the main coronary arteries and the ventricular wall compaction. Fig. 3 illustrates the time-line of cardiac and coronary growth milestones in human embryos.

2.3. Development of coronary ostia and proximal arteries

2.3.1. Localization of the coronary ostia

VEGFs' critical role in the formation of the coronary ostia is initiated by their receptors, at sites destined to form coronary ostia [10], and the proximal coronary trunks [11]. Absence of VEGF, especially the VEGF-B isoform, as well as that of PDGF-BB or FGF-2, and chemokine CXCL12 and its receptor CXCR4 were shown to inhibit ostial formation and limit recruitment of VSMCs [12,13].

2.3.2. Recruitment of VSMCs

Vascular smooth muscle cell precursor cells migrate to the heart with the proepicardium and subsequently differentiate[S.18], their recruitment is induced by the onset of coronary flow and the associated increased shear stress.[S.19] These mechanical factors increase transcription of both FGF-2 and PDGF-BB[S.20], which, in addition to VEGF, facilitate the formation of the tunica media of coronary arteries.

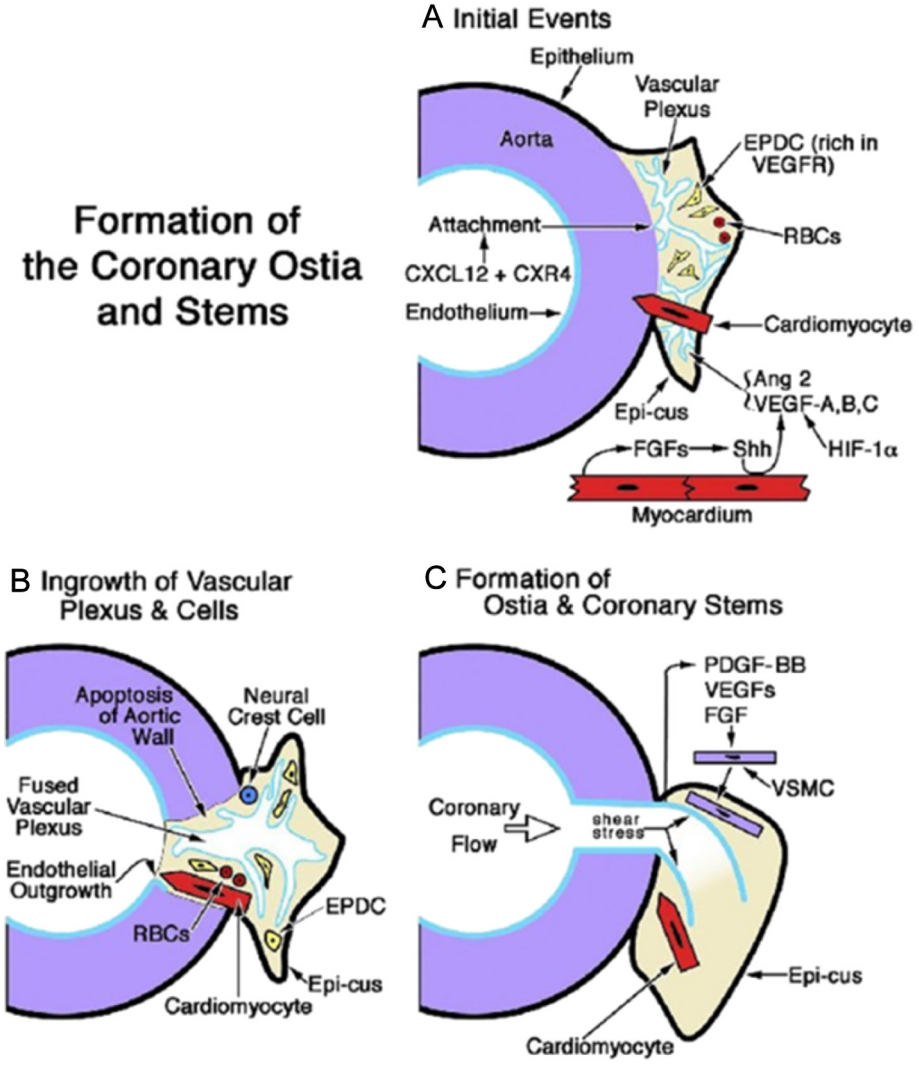

Fig. 1. A. Formation of the coronary ostia and stems is initiated when the capillary ring that encircles the aortic root expands and attaches as a vascular plexus (in response to CXCL12 + CXR4). The sites of ostial formation are adjacent to an epicardial cusp (Epi-cus), a thickened portion of the subepicardium, which contains epicardial derived cells (EPDC) that are rich in VEGF receptors and erythroblasts (RBCs). Cardiomyocytes guide the attachment of the vascular plexus. FGFs from the myocardium promote Sonic hedgehog (Shh) signaling, which together with hypoxia inducible factor-1 (Hif-1) stimulates VEGFs and angiopoietin (Ang) 2, thus facilitating angiogenesis of the vascular plexus. B. Myocardial-derived cardiomyocytes and neural crest cells facilitate the entry of the vascular plexus into an opening in the aortic wall, created by apoptosis. An endothelial ingrowth demarcates the pathway of the forming ostium. C. The onset of coronary flow and shear stress are key to the remodeling of the vascular plexus. Differentiation, migration, and attachment of VSMCs are influenced by 1) PDGF-BB activation in endothelial cells and the ligand's interaction with PDGFR-β in VSMC progenitors, and 2) the influence of VEGFs and FGFs.

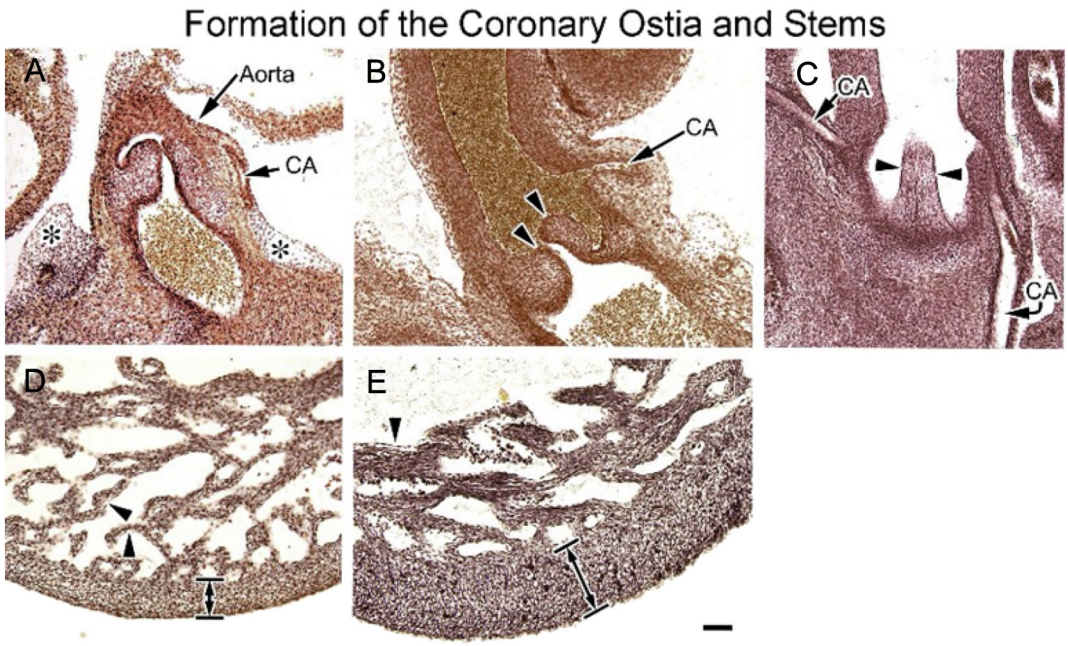

Fig. 2. Histological sections from human embryonic hearts (Carnegie Collection, National Museum of Health and Science, Silver Springs, MD). See reference S.4 for details. A. Formation of the left coronary artery (CA), which precedes formation of the right, passes through the epicardial cusp, an expanded subepicardium (asterisk), in a 44-day embryo. B. By the 52nd day of embryonic life the walls of the aorta and both coronary artery stems have thickened. Note the position of the ostium just above the free edges of aortic leaflets (arrowheads). C. The positions of the two main coronary ostia are seen at similar distances from the aortic valve (arrowheads) in this 54-day embryo. D. In this 47-day embryo, a stage when both ostia and coronary stems are present in all human hearts, the left ventricle's compact region (between the 2 arrows) is still relatively thin, whereas the spongy myocardium (arrowheads) is extensive. E. A significant compaction of the left ventricle occurs between 47 and 56 days (compare the compact regions in D and E). Panel A is from reference S.3 (Tomanek, 2016 with permission from Wiley). The scale bar for all images is 100 μm.

2.3.3. Role of neural crest cardiac cells (NCCs)

NCCs have been found to induce VSMC recruitment to the coronary stems[S.21], and to penetrate the aortic wall, appearing to guide the entry of ECs in chickens.[S.22] NCCs are also key for the recruitment of progenitor cells from the second heart field.[S.23] Moreover, NCCs, derived from progenitor cells originating in the preoptic brain region, migrate to the heart and differentiate into coronary VSMCs.[S.24]

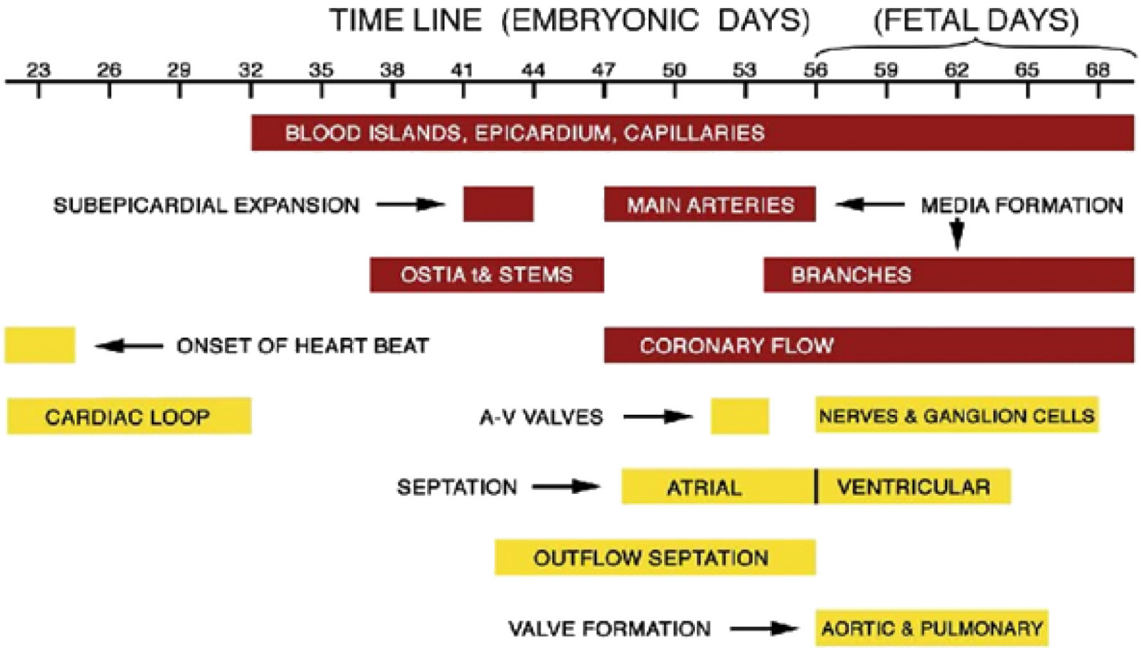

Fig. 3. Timeline of coronary heart developmental events in the human embryo. Blood islands are present in the heart by the onset of the second month, about the time that the heart completes looping and their presence extends into the fetal period. The ostia and coronary stems develop during a period of about 10 days, and coronary blood flow commences with the completion of ostial formation during the middle of the second month. The formation of the major coronary arteries is complete by the end of the second month. However, their branches continue the developmental process throughout the embryonic and early fetal periods. Note the cardiac developmental processes that coincide with coronary arterial formation. Outflow septation begins during the time of ostial and stem formation and is followed by the formation of the aortic and pulmonary valves.

2.4. Insights into coronary anomalies based on animal experiments

Animal models may provide new insights into the mechanisms that regulate formation of the coronary vasculature, especially: 1) revealing associations with developmental anomalies in humans, and 2) documenting errors in signaling pathways and molecules that may be involved in abnormal development. In humans, clinically relevant coronary anomalies occur in normal hearts, but are sometimes associated with congenital cardiac defects, most often persistent common truncus arteriosus, transposition of the great vessels, and tetralogy of Fallot [14,15].[S.25]

2.4.1. Anomalies of coronary origin or absence of a coronary ostium

Anomalous origin of a coronary artery from the aorta or coronary origin from the pulmonary artery have a common defect: the cells of the capillary plexus surrounding the aorta and pulmonary artery fail to reach and/or penetrate the two normal sites on the aorta. A VEGF-C deficiency has been documented to cause fewer aortic cardiomyocytes at the aortic root, sparse peritruncal vessels, and misplaced coronary ostia.[S.26] In Tbx1 mouse mutant hearts, either the left ostium forms at the right ventral sinus, with the right coronary, or the LCA originates from a single ectopic trunk with proximal intramural course (L-ACAOS-IM: see Clinical Portion).[S.27] Tbx1 expression in the myocardium is located adjacent to the left, but not right ostium.[S.28] The expression of Tbx1, and the key growth factor, Wt1 are in part regulated by the Hippo signaling pathway, via its Yap and Taz components, which regulate epicardial cell proliferation, epicardial-mesenchymal transition, and cell fate [16]. The gap junction protein, Cx43 is essential for coronary artery development and patterning, since Cx43α1 knockout mice are characterized by a variety of coronary anomalies.[S.29–S.31]

2.5. Notch signaling plays a major role in coronary vessel morphogenesis

Notch receptors with their ligands Delta and Jagged affect many cardiovascular events, including coronary morphogenesis (Fig. 4) [17–22]. The Notch pathway is crucial for the regulation of cell fate in the developing heart [19]. Ablation of the epicardium-specific Notch 1 receptor disrupts epicardial development, resulting in disorganization of the coronary vascular plexus and a deficit of coronary vessels in the compact ventricular region [17]. These findings suggest that deficits in the Notch pathway may underlie various coronary anomalies, notably, the intricate interplay between Notch and VEGF (reviewed by van den Akker et al. [23]). Notch signaling regulates epicardial-mesenchymal transition and is critical for the differentiation of coronary VSMCs [19]. It acts upstream of TGF-β and PDGFR-β, two key molecules for the induction of genes in epicardium-derived VSMC. Moreover, Notch plays a critical role in the differentiation of neural crest cell precursors into VSMCs[S.32], and endothelial expression of Jagged 1 is required for vascular smooth muscle development [24].

2.6. Coronary vessel growth and development of a mature compacted ventricle

A recent MRI-based study documented an 18.9% prevalence of left ventricular non-compaction (LVNC) in a general population of asymptomatic adolescents, screened by MRI to identify high-risk factors for SCD (sudden cardiac death) during sports activities [3]. LVNC is the most frequent cardiac anomaly in human populations. Animal models (mice) have provided evidence that Notch signaling plays a crucial role in ventricular myocardial structural development and that LVNC is due to altered Notch signaling [22]. The loss of Notch ligands Delta

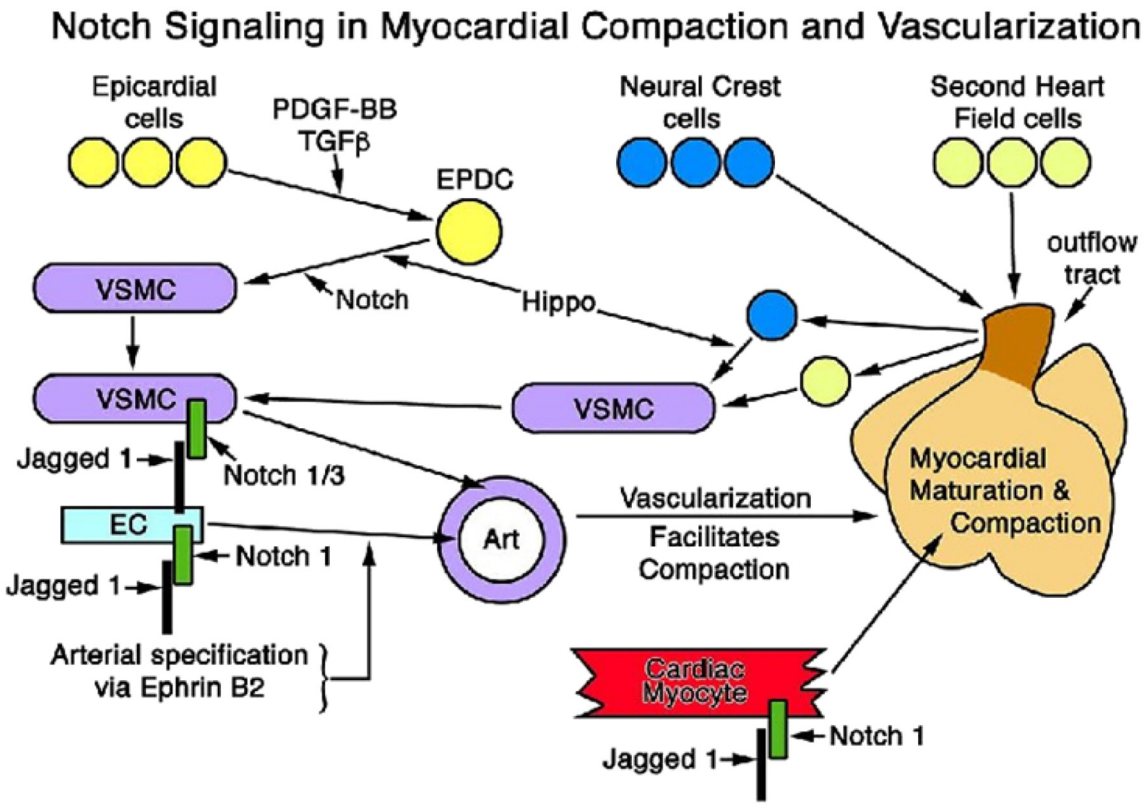

Fig. 4. Notch signaling plays an important role in coronary arterial development. Vascular smooth muscle cells (VSMC) that form the tunica media of coronary arteries are derived from progenitors that arise from the epicardium, neural crest and second heart field. Notch signaling, along with the Hippo pathway (involved with many signaling pathways, e.g., Wnt, and TGF-β) are essential for progenitor VSMC migration and differentiation in VSMCs. Arterial specification occurs via Ephrin B2 in ECs. Development of the tunica media of the coronary artery necessitates signaling from the Jagged 1 ligand from ECs to activate Notch on VSMCs. This ligand-receptor combination also plays a role in cardiomyocyte proliferation, a requirement for myocardial maturation and compaction. Thus, a lack of Notch signaling is a factor in left ventricular non-compaction (LVNC) maldevelopment, and the associated sparsity of coronary vessels in the compact region.

and Jagged is associated with the persistence of hyper trabeculation and LVNC [17]. Notch 1 is required for arterial endothelial commitment and differentiation, as well as vessel wall maturation during coronary vessel and myocardial growth [17]. The relationship between non-compaction and abnormal coronary vascular patterning is further supported by work demonstrating that germ line deletion of 14-3-3ε in mice limited the number and size of coronary vessels, and a lack of organized and remodeled coronary vasculature in the non-compaction phenotype.[S.33]

The relationship between non-compaction and endothelial cell function has most recently been documented in a study that established that deletion of the Ino80 chromatin remodeler in ECs prevents compaction in the mouse embryonic heart.[S.34] Moreover, the study revealed that coronary angiogenesis was dramatically decreased in this model of non-compaction. Using in vitro assays, the investigators found that ECs support myocardial growth independent of blood flow, a finding that supports the conclusion that EC Ino80 is necessary for the expansion of blood vessels needed to support myocardial expansion.

3. Coronary artery anomalies: types, individual severity, and clinical prognosis

Coronary artery anomalies are the product of variable developmental errors, at any suitable embryogenetic time, affecting any of the morphogenetic events mentioned in the preceding section of this manuscript. *Table S1* conceptualizes an anatomic outline of coronary anomalies.

3.1. Normal coronary tree pattern (Table S-1)

The coronary ostium is normally located at the middle, upper third of the appropriate sinus of Valsalva (SV), or respectively the RSV/LSV for the Right Sinus for the Right Coronary Artery (RCA) and the Left Sinus for the Left Coronary Artery (LCA). It is normal, or more frequent than in 1% of the general human population [25], that the coronary ostium is located in the middle third or up to 5 mm above the sinotubular junction, and its proximal arterial trunk courses at about 90 degrees from the aortic wall [25–27]. Coronary arteries are distributed from the ostia towards the periphery, by progressive subdivisions, implying a gradual decrease in their luminal diameters. Normally, the most distal coronary arteries (arterioles) terminate at the capillary network, the main site of metabolic exchanges with cardiac tissues. The arterioles (clinically also called: "microvascular segment") constitute the most important site of coronary vascular resistance and of its physiologic modulation.

The regions of the ventricles that depend on the 3 main coronary arteries are: 1) RCA, free wall of the right ventricle and the inferior-posterior septum (when the RCA is dominant); 2) LAD, anterior 2/3 of the ventricular septum and the anterolateral free wall; 3) Cx, posterolateral free wall of the left ventricle. The LAD and Cx most commonly (98% of cases) share a proximal common trunk (left main). The RCA is dominant (provides the posterior descending artery) in 75–90% of cases [25].

3.2. Spectrum of coronary artery anomalies

3.2.1. Ectopic ostium (Fig. S-1, Table S-1)

Although the left and right ostia may have multiple *alternative ectopic sites of origin* (L-ACAO or R-ACAO respectively) and courses, such ectopic origins may have potentially serious consequences only when featuring an intramural (IM) course (Fig. S-2). *IM proximal course* runs consistently inside the aortic tunica media for 3 to 12 mm, implying a stenosis by lateral compression and hypoplasia of a severity that is variable from case to case. As seen in Figs. S-3, S-4, stenosis also is associated with a phasic worsening during systolic aortic expansion [26–28]. Several specific types of L-ACAOS-IM (Figs. S-2, S-3, S-5) may occur, whereas R-ACAOS-IM occurs essentially in only one type: it originates at the left sinus of Valsalva (LSV), and always features some degree of intramural stenosis [28] (Figs. S-6, S-7). One rare type of L-ACAOS (Orthotopic, OT in Fig. S-5) is characterized by ostial location at the proper LSV, but with an acute proximal acute angulation and intramural proximal course with stenosis. Alternatively, the ostium may be more than 5 mm above the sinotubular junction in the ascending aorta (high-origin, HO) or the posterior, "non-coronary" sinus, where infrequently, it may have an IM course and stenosis (Fig. S-9). The most frequent case of L-ACAOS-IM features origin from the right sinus of Valsalva (isolated, or in common trunk with the RCA), and has the highest risk of SCD [3][S.1,S.26–S.29] due to left main trunk stenosis (Figs. S-2, S-3, S-5, S-8). In young athletes, the typical precipitating cause of SCD in L-ACAOS-IM is strenuous exercise [3]. In a recent large-scale, adolescent population screening by cardiac magnetic imaging, the prevalence of ACAOS was documented to be in the range of 0.44% of a general population exceeding 5000 subjects (Table S-1). In IM course, the mechanism and severity of stenosis is best quantified by intra-vascular ultrasound imaging [28].

Anomalous origin of the LCA or RCA from the pulmonary (*ALCAPA or ARCAPA*, respectively) indicates ectopic origin from the pulmonary artery (most frequently from the sinuses of the pulmonary valve adjacent to the aorta). In these cases, ischemia is not present during fetal life, nor during the first few weeks of postnatal life (because of the normal presence of pulmonary hypertension, before lung maturation). However, acute myocardial infarction may occur in infancy, when the physiologic drop in pulmonary pressure occurs. Myocardial failure can be the dominant clinical feature in adult patients (especially in ALCAPA). It is interesting to note that LV hypokinesia can be partially reversible in adult patients, even after delayed surgical repair of the anomaly (usually done by surgically by transferring the ectopic artery into the ascending aorta). Such an amazing result proves the phenomenon of "chronic hibernation", in which chronically-ischemic, depressed ventricular contractility recovers substantially, following effective revascularization.

L-ACAOS can also take *benign* courses. As seen in Fig. S-1, these include: a) retroaortic (RC), b) intraseptal or infundibular or subpulmonary (SP, Fig. S-4), c) pre-pulmonic (PP), e) retrocardiac (RC) [29–32]. Some anomalous courses (IS, RA, PP, Figs. S-2, S-4, S-10) may occasionally become symptomatic due to spastic angina, as recently documented by the acetylcholine test of endothelial dysfunction [27].

3.2.2. Congenital coronary ostial intrinsic anomalies

These include coronary ostial atresia or Stenosis (COSA). *Coronary Atresia* can be the result of isolated atrophy by occlusive membrane or ostial occlusion by dysplastic aortic valve undergoing progressive adhesion to the ostium. In atresia, the important identifying feature is the presence of a patent distal cul-de-sac of the LCA trunk, in which the distal LCA fills through "congenital collaterals", that are usually large (end-to-end anastomosis) and able to prevent functional ischemia, or myocardial scarring.

The frequently used term "*single coronary artery*" [27] is generally used even though the LAD, CX, and RCA are well formed. In such cases no artery is "missing," rather a common "single ostium" is the real anomaly in which one or two coronary arteries (CX, LAD, and RCA) have an ectopic origin from another sinus or artery. Ischemia is rare in hearts with an isolated "single" coronary artery, unless coronary arteriosclerotic disease is present or the ectopic artery has IM course with stenosis.

3.2.3. Anomalies of the mid-course

The terms "intra-myocardial anomalous course" or "*myocardial bridge* (MB)" indicate that a coronary artery, normally traveling subepicardially in humans, dips into the subjacent myocardium for some distance, and consequently is submitted to intra-myocardial systolic pressure (which is supra-systemic). In humans, such a variant is sometimes considered an anomaly implying dysfunction, but the only usual

and benign consequence is the production of some degree of phasic systolic narrowing resulting in only mild phasic systolic stenosis. Since about 80% of myocardial blood flow occurs in diastole and critical ischemia or infarction are extremely rare. The reasons why patients with myocardial bridges may have chest pain, or positive stress testing, or acute myocardial infarction are still controversial. However, recent evidence seems to suggest that an abnormal spastic tendency could occur intermittently at myocardial bridge sites, due to localized endothelial dysfunction [27]. In this regard, the most significant clinical evidence is based on acetylcholine testing of endothelial dysfunction, which occasionally indicates a transient, but fixed (in both systole and diastole) stenosis, that is immediately reversible with nitroglycerin administration (Figs. S-4, S-10).

3.2.4. Coronary artery aneurysm

Most frequently, ectasia or small aneurysms are idiopathic (atherosclerosis promotes mild coronary dilatation at its early stage), whereas some aneurysms are Kawasaki arteritis-related and appear at young age [33]. The clinical importance of such anomalies is related to a slow flow pattern (leading to mural thrombosis, distal embolism or local occlusion) or to spontaneous rupture (exceptional, in recent decades, since popularization of effective anti-hypertension medication).

3.2.5. Termination

Coronary anomalies of termination consist essentially of coronary artery fistulae, that are caused by either a connection of a distal arteriolar vessel to the left and/or right ventricle (multiple micro-fistulae), or by proximal arteries abnormally and congenitally connected with low-pressure cavities, e.g., systemic veins, or ventricles, or pulmonary arteries or veins. The functional impact of such coronary fistulous malformations varies greatly in human pathology. Multiple micro-fistulae are usually benign. Larger fistulae tend to progressively increase in size/flow with aging. Large fistulas can lead to aneurysmatic dilatation (mural clots and embolism) or they can cause coronary flow "steal" from neighboring arteries, through acquired collaterals; rarely, hemodynamic overload implied by short-circuiting blood (left-to-right blood shunting) can result in congestive heart failure (when the flow is above 750 cm^3/min).

3.2.6. Coronary artery coding system

A recent paper by Gittenberger-de Groot, et al. [34] proposes coding of coronary arterial origins and branching patterns in congenital heart disease. The system is considered as applicable in hearts with altered great artery relationships, "as well as cases with normally related great arteries."

4. Final considerations

Despite their potentially relevant clinical and scientific implications, coronary artery anomalies (CAA) and their development have not received sufficient attention. However, our understanding of the spectrum of CAA in human pathology and pathophysiology has been enhanced by recent discoveries from both basic and clinical sciences, especially by advances in molecular biology.

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Appendix A. Supplementary data

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