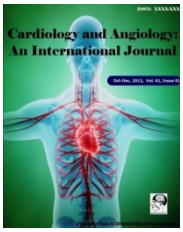

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Coronary Anomalies: Understanding of Normal Coronary Artery Development for Insight in Treatment of Coronary Artery Disease

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

Case Study

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ABSTRACT

Coronary artery anomalies (CAA) are rare congenital abnormalities with incidence of about 1% in the general population.[2]Unfortunately, despite the low incidence, CAA can cause sudden cardiac death. Identifying the course of the artery is critical for appropriate management. We present a rare case of the left coronary artery arising from the right coronary ostium with special emphasis on normal coronary artery development as possible insight for treatment of diseased heart.

Keywords: Coronary artery; coronary anomaly; neural crest cells; left coronary artery; sudden cardiac death.

1. INTRODUCTION

Coronary artery anomalies (CAA) are rare congenital abnormalities in part due to lack of defined symptoms [1]. In large longitudinal studies, the incidence of coronary anomaly is about 1% in the general population and 0.3% at autopsy [2]. Unfortunately, despite the low incidence, they account for 19% of sudden cardiac deaths (SCD) in athletes and is the second most frequent cause of exertion related cardiac deaths [1,5]. In general, CAA is

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diagnosed incidentally during angiography, but rare potential life threatening events such as arrhythmias, syncope, myocardial infarction has been documented [4].

Coronary artery anomalies have been well documented in the literature with published prevalence of the different variants, symptomatology and prognosis [1-5]; however, our understanding of coronary development and origin of coronary anomalies remains poor. We present a rare case of left coronary artery arising from the right coronary ostium. More specifically, we focus on the development of normal coronary vasculature and structural proteins involved in endothelial cell (EC) injury leading to coronary artery disease (CAD).

2. CASEREPORT

A 54 year –old Caucasian female with history of hypertension, hyperlipidemia and smoking was referred to us for evaluation after her outpatient preoperative adenosine cardiolite stress test demonstrated moderate size reversible defect in the anterior wall consistent with lesion in the left anterior descending artery territory. The patient denied chest pain, shortness of breath, or palpitations, though she did admit to having left arm numbness and tingling over a 2-3 week span. Physical examination was benign except for morbid obesity.

A cardiac catheterization was recommended because of abnormal stress test findings and atypical chest pains. The coronary angiography revealed no angiographic disease but demonstrated anomalous left coronary artery arising from right coronary cusp, arising from the same trunk as the right coronary artery Figs. 1-2. The vessel travels and then gives distribution to the anterior descending and circumflex artery. The left ventriculogram was normal. A right heart catheter was placed which revealed normal right heart pressures.

Pulmonary angiography Fig. 2 was performed to establish the course of the coronary artery but was not diagnostic. Follow up coronary CT was performed to confirm the course of the left main coronary artery Figs. 3-7.

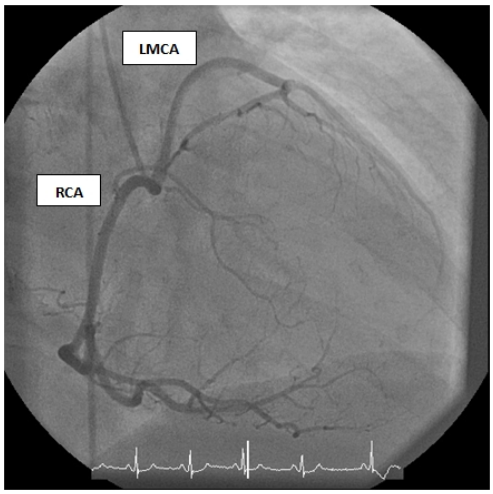

Fig. 1. Angiogram showing left main coronary artery arising from right coronary artery.
LMCA = Left Main Coronary Artery; RCA = Right Coronary Artery

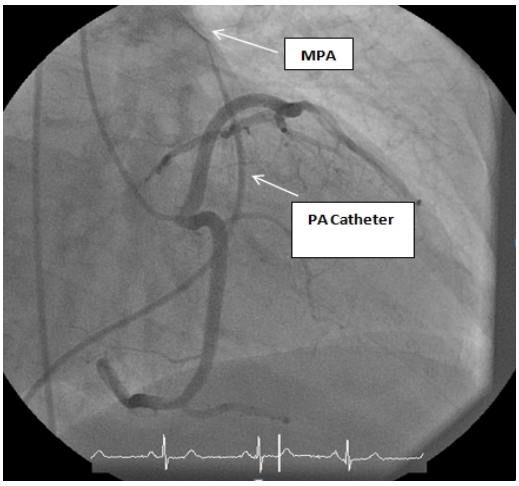

Fig. 2. Pulmonary artery catheter (PA catheter) in the main PA (MPA) with contrast injection to delineate course of anomalous LMCA

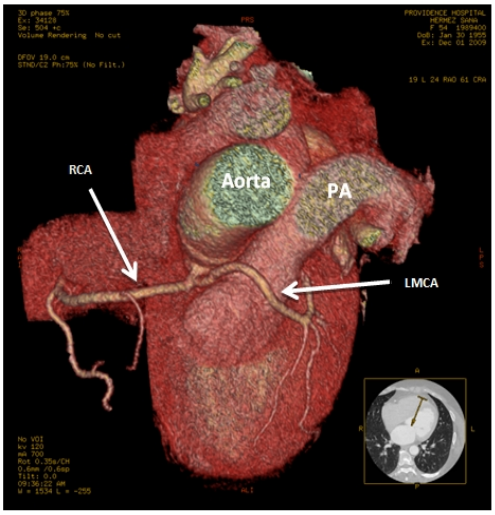

Fig. 3. Volume rendering coronary CTA showing anterior course of the LMCA with respect to main pulmonary artery.
RCA=Right Coronary Artery; LMCA=Left Main Coronary Artery;
PA=Pulmonary Artery

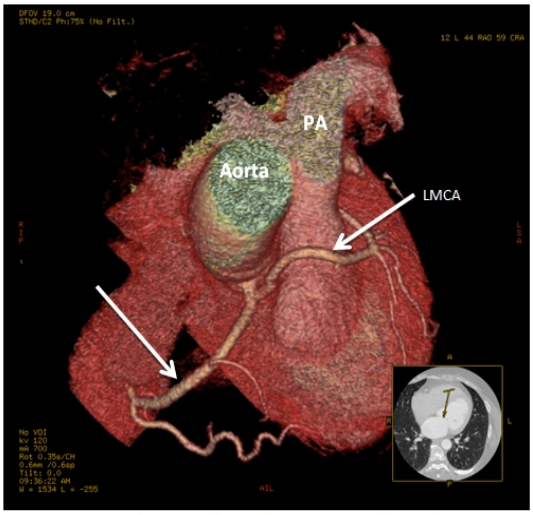

Fig. 4. Volume rendering CTA of anomalous LMCA arising from right coronary artery ostium.
RCA=Right Coronary Artery; LMCA= Left Main Coronary Artery;
PA=Pulmonary Artery

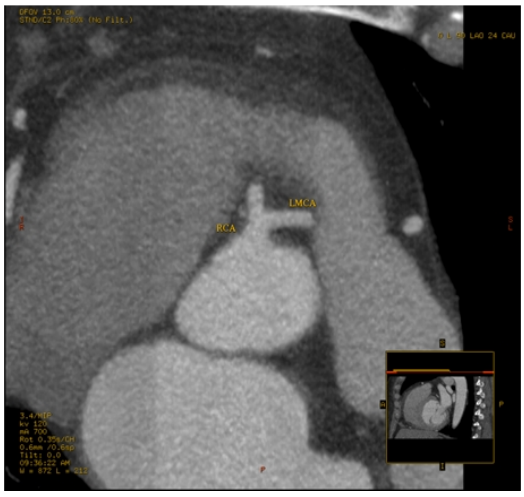

Fig. 5. Coronary CTA showing shared trunk of RCA and LMCA.
LMCA = Left Main Coronary Artery; RCA = Right Coronary Artery

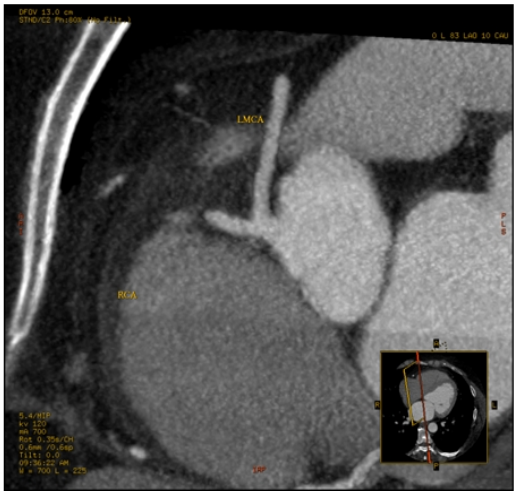

Fig. 6. cCTA showing shared trunk of RCA and LMCA.
cCTA = coronary CT Angiogram, RCA = Right Coronary Artery; LMCA = Left Main Coronary Artery

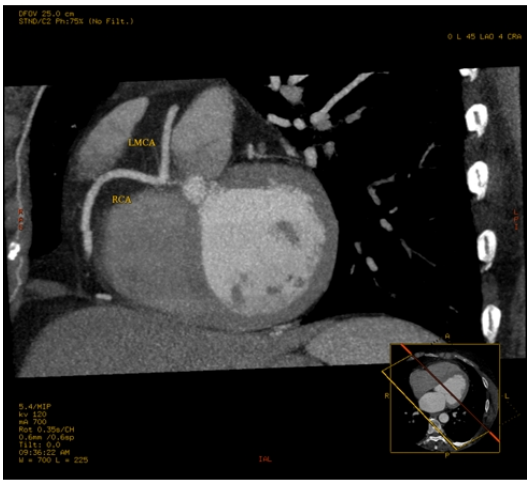

Fig. 7. CT angiogram showing shared ostium between LMCA and RCA.
LMCA = Left Main Coronary Artery; RCA = Right Coronary Artery

3. DISCUSSION

Documented incidence of CAA is reported <1% in the general population and 0.3% in autopsies. Majority (80%) are benign with respect to the anatomical variant and symptoms; however, 20% have life threatening variants resulting in SCD with exertion [4]. Our patient had a rare variant of left main coronary artery (LMCA) arising from the same ostium as the right coronary artery (RCA) and anterior to the pulmonary artery, which has been documented<0.15% in the literature. In this variant it is mandatory to determine whether the

course is malignant (between the aorta and pulmonary artery) or benign (anterior or posterior to the aorta). Fortunately, our patient had a benign course. Additional variants, incidence and potential clinical significance have been well established in the literature [1,2,4,5].

Despite their significance, the complete pathway for development of the coronary anatomy has not been fully elucidated. Hutchins and others developed studies providing a descriptive picture of the normal embryological stages of the human heart using histology with 3D reconstruction [8,21]. In normal development, the first feature of coronary vasculature is appearance of isolated individual blood islands with endothelial cells encapsulating nucleated red blood cells (RBC) during stage 13-15 of embryogenesis. Recent studies indicate strong association between coronary morphogenesis and epicardium. Whether initial coronary plexus arise from ventricular endocardium or sinus venous is still controversial. However, primary coronary plexus arelocated beneath the epicardium before migrating deeper into the myocardium to differentiate into coronary arteries and capillaries.

Over the next few weeks, there is continuous formation and loss of connection between the vascular plexus in the epicardium and myocardium. However, histological studies also show avascular zone around the endocardium during this stage, indicating absence of communication between the endocardium and the developing coronary vascular plexus. Grossly, blood islands appear in the apex at sites of indentation, the interventricular sulcus followed by atrioventricular groove and finally over other regions of the ventricle. Subsequent proliferation of the blood island cells leads to coalescence and formation of rudimentary vascular network. The coronary arterial vasculature forms after the development of venous plexus. Further epicardial formation of the blood islands was associated with loss of myocardial cardiac jelly, situated between the intraventricular cavity and myocardium. These rudimentary vascular plexus migrate up towards the base and the aorta.

Since clonal analysis studies revealed single subepicardial endothelial cells (EC) giving rise to both coronary veins and arteries, what factors are responsible for their final identity? Recent studies have improved our understanding of the initial growth factors and signaling pathways responsible for the primary differentiation of arterial from venous system [21]. By default, sprouting sinus venosus (SV) EC have venous markers such as Ephb4, Vegfr3, Np2 and COUP-TFII. As cells migrate away from SV, venous biomarker expressions begin to express arterial markers such as ephrinB2, Dll4, Notch and Dep [22]. The switch appears more temporo-spatially related but local growth factors such as fibroblast growth factor-1 (FGFR-1) and vascular endothelial growth factor (VEGF) appear to play a significant role in modulating these cell markers via paracrine and autocrine mechnisms [23]. Although arterial fate is believed to be preprogrammed, NOTCH signaling pathway which is upregulated by VEGF is critical for coronary vessel formation [24]. In knockout mice with Notch target receptors Hey1 and Hey2 mutations, the mutant mice phenotype failed to express arterial markers resulting in cardiac and coronary defects.

For long time, coronary arteries were assumed to bud from the aorta, specifically from the right and left coronary sinuses adjacent to the pulmonary artery trunk. Initial experiments failed to document apoptosis thus it was hypothesized that the geometric shape and wall tension of the aortic sinuses determined the development of coronaries arising from the aorta. It was proposed that the saddle shaped or catenoidal configuration of the aortic sinus with low net curvature resulted in increased wall tension in contrast to where the wall had a more positive curvature with less wall tension. The increased wall tension lead to budding of the endothelial tissue to form the initial right and left coronary ostia connection with the

vascular plexus [8]. Unfortunately, this did not provide explanation for mechanism of why the right and left ostia were more preferentially selected.

This paradigm was challenged by recent studies [17]. Despite new insight, exact mechanism for the connections between the vascular plexus and the aorta are still debatable. It was suggested that neural crest cells (NCC) may have a role since the ablation of NCCs result in anomalies between the aorta-coronary artery connections. However, subsequent studies confirmed neural crest cells are responsible for maintaining rather than genesis of coronary arteries [18,19]. More recent experiments with avian and rodents indicate that the vascular plexus surround the aorta and pulmonary trunk that then randomly penetrate the aortic wall in all three of the sinuses. Selection of right and left ostia is determined by local growth factors of specific concentration and density around the aortic sinus [20]. The final budding of the coronary arteries occur via apoptosis, allowing the penetrating vascular plexus to form channels with the aorta; non-ostial cells disappear. Exact mechanism of right and left ostia being selected is unknown but studies have shown that sites adjacent to the high VEGF concentration determined the ostia. The site of sinus aortic apoptosis for EC penetration into aortic wall is at sites with high VEFGR-2 density. Absence or loss of VEGFR-2 and subsequent Notch signaling results in coronary anomalies.

The coronary ostia and main coronaries are synthesized between days 44 and 49 of development (Stages 18-20) [8]. During this time, there are many factors that affect the formation of these coronary arteries, and thus an alteration in one of these factors could be the cause for the anomaly. Dysregulation of family of fibroblast growth factors (FGF) such as VEGF can delay formation or cause various abnormalities [9]. Hypoxia or hyperoxia can lead to defects in the coronary vasculature by affecting the expression of proteins. The HIF-1α protein is expressed at an increased level during hypoxic and hyperoxic conditions and the reduction of HIF-1α helps to rescue some of the coronary defects [10]. As mentioned earlier, NCC were initially believed to cause the formation of coronary ostia, but recent studies proved these cells are more responsible for maturation of the coronary vasculature. Ablation of these cells results in anomalies or conotruncial arteries. Perlecan, a proteoglycan found in basallaminae, has been associated with anomalous RCA if mutated [11].

After birth, the coronary vasculature continues to grow in concert with the increasing cardiac mass because of FGFs, VEGF, Integrin ὰVβ3, PECAM1 and VE-caderins proteins. Cellular turnover and vessel modification continues even after complete maturation occurs. Multiple sources are responsible for the continued angiogenesis, including the bone marrow [22]. Balance of homeostasis is maintained by endothelium derived paracrine factors. Vascular smooth muscle cells, which rarely proliferate under normal physiological state, can be abnormally upregulated to adopt a differentiated, proliferative state resulting in loss of cytoskeletal markers. This loss of delicate balance leads to endothelial cell damage via cytokine activation, upregulation of vasoconstrictor proteins and down regulation of vasoactive proteins and progress to neointimal proliferation and ultimately to arterial stiffness and lipid accumulation.

Fortunately, the heart heals itself by forming collateral circulation; thus, infarction is avoided in majority of the cases. Numerous factors contribute to the development of collaterals including nitric oxide, VEGF and Protein-1 synthesis. However, this process is limited. Regenerative medicine for tissue repair of injured coronary arteries require thorough knowledge of the factors responsible for the initial embryogenesis of the tissue, as well as the proteins involved in the maturation and maintenance. ECs may potentially be a source of

cells for development of genetically modified therapies in patients with coronary and myocardial diseases.

4. CONCLUSION

Coronary artery anomalies have many variants with a spectrum of clinical outcomes; fortunately the majority is benign. Considering the complex molecular mechanisms necessary for coronary vasculogenesis, angiogenesis and arteriogenesis signaling, there are many potential sources that can result in coronary anomalies and endothelial damage. Understanding of normal coronary artery development and potential source of anomalies may provide evidence at the structural, cellular, and molecular level for treatment of the diseased heart.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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