

# Coronary Arterial Development: A Review of Normal and Congenitally Anomalous Patterns

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## ABSTRACT

Coronary artery development is a delicate, complex, and finely tuned process that includes multiple interactions among many pathways, especially in the pericardium and the developing myocardium. There still exists some controversy on the exact origin of certain cellular components. Nevertheless, an understanding of this extremely important developmental process is paramount in identifying some of the causes of anomalous coronary development. There are different patterns of anomalous coronary arteries, with variable risk of myocardial ischemia, malignant arrhythmias, and sudden cardiac death. These anomalies can be broadly categorized into 2 basic anatomic subsets: those with origin of the anomalous coronary artery from the opposite aortic sinus, and those with origin of the anomalous coronary artery from the pulmonary artery. Diagnosis and management of such patterns continues to be challenging. A good knowledge of the normal and abnormal coronary artery development could potentially help us explore new avenues in the treatment of ischemic heart disease as well as anomalous coronary arteries.

### Overview of Embryonic Coronary Artery Development

Coronary artery disease is a major source of morbidity and mortality in the world. Congenital coronary artery anomalies, although less prevalent, are a potential cause for malignant arrhythmias, myocardial ischemia, and myocardial dysfunction.<sup>1</sup> An understanding of the process of coronary artery formation during development could potentially advance treatments, including potential coronary artery regeneration. The origins and mechanisms of coronary vessel development are not fully understood; however, a growing body of literature is emerging on this topic. From an evolutionary standpoint, the coronary arterial system evolved to supply the thick-walled myocardium, which cannot be appropriately supplied with oxygen and nutrients by simple diffusion from the heart lumen, as is the case in invertebrate animals and fish. Before 1989, it was generally believed that coronary arteries and veins developed from outgrowths from the aorta and the systemic venous sinus, respectively. However, in a study by Bogers et al, coronary arteries were identified even before the presence of coronary arterial orifices, which led to the novel concept of ingrowth instead of outgrowth of the coronary arterial vasculature.<sup>2</sup>

Epicardium (historically seen as part of the pericardium and referred to as “visceral pericardium”) is essential for coronary vessel development.<sup>3</sup> The term epimyocardium has been used, implying that the epicardium and myocardium may have a common origin. This theory

was challenged as early as 1909 by Kurkiewicz et al, but only recently has the separate origin of the visceral pericardium and myocardium become widely accepted.<sup>4</sup> The epicardium originates from an extracardiac structure, the proepicardium, which is located near the venous pole of the heart above the liver primordium (Figure 1).<sup>5</sup> Epicardial cells form a sheet of single cells that surround the heart and are necessary for coronary vessel formation. An elaborate interaction of epicardial cells with myocardial cells leads to the transformation of epicardial cells into mesenchymal cells, as precursors of building blocks of coronary vessels.<sup>6</sup> Interestingly, hematopoietic progenitor cells also play an important role in the transformation of epicardial into mesenchymal cells (Lluri et al, unpublished data, 2013). In humans, at about the 25th embryonic day, vessel-like structures are observed in the space between the epicardium and myocardium. However, it should be emphasized that at this point there is no blood flow in these vessel-like structures, which are not necessarily contiguous. In a matter of days, these structures fuse to form a vascular plexus. This diffuse elaborate vascular network ultimately contacts and penetrates the aortic root, leading to abrupt exposure to systemic pressure and high flow (Figure 2). These changes result in the maturation of these vessels, including migration of smooth-muscle cells, proper arrangement of these cells, growth of some vessels, and regression of others through apoptosis. Any abnormalities during this delicate, well-controlled process may lead to congenital coronary artery anomalies.

There are limited data on the molecular pathways involved in the formation of the coronary artery ostia. A high density of vascular endothelial growth factor (VEGF) receptors

The authors have no funding, financial relationships, or conflicts of interest to disclose.

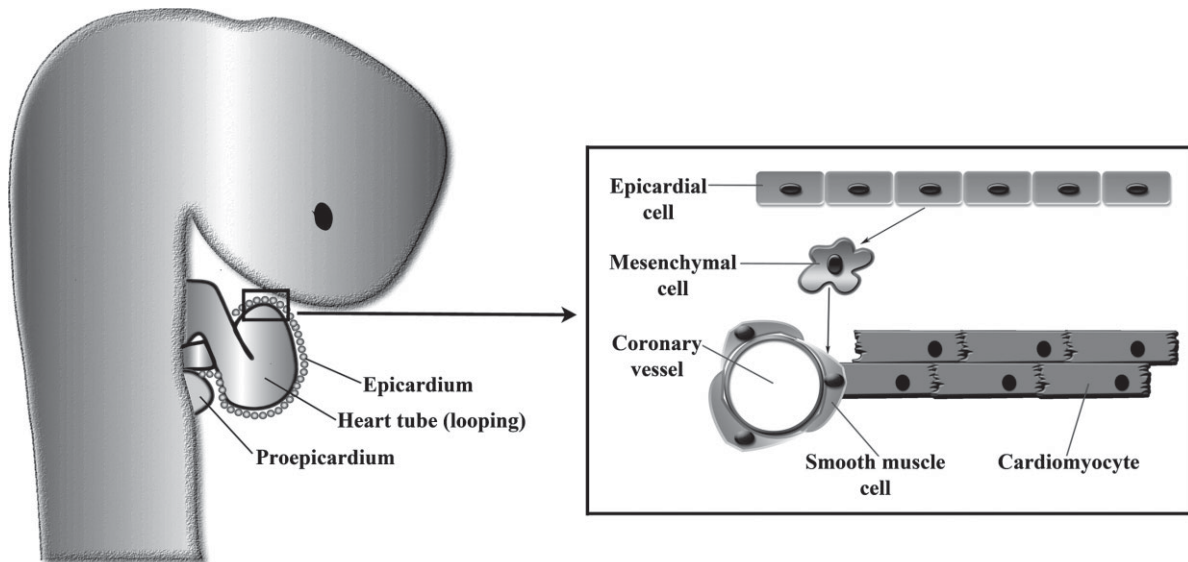


Figure 1. Epicardium and coronary artery development.

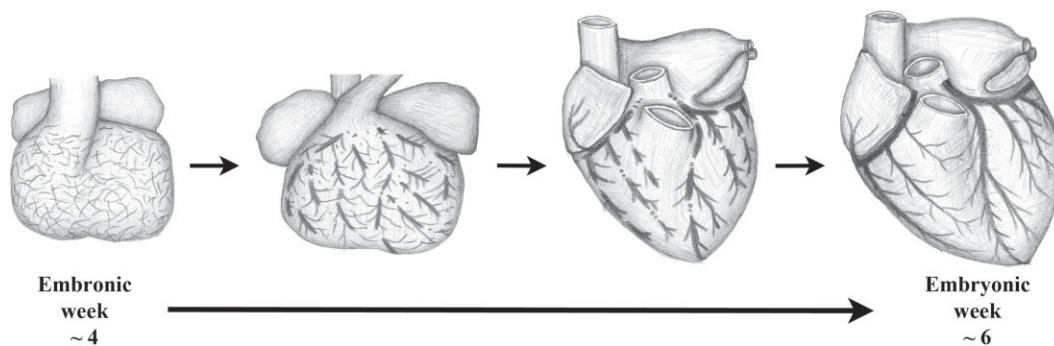


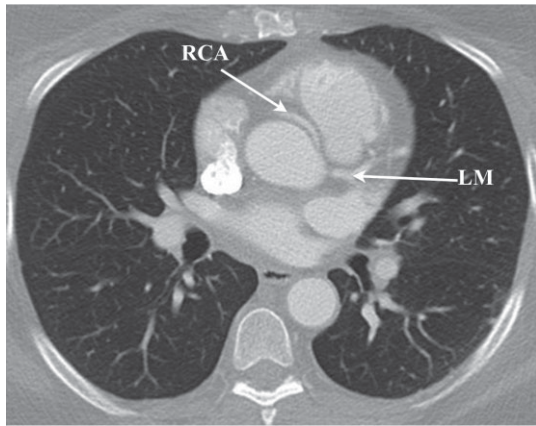
Figure 2. Development of coronary vessels during embryogenesis.

(VEGFR-2 and VEGFR-3) at the sites of coronary ostia underlies the importance of VEGF and its receptors in the process of coronary stem formation and penetration of the aorta.<sup>7</sup> Furthermore, animal studies support the role of neural crest cells in the formation of coronary artery stems; experimental ablation of the neural crest cells results in a single coronary artery stem.<sup>8</sup> In addition, a mutation to perlecan, a heparin sulfate proteoglycan expressed in the basement membrane during development, has been associated with anomalous origin of the coronary arteries.<sup>9</sup> Interestingly, similar coronary anomalies occur with mutations to connexin43, a gap junction complex.<sup>10</sup> Further characterization of these pathways may lead to a better understanding of the molecular signals responsible for the formation of anomalous coronary arteries.

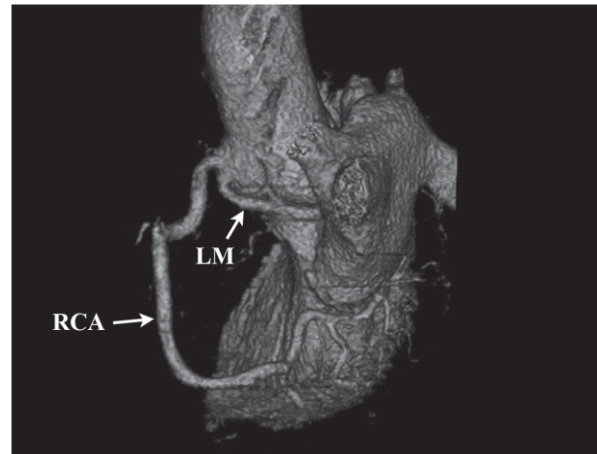
Recent studies suggest that coronary arterial and venous vessel development originates from different endothelial embryonic cell populations, anatomically from different sites, and at different times<sup>11,12</sup> Although there is a growing body of knowledge dealing with coronary arterial development, there is a paucity of knowledge on the embryologic development of the cardiac venous system.

### Coronary Artery Anomalies

Historically, coronary artery anomalies have been defined and described according to an elaborate anatomic classification system.<sup>13,14</sup> However, there has been a growing emphasis on categorization of coronary artery anomalies according to prognostic significance, specifically the increased risk of malignant arrhythmias and sudden cardiac death associated with certain subsets.<sup>1,15</sup> Clinically significant coronary arterial anomalies may be classified into 2 basic anatomic subsets: those with origin of the anomalous coronary artery from the opposite aortic sinus, and those with origin of the anomalous coronary artery from the pulmonary artery (PA). Anomalous coronary artery from the opposite sinus includes the right coronary artery (RCA) arising from the left sinus (ARCA) or the left coronary artery (LCA) arising from the right sinus. In this category, the most common finding is the left circumflex artery (LCX) arising from the right sinus (ALCX).<sup>16</sup> This is followed by ARCA (Figure 3), and lastly the left main coronary artery (LM) arising from the right sinus (ALM; Figure 4). There are other unusual subsets, which include an anomalous left anterior descending artery (LAD) originating from the



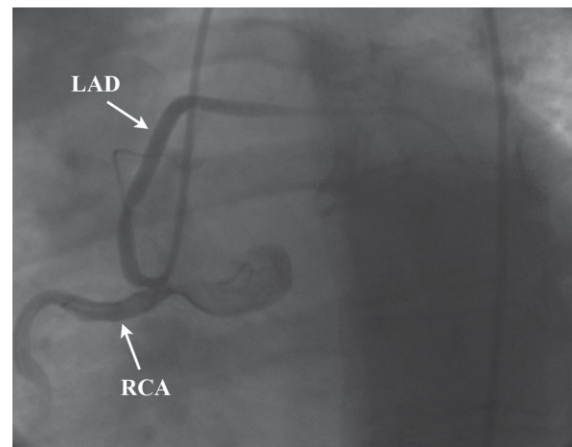
**Figure 3.** RCA arising from left sinus. Abbreviations: LM, left main coronary artery; RCA, right coronary artery.



**Figure 4.** LM arising from right sinus. Abbreviations: LM, left main coronary artery; RCA, right coronary artery.

RCA (Figure 5), occasionally seen in tetralogy of Fallot and other congenital abnormalities.<sup>17</sup> If the anomalous coronary artery courses in the sulcus between the PA and the aorta, which occurs in ALM, there is an increased risk of malignant arrhythmias and sudden death.<sup>18</sup> The increased risk may be due to the intra-arterial course of the anomalous coronary with resultant compression or the larger myocardial mass supplied by anomalies of this type. The presence of a slit-like origin and intramural course of the proximal coronary artery arising from the contralateral sinus likely plays an important role in coronary ischemia and malignant arrhythmias.<sup>19–21</sup> Anginal symptoms and malignant arrhythmias often occur with exercise and are likely caused by myocardial ischemia that may be due to any or all of the above factors.<sup>22</sup> Surgical treatment traditionally has been performed for symptomatic patients, or those with evidence of stress-induced ischemia or ventricular arrhythmias, and is considered standard of care for asymptomatic patients with ALM because of the increased risk of mortality in these patients. Various surgical techniques have been described, from coronary artery bypass grafting to unroofing of the proximal anomalous coronary to reimplantation of the affected coronary artery. Transcatheter interventional angioplasty and stenting is a potential alternative with good immediate results but limited long-term data available.<sup>23</sup> For patients who do not have ALM and who are truly asymptomatic and have no evidence of stress-induced ischemia or stress-induced arrhythmias, there is no clear consensus on management, as the risks of the coronary repair or stenting need to be weighed against the low risk of malignant arrhythmias or death. There may be a role for intravascular ultrasound and invasive fractional flow reserve and pressure measurement at rest and with pharmacologic stress or exercise in determining the hemodynamic significance of an anomalous coronary artery from the contralateral aortic sinus. The limited published case reports on the use of these more nuanced tools for coronary flow and pressure assessment are compelling.<sup>24–27</sup>

A coronary artery originating from the PA is much more rare, occurring in about 1 in 300 000 cases, more commonly involving the LCA originating from the main PA.<sup>15,28</sup> These patients often present early in life with signs of congestive heart failure, dilated cardiomyopathy, and



**Figure 5.** LAD arising from RCA. Abbreviations: LAD, left anterior descending artery; RCA, right coronary artery.

mitral regurgitation. However, in the presence of a well-developed collateral network and pulmonary hypertension, these patients may not be diagnosed until later in life. Nevertheless, surgical therapy is warranted in patients with such anomalies, emphasizing the need for a 2-coronary system for improved survival.<sup>29</sup> Various surgical approaches have been described, including reimplantation of the LCA into the aorta, bypass grafting and ligation of the origin at the PA, and baffling of the aorta to the ostium of the anomalous left coronary.<sup>30</sup>

In certain conditions, the anomaly is not at the origin of the arteries. Myocardial bridging, when a segment of the vessel enters the myocardium and courses for a variable length before reemerging back to the epicardium, was described as early as the 18th century, but its clinical significance was not understood until much later.<sup>31,32</sup> There has been a significant variation on the reporting of the frequency of myocardial bridging. When diagnosed clinically, the frequency ranges from 0.5% to 40%, and 15% to 85% when found at autopsy.<sup>33</sup> This discrepancy suggests that not all myocardial bridges cause symptoms. However,



when symptoms are present, usually they are secondary to ischemia.<sup>34</sup> The most common vessel affected is the middle portion of the LAD artery; however, the RCA and LCX can also be affected.<sup>35</sup> In addition to coronary angiography, newer techniques such as intravascular ultrasound can be used to detect not only the presence of myocardial bridging, but arterial-wall morphology as well.<sup>36</sup> Medical therapy, including  $\beta$ -blockers or calcium channel blockers, is considered first-line therapy for symptomatic patients. If patients continue to remain symptomatic despite medical therapy, supra-arterial myotomy has been reported as an alternative.<sup>37</sup> Stenting is an alternative as well; however, restenosis and stent fracture need to be taken into consideration when choosing this strategy.<sup>38,39</sup>

Finally, a coronary fistula is an abnormal terminal connection between a coronary artery and any of the cardiac chambers or the great vessels. Krause reported coronary fistulas as early as 1865, but it was Maude Abbott in 1906 who described in detail the pathology of this condition.<sup>40</sup> Congenital coronary artery fistulas represent 0.4% of all congenital heart defects.<sup>41</sup> Furthermore, coronary artery fistulas may occur secondary to chest trauma or iatrogenic causes. Most commonly, congenital artery fistulas arise from the RCA and drain into the right heart chambers; those draining in the left ventricle or left atrium comprise 17% and 6%, respectively.<sup>42</sup> Symptoms, including fatigue, shortness of breath, angina, and eventually congestive heart failure, may occur and are related to the size of the fistula and the resultant shunt. Symptoms typically occur in the adult population and are far less common in infants or children.<sup>43</sup> Coronary angiography remains the gold standard for the diagnosis of coronary artery fistulas; however, electrocardiographically gated computed tomography angiography can readily and noninvasively identify these structures. Once diagnosed, the management remains a topic of controversy.<sup>44</sup> Surgical intervention, first described in 1947 by Bjork and Crafoord, is recommended for symptomatic patients.<sup>45</sup> Almost 40 years later, in 1983, the first successful transcatheter closure of a coronary fistula was performed.<sup>46</sup> Since then, transcatheter closure has become an acceptable alternative to surgical repair in select patients.<sup>44</sup> However, there is no clear consensus on the management of asymptomatic coronary fistulas, which are found incidentally. Some authors suggest that if asymptomatic coronary fistulas are hemodynamically significant, they should be closed at the time of diagnosis.<sup>47</sup> Other groups advocate for intervention regardless of symptoms or hemodynamic findings, because of future possible complications.<sup>48</sup>

## Conclusion

Coronary artery development is a delicate and finely tuned process that includes a complex interaction among the pericardium and myocardium, involving multiple cellular pathways and yet-to-be-identified other factors. There has been a growing interest in the study of coronary artery development. Such an understanding is paramount in identifying some of the causes of anomalous coronary development. There are different patterns of anomalous coronary arteries, with variable risk of myocardial ischemia, malignant arrhythmias, and sudden cardiac death. A good understanding of this process could potentially help us explore

new avenues in the treatment of ischemic heart disease as well as clinically relevant anomalous coronary arteries.

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