# Coronary Anomalies

## Incidence, Pathophysiology, and Clinical Relevance

Paolo Angelini, MD; José Antonio Velasco, MD; Scott Flamm, MD

Coronary artery anomalies are some of the most confusing, neglected topics in cardiology. Although the medical community and general public are increasingly aware that coronary anomalies can be fatal (typically in young, previously "healthy" athletes),[1] the reasons for the sudden fatal event and the frequency with which it occurs are generally unclear. To promote a less casual approach to this subject, we review some basic, substantive, and methodological questions about coronary anomalies.

### Definitions and Incidence

According to the literature, coronary anomalies affect ≈1% of the general population; this percentage is derived from cineangiograms performed for suspected obstructive disease.[2–4] Necropsies yield an even lower incidence: in 18 950 necropsies, Alexander and Griffith[5] observed only 54 coronary anomalies (0.3%). Unfortunately, these studies are limited by entry biases and a lack of clear diagnostic criteria.

Angelini and coworkers[6] propose that, because of its substantial variability, normal and anomalous coronary anatomy should be characterized. Accordingly, an anomaly should be defined as any coronary pattern with a feature (number of ostia, proximal course, termination, etc) "rarely" encountered in the general population. By determining the incidence of anatomic variants in a large population, acceptable definitions of normal and anomalous anatomy could be established and the clinical importance of anomalous variants ascertained. Ideally, this effort would be overseen by an expert ad hoc committee and would generate a rational paradigm, perhaps along the lines of Table 1. Previous authors have proposed a preemptive anatomo-clinical classification that considers anomalies as "major" or "minor" (ie, incapable of causing relevant clinical consequences)[2,7–10]; in view of our inadequate knowledge of the pathophysiology and clinical consequences of coronary anomalies, this scheme seems inappropriate.[11]

Additional studies examining the incidence of coronary anomalies in large populations are needed to overcome the classification issue and any referral bias. With regard to the latter point, necropsies are not performed routinely in the United States; rather, they are usually done for medico-legal purposes, after a violent or otherwise non–hospital-based death. Since 1960, the necropsy rate for in-hospital deaths has decreased from 50% to 10%.[12] Therefore, the incidence of coronary anomalies in necropsy patients may be skewed.[6] This issue is fundamental because sudden death is frequently the only symptom of an anomaly. Similarly, angiography is usually performed because ischemia is suspected. Moreover, well-known experts on coronary anomalies are consulted preferentially. The implications of pathological studies at referral centers were summarized by Maron and Roberts.[13] In patients with anomalous left coronary artery arising from the right sinus, most (≈59%) die before age 20, usually during or shortly after vigorous exertion. Such a statement can be made by pathologists to whom unusual cases are referred; it cannot be lightly shared by cardiologists, who during angiography incidentally observe even more of these anomalies than do pathologists.

Van Camp and coworkers[14] reported that coronary anomalies cause 11.8% of deaths in US high school and college athletes. According to the Sudden Death Committee of the American Heart Association,[15] coronary anomalies cause 19% of deaths in athletes. Moreover, Burke and colleagues[16] reported that, in 14- to 40-year-old individuals, coronary anomalies are involved in 12% of sports-related sudden cardiac deaths versus 1.2% of non–sports-related deaths. In assessing 162 sudden deaths in a young general population, Drory and associates[17] found only 1 coronary anomaly. Similar findings suggest that coronary anomalies can be lethal only during or shortly after strenuous physical activity, typically in young individuals (Table 2).[17–19]

Until the pathophysiological mechanisms of ischemia and sudden death are clarified, in patients who die inexplicably, the presence of an anatomically variant coronary pattern should be considered a possible but unproved cause of death. Examples of uncertain assignment of cause-effect relationships in these instances include most reported cases of muscular bridges,[20] single coronary artery (not coursing between the aorta and pulmonary artery),[21,22] and hypoplastic coronary artery.[23,24] Indeed, sudden unexpected death is frequently unexplained even at necropsy.[17]

To our knowledge, the first investigators to adopt strict criteria for assessing coronary normality/abnormality were Angelini and coworkers,[6] who performed an ad hoc study of 1950 consecutive cineangiograms to rule out or evaluate coronary artery disease and found a 5.6% incidence of coronary anomalies (Table 3). This incidence is higher than

From the Departments of Adult Cardiology (P.A., J.A.V.) and Radiology (S.F.), Texas Heart Institute at St Luke's Episcopal Hospital, Houston, Tex.
Guest Editor for this article was Robert A. O'Rourke, MD, University of Texas Health Science Center–San Antonio, San Antonio, Tex.
Correspondence to Paolo Angelini, MD, PO Box 20206, Houston, TX 77030. E-mail leachman@ix.netcom.com
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**TABLE 1. Classification of Coronary Anomalies Observed in (Normal) Human Hearts**

- Anomalies of origination and course
  - Absent left main trunk (split origination of LCA)
  - Anomalous location of coronary ostium within aortic root or near proper aortic sinus of Valsalva (for each artery):
    - High
    - Low
    - Commissural
  - Anomalous location of coronary ostium outside normal "coronary" aortic sinuses
    - Right posterior aortic sinus
    - Ascending aorta
    - Left ventricle
    - Right ventricle
    - Pulmonary artery. Variants:
      - LCA arising from posterior facing sinus (ALCAPA)
      - Cx arising from posterior facing sinus
      - LAD arising from posterior facing sinus
      - RCA arising from anterior right facing sinus
      - Ectopic location (outside facing sinuses) of any coronary artery from pulmonary artery:
        - From anterior left sinus
        - From pulmonary trunk
        - From pulmonary branch
    - Aortic arch
    - Innominate artery
    - Right carotid artery
    - Internal mammary artery
    - Bronchial artery
    - Subclavian artery
    - Descending thoracic aorta
  - Anomalous origination of coronary ostium from opposite, facing "coronary" sinus (which may involve joint origination or adjacent double ostia). Variants:
    - RCA arising from left anterior sinus, with anomalous course:
      - Posterior atrioventricular groove* or retrocardiac
      - Retroaortic*
      - Between aorta and pulmonary artery*
      - Intraseptal*
      - Anterior to pulmonary outflow* or precardiac
      - Posteroanterior interventricular groove*
    - LAD arising from right anterior sinus, with anomalous course:
      - Between aorta and pulmonary artery
      - Intraseptal
      - Anterior to pulmonary outflow or precardiac
      - Posteroanterior interventricular groove
    - Cx arising from right anterior sinus, with anomalous course:
      - Posterior atrioventricular groove
      - Retroaortic
    - LCA arising from right anterior sinus, with anomalous course:
      - Posterior atrioventricular groove* or retrocardiac
      - Retroaortic*
      - Between aorta and pulmonary artery*
      - Intraseptal*
      - Anterior to pulmonary outflow* or precardiac
      - Posteroanterior interventricular groove*
    - Single coronary artery
- Anomalies of intrinsic coronary arterial anatomy
  - Congenital ostial stenosis or atresia (LCA, LAD, RCA, Cx)
  - Coronary ostial dimple
  - Coronary ectasia or aneurysm
  - Absent coronary artery
  - Coronary hypoplasia
  - Intramural coronary artery (muscular bridge)
  - Subendocardial coronary course
  - Coronary crossing
  - Anomalous origination of PD from anterior descending branch or septal penetrating branch
  - Absent PD or split RCA:
    - Proximal+distal PDs, arising from separate RCA sources
    - Proximal PD arising from RCA, distal PD arising from LAD
    - Proximal PD arising from RCA, distal PD arising from Cx
  - Absent LAD or split LAD:
    - Large first septal branch and small distal LAD
    - Double LAD
  - Ectopic origination of first septal branch
- Anomalies of coronary termination
  - Decreased number of arteriolar/capillary ramifications (?)
  - Fistulas from RCA, LCA, or infundibular artery to:
    - Right ventricle
    - Right atrium
    - Coronary sinus
    - Superior vena cava
    - Pulmonary artery
    - Pulmonary vein
    - Left atrium
    - Left ventricle
    - Multiple, right and/or left ventricles
- Anomalous collateral vessels

*If a single, common ostium is present, the pattern is considered to represent "single" coronary artery.

Cx indicates circumflex; LAD, left anterior descending coronary artery; LCA, left coronary artery; PD, posterior descending branch; and RCA, right coronary artery.

Modified from Angelini P. Normal and anomalous coronary arteries: definitions and classification. *Am Heart J.* 1989;117:418–434.

that usually cited in angiographic reports in the literature. The discrepancy probably results from the use of strict methodology rather than a referral bias, which would have inflated the data only mildly. In a specific, detailed, prospective study, the expected incidence of necropsy-diagnosed coronary anomalies would be even higher. For example, if diagnosed with microdissection, myocardial bridges might be common enough to be considered a normal variant. We favor the following definitions: *normal*, any morphological feature

**TABLE 2. Incidence of Sudden Cardiac Death Related to Coronary Artery Anomalies**

| Group (Age) | No. of Deaths | Deaths Related to Coronary Anomalies, % |
|---|---|---|
| Exercising individuals, overall (8–66 y)[18] | 550 | 11 |
| General population (<40 y)[17] | 162 | 0.6 |
| Competitive athletes (mean age, 17 y)[19] | 134 | 23 |
| Joggers and marathon runners (30–46 y)[18] | 120 | 1.6 |
| Exercising individuals, Maryland State[18] | 62 | 0 |

observed in >1% of an unselected population; *normal variant*, an alternative, relatively unusual, morphological feature seen in >1% of the same population; and *anomaly*, a morphological feature seen in <1% of that population.

The incidence of coronary anomalies is relevant not only for conceptual and educational purposes but, more importantly, for public health issues. Though obtained from small studies, the data imply that, of the total American population (285 000 000), ≈16 000 000 individuals (5.6%)[6] have some kind of coronary anomaly. If 19% of sudden deaths in young athletes are related to these anomalies,[15] they should be a healthcare priority (with regard to screening, clinical recommendations, prevention, and treatment).

## Noninvasive Imaging and Screening Methods

In addition to coronary angiography, transesophageal echocardiography[25–27] also may clinically detect coronary anomalies, but this method is not totally noninvasive and is too costly for screening large populations. In a continuous series of 2388 transthoracic echocardiograms obtained in children, Davis and colleagues[28] found 4 anomalies of coronary origination (0.17%); in 1 case, a negative echocardiographic finding was followed by sudden death related to a coronary anomaly newly found at necropsy, raising doubts about this method's predictive value.

Contrast-enhanced electron-beam tomography[29] has also been recommended. It offers excellent spatial resolution and identifies most anomalies of coronary course, but it uses ionizing radiation and potentially nephrotoxic or allergenic contrast agents.

MRI[30–33] holds the greatest appeal because it avoids radiation and contrast agents and yields excellent images at expert centers. In determining coronary origination, MRI may surpass conventional angiography, especially in patients with congenital defects.[33] For isolated coronary anomalies, MRI is similarly successful,[30–33] although series remain small. Its greatest limitation is in determining the distal coronary course. Therefore, this technique is less helpful in evaluating fistulas, coronary origination outside the normal sinuses (eg, from a ventricle or pulmonary artery), and collateral vessels. Furthermore, visualization of the posterior descending branch is problematic.

## Pathophysiological Mechanisms

Coronary anomalies have been implicated in chest pain, sudden death, cardiomyopathy, syncope, dyspnea, ventricular fibrillation, and myocardial infarction.[6] Quite rarely, they have been related to reproducible effort angina, as seen in coronary obstructive disease. A causal relationship may be suggested by solid evidence (for example, the relationship between anomalous origin of left coronary artery from pulmonary artery [ALCAPA] and acute anterolateral myocardial infarction in newborns) or by circumstantial, but inadequate, evidence (for example, myocardial bridges in sudden-death victims).[11] Anomalous origination of the left coronary artery from the right sinus is consistently related to sudden death (59% of cases), which follows exercise in 81% of events.[18]

Coronary anomalies are usually compatible with normal prenatal myocardial development and postnatal growth and function, even permitting intense athletic activity. Nevertheless, the anomaly sometimes leads to a pathological state, which usually originates suddenly and may have catastrophic consequences. Nonhuman models of anomalies do exist; many mammals and birds have muscular bridges,[6] and anomalous coronary origination is frequently seen in inbred Syrian hamsters,[34] but these animal models have not undergone functional testing. Such testing would be a unique opportunity for studying pathophysiological mechanisms.

Coronary anomalies might have clinical consequences other than those strictly related to myocardial ischemia (Table 4); these consequences might include volume overload (in cases of coronary fistulas), aortic-root distortion (in cases of very large coronary fistulas or aneurysms), bacterial endocarditis, complications during aortic valve surgery or coronary angioplasty, and misdiagnosis (as in many cases of "missing" coronary arteries).[6] However, because the coronary vessels primarily supply metabolic support to the dependent myocar-

**TABLE 3. Incidence of Coronary Anomalies and Dominance Patterns, as Observed in a Continuous Series of 1950 Angiograms[6]**

| Variable | Number | Percentage |
|---|---|---|
| Coronary anomalies (total) | 110 | 5.64 |
| Split RCA | 24 | 1.23 |
| Ectopic RCA (right cusp) | 22 | 1.13 |
| Ectopic RCA (left cusp) | 18 | 0.92 |
| Fistulas | 17 | 0.87 |
| Absent left main coronary artery | 13 | 0.67 |
| Cx arising from right cusp | 13 | 0.67 |
| LCA arising from right cusp | 3 | 0.15 |
| Low origination of RCA | 2 | 0.10 |
| Other anomalies | 3 | 0.27 |
| Coronary dominance patterns | | |
| Dominant RCA | 1641 | 89.1 |
| Dominant LCA (Cx) | 164 | 8.4 |
| Codominant arteries (RCA, Cx) | 48 | 2.5 |

Cx indicates circumflex artery; LCA, left coronary artery; RCA, right coronary artery; and split RCA, duplication of the posterior descending branch of the right coronary artery.

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**TABLE 4. Possible Clinical Consequences of Coronary Anomalies[6]**

| | | Proof of Action | | |
|---|---|---|---|---|
| Clinical Consequence | Coronary Anomaly | Certain | Possible | Unlikely |
| Misdiagnosis | Missing coronary artery | + | | |
| | Hypoplastic coronary artery | | + | |
| Myocardial ischemia, primary (fixed) | Absent coronary artery | | | + |
| | Hypoplastic coronary artery | | | + |
| | Ostial atresia | + | | |
| | Ostial stenosis | + | | |
| | Coronary fistula | | + | |
| | ALCAPA | + | | |
| | Muscular bridge | | | + |
| Myocardial ischemia, secondary (episodic) | Tangential origin | | + | |
| | Ectopic origin (opposite sinus) | | + | |
| | Myocardial bridge | | + | |
| | Coronary ectasia | | + | |
| | Coronary fistula | | + | |
| | ALCAPA, neonatal | + | | |
| | ALCAPA, adult | | + | |
| Increased risk of fixed coronary atherosclerotic disease | Coronary fistula | | + | |
| | ALCAPA | + | | |
| | Coronary ectasia | | + | |
| | Ectopic origin | | + | |
| | Muscular bridge (proximal) | | + | |
| Secondary aortic valve disease | Coronary aneurysm | | + | |
| | Coronary fistula | | + | |
| | ALCAPA | | + | |
| Increased risk of bacterial endocarditis | Coronary fistula | | + | |
| Ischemic cardiomyopathy (hibernation) | ALCAPA | + | | |
| | Coronary fistula | | + | |
| | Ectopic ostia | | + | |
| Volume overload | Coronary fistula | + | | |
| | ALCAPA | + | | |
| Unusual technical difficulties during coronary angioplasty | Ectopic ostia | + | | |
| | Split left coronary artery | | + | |
| | Coronary fistula | | + | |
| Complications during cardiac surgery | Ectopic ostia | + | | |
| | Muscular bridge | + | | |

ALCAPA indicates anomalous origination of the left coronary artery from the pulmonary artery.

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dium, physiological alterations in this function should be the main consideration. Unlike effort-related ischemia typical of fixed obstructive lesions, ischemia associated with coronary anomalies is reproducible with stress testing or is able to be fixed in only a few conditions (ALCAPA, coronary stenosis, or coronary atresia). In other anomalies, ischemia occurs only under inconsistent or extreme clinical conditions.[13,18,19,22,35,36]

Clinically, angiographic documentation of abnormal coronary anatomy has not led to any effective or widely agreed-upon recommendations for functional testing and treatment.[11,35] Exercise tests, intended to reproduce symptoms or to induce changes in electrocardiographic or nuclear-imaging parameters, often produce false-negative or confusing results.[6,35] Reduced coronary functional reserve[37–39] or abnor-

mal flow patterns during intravascular Doppler testing might characterize certain anomalies but, alone, these are usually inadequate for implicating a specific pathophysiological mechanism of critical ischemia.

Although some anomalies may manifest only under exceptional conditions such as extreme exertion, no means of testing this hypothesis is available. Standard clinical submaximal stress-test protocols are frustratingly inadequate for identifying the presence and prognosis of most anomalies; indeed, long-term Holter monitoring (for arrhythmias and ST-segment changes) might be more informative.[15,22] During extreme exertion, certain stimulants and/or intervening autocrine dysfunction may induce autonomic and/or endothelial dysfunction, causing spasm and/or thrombosis at anomalous sites.[11] Arguing against the thrombotic theory is the fact that intracoronary clotting is rare in necropsies of sudden death victims with coronary anomalies,[40] but histological correlates of ischemic events (parcellar, intramural infarcts) are frequently documented.[35] All of the above findings may suggest that sudden death in patients with coronary anomalies is due to coronary spasm, typically of a proximal trunk, in the absence of collateral flow, with secondary collapse and/or ventricular fibrillation (as in critical stenosis of the left main trunk). To test this theory, an ergonovine or acetylcholine challenge might be essential. Intravascular ultrasonography could supplement angiography during evaluation of coronary spasm.

Is there a relationship between coronary obstructive disease and coronary anomalies? Do some anomalies predispose to obstructive atherosclerotic disease? Some authors claim, whereas others refute, such an association.[8,41] According to prevailing opinion, coronary segments with an anomalous course are no more vulnerable to obstructive disease than are normal segments in the same individual. Particularly interesting are the findings from angiograms performed for suspected ischemic disease that indicate that coronary anomalies were more common in women (7.6% versus 4.8% in men; $P=0.01$), and 57 (52%) of the 110 patients with coronary anomalies had no obstructive disease.[6,41] Conversely, patients without obstructive disease had an increased incidence of coronary anomalies (8.6% versus 4.9%; $P=0.001$). This study confirmed the high probability (26.7%) that a coronary anomaly will accompany an aortic valve defect.[6]

Pathologists consistently observe a fibrous ridge at the ostium of tangentially oriented ectopic coronary arteries.[7,42–44] Such ridges are often said to have potentially catastrophic consequences.[44] Nevertheless, plaque activation or rupture is seldom documented,[40] even on examination of the histological anatomy.[7,42–44]

With regard to coronary fistulas, a recurrent debate concerns whether coronary steal could be a clinically relevant mechanism. Whenever coronary flow from a single source entails in-parallel competition between coronary fistulous and nutrient branches, a steal could indeed occur at the expense of nutrient (higher-resistance) territory. However, the following facts argue against this mechanism as a cause of critical ischemia: (1) During functional testing, few coronary fistulas cause chest pain or reversible ischemia.[6,11] (2) During exercise, the nutrient branches undergo vasodilatation (owing to an increased myocardial workload), but pressure at the fistulous runoff site may only increase, favorably readjusting the nutrient/fistulous flow ratio. (3) If a significant coronary steal occurred under resting conditions, it would cause myocardial infarction, hibernation, or resting chest pain, none of which has been observed.

## Clinical Relevance and a Call for Action

The greatest clinical challenge presented by coronary anomalies is understanding the variability of their functional repercussions. Some anomalies (including most of those in unselected necropsy series) seem to be only curiosities. Other anomalies are potentially lethal. Still, cardiologists can only guess at possible pathophysiological mechanisms for the latter while lacking the information necessary to make sound clinical recommendations.

For these reasons, Virmani,[44] Willerson,[45] and Williams[1] have independently proposed some innovative, cooperative approaches to studying coronary anomalies. The time seems ripe for establishing a worldwide network of specialists capable of gathering meaningful data and of eventually providing sound clinical guidelines while participating in prospective, coordinated studies. We must transcend our current predominant approach, characterized by no more than the periodic publication of dramatic case reports. Our knowledge about the clinical expression of coronary anomalies could be greatly enhanced by a multicenter database capable of prospectively collecting information about the following fundamental issues: (1) the incidence of each anomaly, as an anatomic entity, in unselected general populations, based on strict, prospectively agreed-on diagnostic criteria; (2) the type and incidence of clinical manifestations associated with each type of anomaly and the specific features of each instance; (3) the detailed clinical history of each patient with a given anomaly who experiences a clinical event, with particular attention to objective documentation of the event itself and the relevant clinical circumstances (exercise, dehydration, smoking, drugs, etc); and (4) the treatment (behavorial, medical, or surgical) used for a given patient with a coronary anomaly, whether identified during life or after death. Living patients should undergo long-term observation to clarify the anomaly's natural history and the influence of any empirical intervention.

Using powerful databases (ideally under the auspices of a large professional organization), such a network of experts should implement coordinated, pre-established protocols for clinical investigations. These experts should also support educational efforts, publish periodic documents, and foster pertinent discussions by holding regular meetings.

In conclusion, if 19% of sudden deaths in young athletes are due to coronary anomalies, and if most anomalies are harmless but the rest require aggressive intervention, we owe our patients and colleagues a precise, objective source of information that can lead to sound recommendations and safe treatment.

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Paolo Angelini, José Antonio Velasco and Scott Flamm

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