

Congenital Coronary Artery Anomalies at Risk of Myocardial Ischemia and Sudden Death

a report by

Cristina Basso, MD and **Gaetano Thiene, MD**

Institute of Pathologic Anatomy, University of Padua Medical School

Cristina Basso, MD, is Associate Professor of Cardiovascular Pathology at the University of Padua. She has written 160 papers per-*extenso*, of which 70 have appeared in English peer-review journals, including the *New England Journal of Medicine*, *Circulation*, *Journal of the American College of Cardiology* and *American Journal of Pathology*. She has given nearly 300 personal lectures and communications at scientific meetings and is co-author of two monographs. She is a Fellow and member of Società Italiana di Cardiologia, of Gruppo di Studio Italiano di Patologia Cardiovascolare, the Society for Cardiovascular Pathology, the European Association for Cardiovascular Pathology and of European Society of Cardiology (ESC). She has been awarded 10 national and international prizes. Dr Basso graduated with a degree in medicine from the University Medical School in Padua in 1990 and then undertook postgraduate courses in cardiology and a PhD in Cardiological Sciences.

Despite the low prevalence in the overall population, congenital coronary artery (CA) anomalies are frequently found as the cause of sudden death (SD) in the young, particularly in the athletic field.¹⁻¹¹ These anomalies are observed both in pediatric and adult patients, with an equal incidence of SD. Why a patient may survive asymptomatic until adulthood and then suffer from angina, myocardial infarction (MI) or SD without superimposition of coronary atherosclerosis, remains intriguing.

CA Anomaly Types

CA anomalies consist of a wide range of abnormalities, which includes anomalous origin, anomalous course, or both.^{1,7,8} Leaving aside the anomalous origin of a CA from the pulmonary trunk – which is in fact a ‘major’ CA anomaly highly symptomatic in infancy (‘Bland-White-Garland syndrome’) and due to coronary blood steal from the aorta to the pulmonary artery, thus accounting for extensive MI with either SD or congestive heart failure (HF)¹⁸ – a wide range of so-called ‘minor’ abnormalities do exist that are characterized by the fact that the CAs still arise from the aorta.^{1,7,8}

Coronary Ostia Malformations

Coronary ostia malformations consist of severe lumen stenosis, either of the right or of the left, by plication of the aortic wall leading to a valve-like ridge that may act as a door blocking the inflow during diastolic filling, with consequent ischemia, eliciting life-threatening arrhythmias.^{1,19} This anomaly is considered to be significant to possibly account for SD if the surface area of the ridge exceeds 50% of the coronary ostial luminal area.¹⁹ A severe obstruction of coronary ostia and of the proximal coronary segment course may also be observed in the setting of hyperelastosis of the aortic wall, i.e. ‘macarony disease’, which is a relatively common observation in infants who die suddenly;²⁰ a similar picture is described in William’s syndrome with supravalvular aortic stenosis in which the coronary ostia may be totally or partially insulated from the aortic lumen, due to fusion of the aortic leaflets with the wall.

High Take-off of the CA from the Aortic Wall

High take-off of the CA from the aortic wall has been mostly considered a variant within normal,¹⁹ without consequences unless surgical procedures are performed; however, it has been recently described in otherwise unexplained SD cases.² A take-off higher than 2.5mm above the sino-tubular junction may account for a vertical intramural aortic course of the CA, before reaching the aortic root and then the atrioventricular sulcus. Moreover, a funnel-like ostium with a slit-like lumen along the intramural aortic course might account for myocardial ischemia.²

Anomalous CA Origin from the Wrong Aortic Sinus

Anomalous CA origin, either the left main CA from the right sinus of Valsalva or the right CA from the left sinus, represents a rare congenital defect that has been found in 0.17% of patients undergoing autopsy²¹ and in 1.2% of all patients undergoing coronary angiography.²² Recently, Davis et al.²³ confirmed these figures, reporting a prevalence of 0.17% derived from a population of 2,388 children and adolescents prospectively evaluated by transthoracic echocardiography (ECG). Their population cannot be considered ‘normal’ since it comprises asymptomatic children and adolescents referred for cardiovascular (CV) investigation; thus, the prevalence in a large and unselected population is likely to be lower.²⁴

Either the right CA origin from the left coronary sinus or left CA origin from the right coronary sinus are hidden conditions at highest risk of SD. In this setting, the proximal segment of the anomalous CA may run anterior to the pulmonary trunk, posterior to the aorta, or between the pulmonary artery and the aorta itself. The latter condition is considered at risk from myocardial ischemia, particularly during exercise, through CA squeezing due to the increased cardiac output with diastolic expansion of great vessels.^{1-3,25-28} Although both right and left CA anomalous origin from the wrong aortic sinus are at impending risk of SD, the anomalous left CA from

the right sinus is considered more malignant because of the large amount of left ventricular (LV) myocardium at ischemic risk. In the review by Roberts³ of 43 necropsy patients, 34 (79%) died due to the CA anomaly; of these, 26 (76%) died suddenly in the first two decades of life and all but one during or shortly after vigorous exertion. On the contrary, anomalous right CA origin from the left sinus may be an incidental angiographic or autopsic observation and until recently has been considered a minor congenital anomaly of no clinical significance. In a recent paper it was found that all the cases with anomalous left CA died suddenly, compared with 43% of cases with anomalous right CA.² As far as anomalous origin of left CA from the posterior aortic sinus is concerned, the coronary malformation is quite rare and even more rarely associated with SD.²⁹

The anomalous origin of the left circumflex branch from the right CA or sinus itself with a separate ostium is considered the most frequent CA anomaly,^{3,19} with an angiographic incidence of up to 0.67%.^{30,31} Although it is frequently an incidental autopsy finding, it has also been described in victims of unexpected arrhythmic SD.^{1,2,32} After the anomalous take-off, the left circumflex branch shows an abnormal retro-aortic course to reach the left atrioventricular groove crossing the mitro-aortic fibrous continuity. This anomaly has been considered a benign condition, having been observed at autopsy or angiography in association with obstructive coronary atherosclerosis, until cases have been reported with evidence of MI or SD in the absence of any other explanation other than the malformation itself.

Myocardial Bridge or Tunneled Epicardial CA

A coronary epicardial stem, usually the left anterior descending branch, may become deeper within the myocardium, thus presenting with an intramural course.^{33,34} Thin loops of myocardium surrounding a CA have been reported in up to 70% of patients dying from different causes and thus should be considered as a variant of normal.³⁴ Myocardial ischemia has been reported in patients in whom coronary angiography detected nothing but a vessel constriction (the so-called 'milking effect') and in whom surgical debridging was revealed to be effective in relieving both signs and symptoms.³⁵⁻³⁷ Moreover, SD has been described in patients with myocardial bridge as the only plausible substrate accounting for SD.^{5-7,38} Tunneled CAs have been reported in approximately 5% of athletics field deaths by Maron et al.^{5,6} in the absence of any other structural anomaly. Effort-induced ischemia has been

attributed to tachycardia, which increases the myocardial oxygen requirement and reduces the coronary flow during diastole. Fine histopathologic analysis has established that this anomaly presents with pathologic significance when it has a long (2-3cm) and deep (2-3mm) intramural course.³⁹ Moreover, it was found that the myocardium encircling the intramural coronary segment presents with the feature of a sheath acting as a sphincter and shows disarray and fibrosis, further hindering diastolic vessel filling.⁷ All these features are in keeping not only with a systolic lumen obliteration, but also with persistent occlusion during diastole, when coronary blood filling occurs due to unpaired relaxation of the myocardium surrounding the anomalous coronary segment. This hypothesis has been recently confirmed by intravascular ultrasound investigations.⁴⁰ The occurrence of myocardial ischemia at rest could also be due to vasospasm of the intramural coronary segment⁴¹ and transient platelet aggregate deposition and thrombosis provoked by mechanical trauma of the vessel wall.^{35,36} As for therapy, not only surgical debridging but also interventional therapy with stent implantation has been successfully carried out.⁴²

Anomalous CA Origin from the Wrong Aortic Sinus

Pathophysiology of Myocardial Ischemia

Myocardial ischemia is the consequence of several mechanisms limiting the blood flow in the anomalous CA, including the acute angle take-off from the aorta, the narrowed slit-like lumen with a potential for a flap-like closure of the orifice, the proximal intramural course of the anomalous vessel within the aortic tunica media, which may further aggravate the obstruction, and the squeezing of the vessel along its course between the aorta and the pulmonary artery, particularly during exercise when there is an increased cardiac output with expansion of the great vessels. A spasm of the anomalous CA, possibly as a result of endothelial injury, has also been advocated.⁴³ The authors' findings, showing normal ECG patterns associated with pathologic evidence of acute myocardial ischemic damage and/or chronic ischemic injury with replacement-type fibrosis,²⁸ suggest that myocardial ischemia is episodic in nature, probably occurring in infrequent bursts that may be cumulative with time. In a recent study, by comparing the various cardiovascular diseases (CVDs) accounting for SD in athletes compared with non-athletes, it was found that congenital anomalies of CA occurred more frequently in athletes than in non-athletes (12.2% compared with 0.5%), confirming that they are particularly prone to cardiac arrest during effort.¹¹

In Vivo Diagnosis

These CA anomalies are rarely suspected or identified during life and are usually first recognized at autopsy, largely because there is insufficient clinical suspicion, as well as due to the difficulties implicit in routine examination or clinical testing. Although SD is frequently the first manifestation of the disease, by studying a series of young competitive athletes who died suddenly due to these malformations, it was recently demonstrated that premonitory cardiac symptoms commonly occurred shortly before SD, particularly in the setting of anomalous left main CA origin, suggesting that a history of exertional syncope or chest pain requires exclusion of this anomaly.²⁸ The observation that the conventional 12-lead ECG and even maximal exercise stress test are usually within normal limits, i.e. without evidence of myocardial ischemia, suggests that this event is only periodically present in this disease. These findings have important implications for preventive strategies and *in vivo* identification. In a recent investigation describing the anatomical and clinical profile of young athletes with wrong sinus CA origin, it was reported that all the resting 12-lead and exercise ECGs available during life were normal. Moreover, by reviewing the literature concerning exercise ECG findings in young patients with documented CA anomalies, only four in 18 (22%), including two who were already symptomatic, showed ischemic changes.

ECG stress testing and myocardial perfusion scintigraphy may therefore provide little or no diagnostic information in patients with suspected anomalous CA origin. If the index of suspicion is sufficiently high because of potential clinical markers such as exertional syncope or chest pain, even in the setting of normal 12-lead and effort ECGs, the origin and proximal course of CA should be defined non-invasively by transthoracic or transesophageal ECG. Indeed, in young individuals presenting with symptoms and/or ECG changes, ECG provided the correct identification of incorrect aortic sinus origin, which was subsequently confirmed by coronary angiography.^{44,45}

ECG has the potential to address the correct diagnosis, because it provides good anatomic definition of the ostium and proximal epicardial course of CA. Pelliccia et al.,²⁴ in a series of 1,360 young athletes prospectively evaluated by ECG, were able to visualize the ostium and proximal course of the left CA in 97% and right CA in

80% of subjects. As a consequence, the failure to demonstrate that CAs actually originate from their usual location in young people with impaired consciousness or angina, suggests the need for further anatomic investigation by angiography or possibly magnetic resonance imaging (MRI) and computed tomography (CT).^{46–48} False negatives may occur when using transthoracic ECG, as demonstrated by Davis et al.²³, due to either misinterpretations or the inability to fully identify CA origin because of poor acoustic windows.

Clinical Management

Timely *in vivo* diagnosis of CA anomalies raises a question of the clinical management of affected patients. The big challenge is the identification of high-risk subsets to decide when and which patients should undergo surgical therapy.

If such an anomaly, of either right or left CA anomalous origin, is found in a symptomatic patient or in an asymptomatic patient with clinical evidence of myocardial ischemia, surgery is mandatory. Because it has been clearly demonstrated that SD is precipitated by exercise, sport and strenuous effort should be strongly discouraged.⁴⁹ Surgical correction may be accomplished either by CA bypass grafting or newer techniques such as re-implantation of the anomalous vessel in the proper coronary sinus or by 'unroofing' the common wall between the aorta and the anomalous CA, resulting in a new orifice with a more natural take-off.^{50,51}

Treatment decisions for the asymptomatic young patient without evidence of ischemia in the corresponding myocardial region are less clear. In this setting, the type of anomaly, whether right or left anomalous CA origin, would make the difference; most of the physicians would still recommend surgery since cardiac arrest remains unpredictable in the setting of anomalous left CA, whereas right CA anomalous origin seems to bear a more benign clinical course. A clinical registry of affected patients is warranted to gain an insight into the clinical profile as well as on the impact of surgical correction on the prognosis of patients with anomalous CA origin. ■

Supported by MURST, Rom; and Fondazione Cassa di Risparmi, Padova-Rovigo, Italy.

References

1. Roberts W C, "Major anomalies of coronary arterial origin seen in adulthood", *Am. Heart J.* (1986);111: pp. 941–963.
2. Frescura C, Basso C, Thiene G et al., "Anomalous origin of coronary arteries and risk of sudden death: a study based on an autopsy population of congenital heart disease", *Hum. Pathol.* (1998);29: pp. 689–695.
3. Roberts W C, "Congenital coronary arterial anomalies unassociated with major anomalies of the heart and great vessels", in: Roberts W C (ed.), *Adult congenital heart diseases*, Philadelphia: FA Davis Company (1987); pp. 583–630.
4. Liberthson R R, "Sudden death from cardiac causes in children and young adults", *N. Engl. J. Med.* (1996);334: pp. 1,039–1,044.
5. Maron B J, Roberts W C, McAllister H A et al., "Sudden death in young athletes", *Circulation* (1980);62: pp. 218–229.
6. Maron B J, Shirani J, Poliac L C et al., "Sudden death in young competitive athletes: clinical, demographic, and pathological profiles", *JAMA* (1996);276: pp. 199–204.
7. Corrado D, Thiene G, Cocco P, Frescura C, "Non-atherosclerotic coronary artery disease and sudden death in the young", *Br. Heart J.* (1992);68: pp. 601–607.
8. Basso C, Frescura C, Corrado D et al., "Congenital heart disease and sudden death in the young", *Hum. Pathol.* (1995);26: pp. 1,065–1,072.
9. Taylor A J, Rogan K M, Virmani R, "Sudden cardiac death associated with isolated congenital coronary artery anomalies", *J. Am. Coll. Cardiol.* (1992);20: pp. 640–647.
10. Burke A P, Farb A, Virmani R et al., "Sports-related and non-sports-related sudden cardiac death in young adults", *Am. Heart J.* (1991);121: pp. 568–575.
11. Corrado D, Basso C, Schiavon M, Thiene G, "Screening for hypertrophic cardiomyopathy in young athletes", *N. Engl. J. Med.* (1998);339: pp. 364–369.
12. Drory Y, Turetz Y, Hiss Y et al., "Sudden unexpected death in persons less than 40 years of age", *Am. J. Cardiol.* (1991);68: pp. 1,388–1,392.
13. Neuspiel D R, Kuller L H, "Sudden and unexpected natural death in childhood and adolescence", *JAMA* (1985);254: pp. 1,321–1,325.
14. Topaz O, Edwards J E, "Pathologic features of sudden death in children, adolescents, and young adults", *Chest* (1985);87: pp. 476–482.
15. Philips M, Robinowitz M, Higgins J R et al., "Sudden cardiac death in Air Force recruits: a 20-year review", *JAMA* (1986);256: pp. 2,696–2,699.
16. Kramer M R, Drory Y, Lev B, "Sudden death in young Israeli soldiers: analysis of 83 cases", *Isr. J. Med. Sci.* (1989);25: pp. 620–624.
17. Basso C, Calabrese F, Corrado D, Thiene G, "Postmortem diagnosis in sudden cardiac death victims: macroscopic, microscopic and molecular findings", *Cardiovasc. Res.* (2001);50: pp. 290–330.
18. Moodie D S, Fyfe D, Gill C C et al., "Anomalous origin of the left coronary artery from the pulmonary artery (Bland-White-Garland syndrome) in adult patients: long-term follow-up after surgery", *Am. Heart J.* (1983);106: pp. 381–388.
19. Virmani R, Rogan K, Cheitlin M D, "Congenital coronary artery anomalies: pathologic aspects", in: Virmani R, Forman M B (eds), *Nonatherosclerotic ischemic heart disease*, Raven Press, New York (1989), pp. 153–183.
20. Thiene G, Ho S Y, "Aortic root pathology and sudden death in youth: review of anatomical varieties", *Appl. Pathol.* (1986);14: p. 237.
21. Alexander R W, Griffith G C, "Anomalies of the coronary arteries and their clinical significance", *Circulation* (1956);14: pp. 800–805.
22. Engel H J, Torres C, Page H L, "Major variations in anatomical origin of the coronary arteries: angiographic observations in 4,250 patients without associated congenital heart disease", *Cathet. Cardiovasc. Diagn.* (1975);1: pp. 157–169.
23. Davis J A, Cecchin F, Jones T K, Portman M A, "Major coronary artery anomalies in a pediatric population: incidence and clinical importance", *J. Am. Coll. Cardiol.* (2001);37: pp. 593–597.
24. Pelliccia A, Spataro A, Maron B J, "Prospective echocardiographic screening for coronary artery anomalies in 1,360 elite competitive athletes", *Am. J. Cardiol.* (1993);72: pp. 978–979.
25. Cheitlin M D, De Castro C M, McAllister H A, "Sudden death as a complication of anomalous left coronary origin from the anterior sinus of Valsalva. A not-so-minor congenital anomaly", *Circulation* (1974);50: pp. 780–787.
26. Barth III C W, Roberts W C, "Left main coronary artery originating from the right sinus of Valsalva and coursing between the aorta and pulmonary trunk", *J. Am. Coll. Cardiol.* (1986);7: pp. 366–373.
27. Liberthson R R, Dinsmore R E, Fallon J T, "Aberrant coronary artery origin from the aorta: Report of 18 patients, review of the literature and delineation of natural history and management", *Circulation* (1979);59: pp. 748–754.
28. Basso C, Maron B J, Corrado D, Thiene G, "Clinical profile of congenital coronary artery anomalies with origin from the wrong aortic sinus leading to sudden death in young competitive athletes", *J. Am. Coll. Cardiol.* (2000);35: pp. 1,493–1,501.
29. Lipssett J, Byard R W, Carpenter B F, Jimenez C L, Bourne A J, "Anomalous coronary arteries arising from the aorta associated

- with sudden death in infancy and early childhood", *Arch. Pathol. Lab. Med.* (1991);115: pp. 770–773.
30. Page H L, Engel H J, Campbell W B, Thomas C S, "Anomalous origin of the left circumflex coronary artery: recognition, angiographic demonstration and clinical significance", *Circulation* (1974);50: pp. 768–773.
 31. Chaitman B R, Lespérance J, Saltiel J, Bourasse M G, "Clinical, angiographic and hemodynamic findings in patients with anomalous origin of the coronary arteries", *Circulation* (1976);53: pp. 122–131.
 32. Corrado D, Pennelli T, Piovesana P, Thiene G, "Anomalous origin of the left circumflex coronary artery from the right aortic sinus of Valsalva and sudden death", *Cardiovasc. Pathol.* (1994);3: pp. 269–271.
 33. Angelini P, Trivellato M, Donis J, Leachman R D, "Myocardial bridges: a review", *Prog. Cardiovasc.* (1983); 26: pp. 75–88.
 34. Polacek P, "Relation of myocardial bridges and loops on the coronary arteries to coronary occlusions", *Am. Heart J.* (1961); 61: pp. 44–52.
 35. Feldman A M, Baughman K L, "Myocardial infarction associated with a myocardial bridge", *Am. Heart J.* (1986); 111: pp. 784–787.
 36. Vasan R S, Bahl V K, Rajani M, "Myocardial infarction associated with a myocardial bridge", *Int. J. Cardiol.* (1989); 25: pp. 240–241.
 37. Fanuqui A M, Maloy W C, Felner J M et al., "Symptomatic myocardial bridging of coronary artery", *Am. J. Cardiol.* (1978);41: pp. 1,305–1,309.
 38. Morales A R, Romanelli R, Boucek R J, "The mural left anterior descending coronary artery, strenuous exercise and sudden death", *Circulation* (1980);62: pp. 230–237.
 39. Ferreira A G, Trotter S E, Konig B et al., "Myocardial bridges: morphological and functional aspects", *Br. Heart J.* (1991);66: pp. 364–367.
 40. Ge J, Erbel R, Rupprecht H J et al., "Comparison of intravascular ultrasound and angiography in the assessment of myocardial bridging", *Circulation* (1994);89: p. 1,725.
 41. Ciampriotti R, El Gamal M, "Vasospastic coronary occlusion associated with a myocardial bridge", *Cath. Cardiovasc. Diagn.* (1988);14: pp. 118–120.
 42. Haager P K, Schwarz E R, vom-Dahl J, Klues H G, Reffelmann T, Hanrath P, "Long term angiographic and clinical follow up in patients with stent implantation for symptomatic myocardial bridging", *Heart* (2000);84: pp. 403–408.
 43. Cheitlin M D, "Coronary anomalies as a cause of sudden death in the athlete", in: Estes N A M, Salem D N, Wang P J (Ed.), *Sudden cardiac death in the athlete*, Armonk, NY, Futura (1998): pp. 379–391.
 44. Maron B J, Leon M B, Swain J A et al., "Prospective identification by two dimensional echocardiography of anomalous origin of the left main coronary artery from the right sinus of Valsalva", *Am. J. Cardiol.* (1991);68: pp. 140–142.
 45. Zeppilli P, Dello Russo A, Santini C et al., "In vivo detection of coronary artery anomalies in asymptomatic athletes by echocardiographic screening", *Chest* (1998);114: pp. 89–93.
 46. Serota H, Barth C W III, Seuc C A et al., "Rapid identification of course of anomalous coronary arteries in adults: the 'dot and eye' method", *Am. J. Cardiol.* (1990);65: pp. 891–898.
 47. McConnell M V, Ganz P, Selwyn A P et al., "Identification of anomalous coronary arteries and their anatomic course by magnetic resonance coronary angiography", *Circulation* (1995);92: pp. 3,158–3,162.
 48. Mousseaux E, Hernigou A, Sapoval M et al., "Coronary arteries arising from the contralateral aortic sinus: electron beam computed tomographic demonstration of the initial course of the artery with respect to the aorta and right ventricular outflow tract", *J. Thorac. Cardiovasc. Surg.* (1996);112: pp. 836–840.
 49. Maron B J, Mitchell J E, "26th Bethesda Conference: Recommendations for determining eligibility for competition in athletes with cardiovascular abnormalities", *J. Am. Coll. Cardiol.* (1994);24: pp. 845–899.
 50. Cohen A J, Grishkin B A, Helsel R A, Head H D, "Surgical therapy in the management of coronary anomalies: emphasis on utility of internal mammary artery grafts", *Ann. Thorac. Surg.* (1989);47: pp. 630–637.
 51. Van Son J A M, Haas G S, "Anomalous origin of left main coronary artery from right sinus of Valsalva: modified surgical treatment to avoid neo-coronary ostial stenosis", *Eur. J. Cardio-thorac. Surg.* (1996);10: pp. 467–469.