Cardiology in the Young 2014; Page 1 of 18
doi:10.1017/S1047951114000250

Review Article

Abnormal origins of the coronary arteries from the aortic root

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Abstract Anomalous origin of a coronary artery from the aorta is a potentially serious anomaly that occurs in about 0.1–0.2% of the population. This percentage is small; however, it translates into about 4000 annual births with these anomalies. The clinical presentation of these anomalies is rare, and hence most are and will remain asymptomatic. The various anatomic anomalies are described, with anomalous origin of the left coronary artery that then passes between the aorta and pulmonary artery being the most serious of these anomalies. The pathophysiology resulting from these anomalies is described, as are methods for identifying those who require treatment; however, we still do not know the best methods of determining which patients need treatment.

Keywords: Left coronary artery; right coronary artery; single coronary artery

Received: 20 December 2013; Accepted: 23 January 2014

Origins of coronary arteries from abnormal sites in the aortic root are well known, but there are unresolved problems about their incidence and prevalence, natural history, the mechanisms producing myocardial ischaemia, the need for treatment, and the optimal form of treatment.

There are many different anomalies.[1–5]

Normal variants

A separate origin of the conal branch from the right sinus of Valsalva occurs in 35–50% of people. Separate origins of the left circumflex and left anterior descending coronary arteries from the left sinus of Valsalva occur in about 1% of people.[6] These are benign variations that do not cause pathophysiology in the absence of coronary atheroma.

Less frequent but usually benign anomalies

The next most common anomaly of origin is the attachment of the left circumflex coronary artery to the right sinus of Valsalva or the proximal right coronary artery. This anomaly occurs often in patients with tetralogy of Fallot and other congenital heart lesions, but can be isolated. Apart from the risk for coronary atheroma or surgical injury, this anomaly does not usually cause myocardial ischaemia, although sudden death has occurred in a patient with this anomaly.[7] The anomalous artery arises obliquely from the sinus and may have a slit-like orifice,[8] and it is surprising that more complications are not reported.

Rarely, the left anterior descending coronary artery, isolated or as part of a dual left anterior coronary artery, or both it and the left circumflex coronary artery arise from the right sinus of Valsalva.[9,10] The aberrant left anterior coronary artery usually passes anterior to the pulmonary outflow tract, but it may pass between the two great arteries or through the ventricular septum. These anomalies, too, are rarely a cause of heart disease in the absence of coronary atherosclerosis. In one patient with effort angina, however, the anomalous left anterior coronary artery left the aorta at an acute angle and then passed between the great arteries; symptoms were relieved by surgery.[11]

Potentially serious anomalies

The major potentially serious anomalies of origin of the coronary arteries are the attachment of the right coronary artery to the left sinus of Valsalva, the attachment of the left main coronary artery to the

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right sinus of Valsalva, the attachment of one or both major coronary arteries to the posterior – non-coronary or non-facing – sinus of Valsalva, and the single coronary artery that has only one aortic orifice and main stem but then divides to supply branches to the whole heart (see below). A high origin of a main coronary artery above the sinus of Valsalva is often recorded as abnormal, but is uncommon; it is not usually a major threat to health, and will not be discussed further here.

Incidence and prevalence

Ideally, to study the incidence, prevalence, and natural history of these lesions, we would study a large, randomly selected group of subjects of all ages with a diagnostic method that is 100% sensitive and 100% specific. If the anomaly causes many deaths in young patients, then its prevalence will be less in older than in younger subjects. The studies that have been performed using autopsy, echocardiography, cardiac catheterisation, and coronary angiography, and imaged by computerised tomography or magnetic resonance fall short of these ideals.

Autopsy studies by experienced pathologists lead to unambiguous diagnoses of these anomalies, but the requirement for random selection of subjects may not be met. In the study by Cheitlin et al[12], from the Armed Forces Institute of Pathology, there were 19 patients with an anomalous left main coronary artery from the right sinus of Valsalva, but only nine patients in whom the right coronary artery arose from the left sinus of Valsalva. This reversal of the expected ratio (see below) indicates non-random referral of patients. The authors estimated that, over the time of acquisition of these hearts, about 475,000 hearts had been sent to the Armed Forces Institute of Pathology for an incidence of these coronary origin anomalies of 0.01%. Frescura et al[13] studied a small series of autopsies of children with congenital heart disease and found a high incidence of major abnormalities of coronary origins, but this figure is biased by the 13/27 patients who died because of the abnormalities. The studies from a general hospital by Alexander and Griffith[14] and from a group of children's hospitals by Lipsett et al[15] are probably unbiased (Table 1).

Echocardiography may often miss some of these anomalies. In three series in which children and young athletes were studied,[16–18] of a total of 6898 subjects, there were three with a left coronary artery arising from the right sinus of Valsalva and four with the right coronary artery arising from the left sinus of Valsalva. These must underestimate the true incidence, because anomalous origin is much more common for the right than the left coronary artery, and the sample sizes are small. A study of 14,546 echocardiograms taken in children seen in a hospital setting for possible heart disease revealed 52 anomalies of coronary aortic origin.[19] One large study by Werner et al[20] on 62,320 children having diagnostic echocardiography described only six patients with a coronary artery anomaly – an anomalous left circumflex coronary artery. These were routine echocardiography studies, and it is probable that many anomalies were missed (Table 2).

Coronary angiography provides a much larger number of patients but is open to the criticism that most patients with coronary arterial anomalies have angiography because of their symptoms, thus inflating their apparent incidence. This may explain why the incidence is usually higher for angiographic studies than those

Table 1. Incidence of selected CAA on the basis of autopsies.

Reference	Total patients	CAA	LCx or LAD from RSV or RCA	RCA from LSV	LCA from RSV	SA	Comments
White and Edwards.[15]	600	4 (0.67)	2 (0.33)	1 (0.17)		1 (0.17)	Unselected autopsies 30–89 years of age
Alexander and Griffith[13]	18.950	12 (0.28)	4 (0.06)		1 (0.005)	7 (0.03)	Unselected autopsies
Ogden[16]		35	14	11		10	Coronary anomalies only
Cheitlin et al[11]	~475,000	5 (0.01)		9 (0.007)	19 (0.004)	23	AFIP autopsies
Lipsett et al[14]	7857	15 (0.19)		3 (0.04)	3 (0.04)	4 (0.05)	Children's Hospitals routine autopsies
Frescura et al[12]	1200	14 (2.25)	3 (0.25)	7 (0.58)	4 (0.33)		Collection of pathologic hearts

AFIP = Armed Forces Institute of Pathology; CAA = coronary artery anomalies; LAD = left anterior descending coronary artery; LCA = left main coronary artery; LCx = left circumflex coronary artery; LSV = left sinus of Valsalva; RCA = right coronary artery; RSV = right sinus of Valsalva; SA = single coronary artery

Percentages in parentheses are related to the total population studied

Congenital coronary arterial fistulae or coronary arteries arising from the pulmonary artery are excluded from this table

Table 2. Incidence of selected coronary artery anomalies on the basis of echocardiography in children and young adults.

	Total patients	LCx or LAD from RSV or RCA	RCA from LSV	LCA from RSV	SA	Comments
Pellicia et al[17]	1273					Consecutive athletes
Zeppilli et al[18]	3150		2 (0.06)	1 (0.03)		Random athletes
Davis et al[21]	2388		2 (0.08) one inferior wall ischaemia	2 (0.08) one with SVT		Children referred for diagnostic echocardiography
Werner et al[21]	62,320	6 (0.01)			1 (0.002)	Children referred for diagnostic echocardiography
Lytrivi et al[20]	14,546	9 (0.06)	24 (0.16)	6 (0.04)	11 (0.054)	Children referred for diagnostic echocardiography

LAD = left anterior descending coronary artery; LCA = left main coronary artery; LCx = left circumflex coronary artery; LSV = left sinus of Valsalva; RCA = right coronary artery; RSV = right sinus of Valsalva; SA = single coronary artery

conducted with echocardiography or autopsy (Fig 1). Computerised tomographic angiography provides more certain diagnosis, but the studies have relatively small sample sizes. A variety of tomographic techniques have been used, such as 64- or 128-slice multidetector computerised tomography, dual-source computerised tomography, or magnetic resonance imaging.

When assessing the frequency with which each of these major anomalies occurs, there is bound to be even more variation, but we can get some information by pooling data from several series. In 21 large series, each with over 7000 patients,[10,21–40] 104/526,500 patients had an anomalous left coronary artery (0.020%) and 523/526,500 patients had an anomalous right coronary artery (0.099%). In 23 large series with a total of 585,000 patients,[10,21–42] 148 (0.025%) had a single coronary artery, the proportion being lower than the 11/26,807 (0.0373%) single coronary arteries in autopsied patients,[14,15] and the 33/50,000 (0.066%) found angiographically by Desmet et al.[41] In some angiographic studies, it is likely that single coronary arteries were not recorded. Finally, the most common anomaly – the anomalous left circumflex coronary artery arising from the right sinus of Valsalva or the right coronary artery – occurred in 1074/536,716 (0.200%) of angiograms.[8,10,21–40]

Some of these data are displayed in Supplementary Tables 1 and 2.

The incidence of origin of a main coronary artery from the posterior sinus of Valsalva is extremely rare. Up to 2013, after a MEDLINE search, we found only 30 such patients described. Therefore, they have negligible influence on the total incidence or on the prevalence of these major anomalies of origin.

Omitting the anomalous left circumflex coronary artery, the percentages of major anomalies reported are shown in Figure 1.

On the basis of the studies with larger sample sizes of over 10,000 patients, it appears that the incidence of these major anomalies is under 0.4%, with a possible average of 0.2%. Adding up the percentage incidence of the three major lesions separately gives a total incidence of 0.156%; hence, a range of 0.1–0.2% seems appropriate.

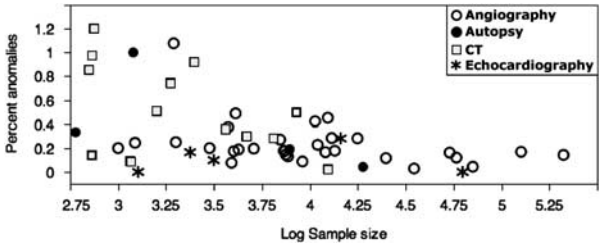

Figure 1.
Total of the three major anomalies as a percentage of the total number of patients studied. The horizontal scale is logarithmic (base 10). The percentages are usually lower for data obtained by echocardiography and autopsies than those by angiography; the autopsy exception[13] was based on a study on congenital heart disease lesions. As expected, there is more variation in the groups with the smaller sample sizes. Studies conducted by computed tomography tend to have higher values because of small sample size and bias by referral of patients suspected of having anomalies after inconclusive angiography.

Gross anatomy of anomalies

A recent publication by the Congenital Heart Surgeons Society AAOCA Working group[5] described four grades on the basis of the relationship of the coronary ostia:

1. Two separate non-confluent orifices within the same sinus.
2. Two confluent (adjacent) orifices within the same sinus.
3. The sinus has a single orifice that bifurcates immediately within the aortic wall into two major coronary arteries.
4. The sinus has a single orifice that forms a common trunk that bifurcates into two major coronary arteries outside the aorta.

This description does not include an anomalous coronary artery arising from the non-coronary sinus or the origin of the left circumflex coronary artery from the right sinus of Valsalva.

Grades 1 and 2

A left main coronary artery arising from the right sinus of Valsalva may take one of several pathways after leaving the aorta. In patients in whom the anomaly was unrelated to their illness, about 60% passed anteriorly between the aorta and the right ventricular outflow tract or the main pulmonary artery – inter-arterial course – 18% were retroaortic, 16% passed through the ventricular septum to emerge on the anterior surface of the left ventricle, and 6% ran in front of the main pulmonary artery.[6] If the left main coronary artery takes the common inter-arterial course, it often has a long intramural pathway in the aortic wall, its origin may be narrower than normal, it may have a slit-like ostium partly covered by a thin flap, and it may emerge tangentially from the sinus of Valsalva instead of at approximately a right angle to it, or else emerge at right angles but immediately take a sharp bend. Sometimes, the initial portion of the artery is narrowed after leaving the aorta.

If the right coronary artery arises from the left sinus of Valsalva, it usually (>90%) takes an inter-arterial course between the aorta and the main pulmonary artery or the right ventricular outflow tract. Occasionally, it runs retroaortic or anterior to the right ventricular outflow tract. The arterial origin may have an intramural course and arise tangentially from the sinus of Valsalva, and may show localised narrowing as it leaves the sinus of Valsalva or passes between the great arteries.[43] In other patients, the right coronary artery is relatively far from the main pulmonary artery.[44]

A left main coronary artery arising from the posterior sinus of Valsalva frequently has a slit-like orifice, intramural course in the aortic wall, or an acute angulation as it leaves the aortic root. Of the 21 patients with this anomaly, one or other of these abnormal features occurred in 11 patients, eight had no such abnormalities, and in four patients no description was provided. After leaving the aorta, the left main coronary artery passes between the aortic root and the left atrium, and then branches normally. There were six patients with the right coronary artery arising from the posterior sinus of Valsalva, and in none of these were there any other abnormal features.

Grades 3 and 4

The single coronary artery arises with equal frequency from the right or the left sinus of Valsalva;[6,45] rarely, it arises from the posterior – non-coronary – sinus. About 40% have associated congenital heart disease. The main anatomic types[46,47] are shown in Table 3 in a classification based on three levels: the side of origin (R or L), the proximal anatomy of anomaly (Group I, II, or III), and the distal anatomy where the anomalous artery crosses to the contralateral side of the heart (A,B,P,S, or C). Thus, for example, an anomaly may be classified as RIIB (see Table 3). Occasionally, the right coronary artery arises from the left anterior descending coronary artery; some rarer types are also described.[6,46,47] The aberrant branch – left main coronary artery in a single right coronary artery or

Table 3. Classification of single coronary artery on the basis of references 46 and 47; table format based on publication by Ay et al.[130]

Variable	Classification	Description
Site of origin	R (~50%)	Single CA arising from RSV
	L (~50%)	Single CA arising from LSV
Proximal anatomy of arteries	Group I (34%)	Anomalous CA comes from distal part of normal-sided artery. In RI the LCA come off the RCA; in LI the RCA comes from the continuation of the LCx or the LAD.
	Group II (61%)	Anomalous CA comes from main stem of the single CA and then crosses to supply the contralateral heart muscle with normal branches
	Group III	LAD and LCx arise separately from the proximal part of the normal RCA
	Group IV	Miscellaneous patterns
Distal patterns of crossing the base of the heart	A (anterior)	Anomalous CA passes to the contralateral side anterior to MPA
	B (between or inter-arterial)	Anomalous CA passes to the contralateral side between the bases of the aorta and the base of the MPA
	P (posterior)	Anomalous CA passes to the contralateral side posterior to the aorta
	S (septal)	Anomalous CA passes to the contralateral side through the interventricular septum
	C (combined)	Anomalous LAD and LCx cross by different courses; usually the LCx passes behind the aorta, but the LAD may take any path

CA = coronary artery; LAD = left anterior descending coronary artery; LCA = left main coronary artery; LCx = left circumflex coronary artery; LSV = left sinus of Valsalva; MPA = main pulmonary artery; RCA = right coronary artery; RSV = right sinus of Valsalva; SA = single coronary artery

the right coronary artery in a single left coronary artery – often joins the main stem at the aortic wall (grade 3) and usually runs close to the aortic root so that there is a tangential origin of the aberrant artery. Occasional patients with one of these anomalies of origin have hypoplastic coronary artery branches.

In the collected literature,[6] whether or not symptoms were mentioned, right and left single coronary arteries were about equally represented. About 25% were type I, mostly with a left single coronary artery. About 60% were type II, and of these only 20% had an intra-arterial passage.

Natural history

This is even more difficult to ascertain than the true incidence and prevalence because of the unknown number of asymptomatic subjects. A careful analysis of the issue by Peñalver et al[48] pointed out that if the prevalence of these anomalies was indeed 0.1–0.2% (1000–2000 per million population), in the United States alone there would be a total of 300,000–600,000 affected people and a yearly addition of 4000–8000 infants born with one of these anomalies. A similar point was made by Angelini[44] who used somewhat higher figures. There is nowhere near these numbers of clinically significant patients that have been reported – for example, Tables 1–4 record <2500 patients worldwide with these anomalies; hence, their conclusion was that the vast majority of these anomalies were asymptomatic and not a risk to health and life. Not all subjects with these anomalies will have been reported, but with the interest in these anomalies and in coronary artery disease in general there should have been many larger series of patients undergoing surgery than have been reported. The reports of surgical treatment of these anomalies from single centres with the largest numbers of patients were by Mainwaring et al[49] who described 50 patients treated over 11 years, with an average of about 5/year; Davies et al[50] who operated upon 36 patients in 16 years, with an average of 2.25/year; and Brothers et al[51] who reported 27 patients operated upon in 5.25 years – with an average of about 5/year. The Congenital Heart Surgeons Society AAOCA Working Group 5 reported 198 patients seen over 11 years among 25 collaborating institutions, with an average of less than one patient per institution per year. On comparing these figures with the number of patients with anomalous left coronary artery arising from the pulmonary artery treated per year, an average of 1.5 patients was reported by Azakie et al[52] or two patients by Alex-Meskishvili et al[53] for an anomaly with one-tenth to one-twentieth the assumed incidence of anomalous origin of a coronary artery from the aorta.

Table 4. Estimates of proportion of patients with anomalous arteries who had coronary angiography of symptoms or death due to their anomaly and not another cause.

Reference	Comments
Alexander and Griffith[13]	All 12/12 died from causes other than the anomaly (Routine autopsies)
Frescura et al[12]	8/11 deaths with coronary artery from opposite sinus of Valsalva were related to the anomaly (collection of pathologic hearts)
Kragel and Roberts[88]	5/7 deaths with left main coronary artery from the right sinus of Valsalva were due to anomaly. 8/23 deaths with right coronary artery from left sinus of Valsalva were due to the anomaly (collection of pathologic hearts)
Cieslinski et al[50]	10/39 with symptoms, all had coronary atheroma
Kaku et al[29]	7/45 had symptoms but no other disease
Donaldson et al[24]	20/82 had symptoms attributed to the anomalous vessel
Barriales Villa et al[31]	3/3 with left main coronary artery from right sinus of Valsalva had symptoms and 11/15 with right coronary artery from the left sinus of Valsalva had symptoms; none had other heart disease
Wilkins[25]	1/3 with left main coronary artery from the right sinus of Valsalva had symptoms but no other disease; 4/30 with right coronary artery from the left sinus of Valsalva had no symptoms, and 3/30 had symptoms but no other disease
Liberthson et al[22]	All 4/4 with right coronary artery from the left sinus of Valsalva had other disease
Lytrivi et al[20]	1/5 with left main coronary artery from the right sinus of Valsalva had chest pain but no other disease; 2/24 with right coronary artery from left sinus of Valsalva had chest pain and no other disease
Topaz et al[28]	Only 6% of anomalous arteries were the cause of the symptoms
Xu et al[35]	50 patients had an inter-arterial course. All had symptoms, 15 had severe coronary artery disease, and 21 had no disease
Desmet[42]	Only 4/33 with single coronary artery had symptoms possibly due to the anomaly (angiography)
Shirani and Roberts[80]	Only 8/53 with single coronary artery had myocardial ischaemia due to the anomaly (autopsy and angiography)
Opolski et al[39]	All 31 patients with anomalous arteries had ischaemic symptoms, and 8 of them had significant coronary atherosclerosis
Schmitt et al[89]	In 24/44 patients, the anomaly was not the cause of the symptoms

It therefore is of great importance to know whether the incidence of major coronary anomalies of 0.1–0.2% derived from the above studies was inflated by symptomatic patients. Unfortunately, many publications do not distinguish between patients with anomalous arteries who have or do not have other causes for their symptoms. Those who do are summarised in Table 4.

With the exception of the studies by Xu et al,[34] who described that at least 21/50 with an inter-arterial course had no other cause for their symptoms, the study by Opolski et al,[38] who found that about 25% of symptomatic patients with an anomalous left or right coronary artery had unrelated causes for their symptoms, and the autopsy studies on patients with heart disease, less than 25% of the patients with anomalous arteries were studied because of symptoms due to their anomalies, and all the others were found incidentally while studying other diseases. Even if we assume that half of the patients were studied because of symptoms due to their anomaly, that still leaves the prevalence of asymptomatic anomalies at 0.05–0.1%, and suggests that only a minority have symptoms due to their anomaly. This confirms the opinion of Peńalver et al.[48] It also confirms the low risk for serious complications of these anomalies observed by Eckart et al[54] who found only 21 deaths due to a left main coronary artery arising from the right sinus of Valsalva in 6,300,000 army recruits between 1977 and 2001.

If the prevalence of this anomaly is 200/million population (see above), then the population of army recruits surveyed by Eckart et al should have had 1260 subjects with a left main coronary artery arising from the right sinus of Valsalva. If so, the risk of death with this anomaly would be 21/1260 = 1.67%, and most would be asymptomatic. Even if the prevalence was one-quarter of the figure cited above, the majority of subjects with this anomaly would not have problems from it.

The most lethal form of these anomalies appears to be the left main coronary artery arising from the right sinus of Valsalva, especially if it takes an inter-arterial course. On the basis of the data collected from the literature, 85% of patients with this anomaly who died or had symptoms had an inter-arterial course, whereas only 60% of patients whose clinical course was judged to be unrelated to the anomaly had an inter-arterial course; in these patients, the coronary anomaly was discovered serendipitously.[6] This implies that those with an inter-arterial course are more likely to have symptoms. An overlapping series reported by Moustafa et al[55] reached identical conclusions. On the basis of the literature, there are few patients above 30 years of age who died or had symptoms due to a left main coronary artery arising from the right sinus of Valsalva.

Figure 2 summarises the reports of the age distribution of patients with a left main coronary artery arising from the right sinus of Valsalva. Figure 2**a** shows those in whom the anomaly caused symptoms, including death (Figure 2**a**), and only those who died (Figure 2**b**).

The data shown in Figure 2**a** and **b** are not unbiased because they come mainly from reports of one or few patients who were found to have this unusual and interesting anomaly. Nevertheless, there is no reason to think that the age distribution is biased; an older patient with cardiac arrest from this anomaly is probably more likely than a young patient to be the patient of a short report. In addition, cardiac arrest due to a left main coronary artery arising from the right sinus of Valsalva and not passing between the great arteries is unusual enough that it is likely to be reported. Therefore, in these figures the relative numbers per decade and the distribution of the numbers with intra-arterial versus other passage probably reflect the relative differences well. Those in whom the anomaly was found incidental to some other pathology (Fig 2**c**) are relatively unbiased; however, when reports of patients whose ages were not mentioned are examined, the proportion with inter-arterial passage is slightly higher.

As shown in Figure 2**a** and **b**, most of the deaths occur between 10 and 30 years of age, and almost all deaths are due to inter-arterial passage of the left main coronary artery. The age distribution of those whose symptoms or death were not due to the anomaly (Fig 2**c**) is almost flat, and inter-arterial passage does not predominate. The vertical scales are the same in all the figures, and hence reports of symptomatic patients are the majority, probably reflecting selection bias. It is possible that the slight deficit of patients under 30 years of age in Figure 2**c** is due to their removal because of symptoms. We have no way of knowing whether a large pool of asymptomatic subjects exists, but their rarity suggests that most of these patients come to medical attention when young.

There is less good information about the right coronary artery arising from the left sinus of Valsalva (Fig 3). As described in the literature, by 2013 death or symptoms due to the anomaly were less frequent than those reported in patients with left main coronary artery from the right sinus of Valsalva. There appear to be five to ten times as many patients with an anomalous right than an anomalous left coronary artery, and thus these data strongly suggest that most of the right coronary artery anomalies are benign. Deaths when they occur are predominantly below 30 years of age, but are more spread out than for the anomalous left main coronary artery because of a

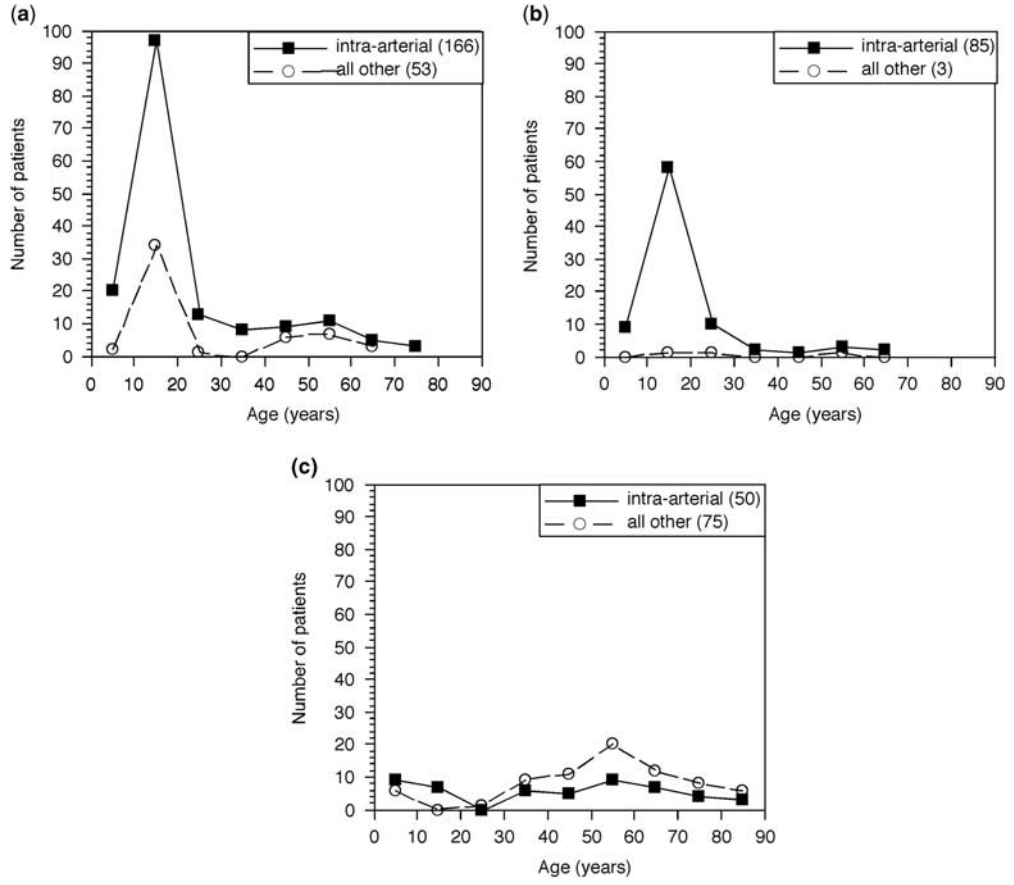

Figure 2.
*Age distribution for left main coronary artery arising from the right sinus of Valsalva. Symptoms due to the anomaly: (**a**) Any symptoms, including death, (**b**) Only deaths, (**c**) All symptoms, including death, not due to the anomaly, or no symptoms. The numbers in parentheses are the totals for that group. There are far fewer patients here than cited in the tables above because many reports do not list individual ages. In many early studies conducted without autopsy or angiography, it is often difficult to decide if the symptoms were due to coronary artery disease or the arterial anomaly.*

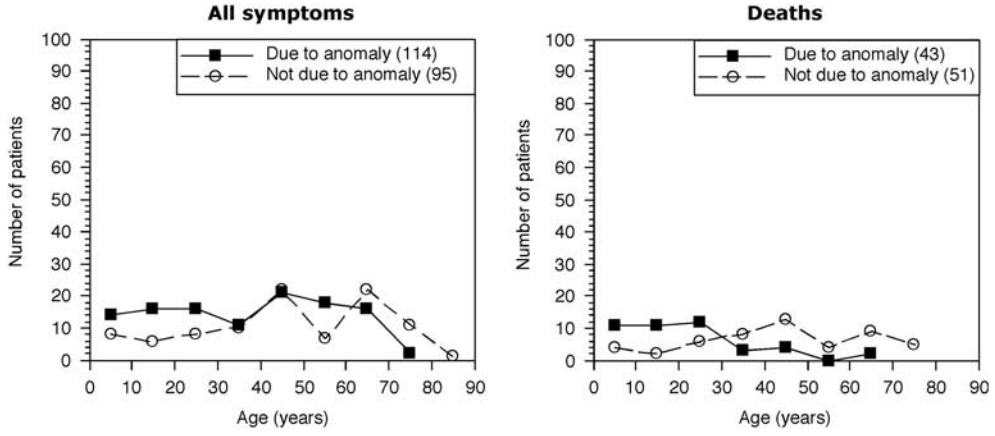

Figure 3.
Age distribution for right coronary artery arising from the left sinus of Valsalva. The numbers in parentheses are the totals for that group. The group listed as symptom not due to the anomaly includes a few with no symptoms.

slightly greater number below 10 years of age. Deaths also occur mainly with respect to strenuous exercise. Those with any symptoms due to the anomaly are spread fairly evenly over all age groups; the higher death rate under 30 years of age may reflect the lesser likelihood of severe exertion over that age.

Single coronary arteries appear to be more benign. In three large series, only 17/108 (16%) had ischaemia due to the anomaly. In the data described below, at most 21% had evidence of ischaemia. The age distribution of single coronary arteries that did or did not cause symptoms or death is shown in Figure 4.

Older patients predominate in those in whom the anomaly did not cause symptoms or death because often the anomaly is discovered during diagnosis and treatment of coronary heart disease. A smaller increase under 10 years of age reflects single coronary arteries to be found coincidentally during diagnosis of congenital heart disease. Those with symptoms or death are spread out evenly across the age groups from 10 to 60 years. Most deaths occurred during or after extreme exertion.

Of those with symptoms or death due to the anomaly, there were 20/131 (15%) with intra-arterial passage and 18/47 (38%) with other anatomic courses. Thus, although the collected literature demonstrates a predominance with intra-arterial passage, the morbidity with intra-arterial passage is significantly lower than for other anatomic variants (χ^2, 1.93, $p = 0.00$, odds ratio 0.29 with 95% confidence limits of 0.127–0.661).

Data for abnormal origin from the posterior sinus of Valsalva are sparse enough to be presented singly in Table 5.

An ectopic left main coronary artery arising from the posterior sinus, non-facing sinus, of Valsalva is much more often described than an ectopic right coronary artery, but whether this reflects a difference in incidence or is due to selection bias is unknown. All 10 ectopic left main coronary arteries thought to have caused symptoms or death, including one patient with both main coronary arteries ectopic, had one or more abnormal anatomic features – intramural course, acute angulation at exit from aorta, or a slit-like orifice. In one 11-year-old child who developed ventricular fibrillation while running, none of these abnormalities were found. With one exception, a 72-year-old man with infective endocarditis and aortic valve disease, these abnormal anatomic features were not described for those in whom the cause of symptoms was not defined or else due to coronary artery disease or some other disease. Therefore, despite their rarity, these anomalies should be investigated for anatomic or physiologic perfusion abnormalities as for any other form of ectopic origin of a coronary artery.

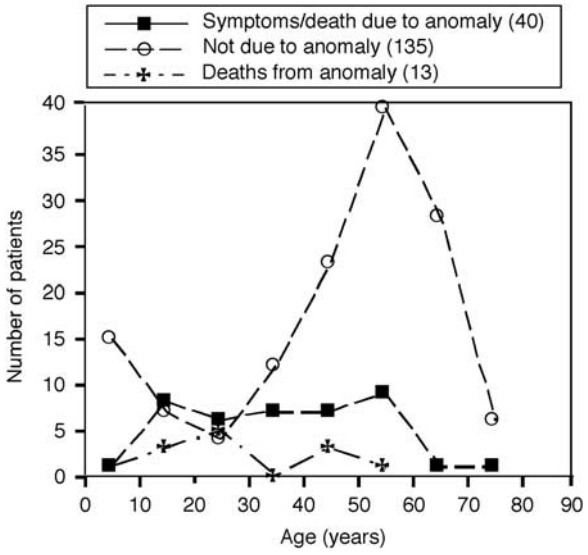

Figure 4.
Age distribution of patients with a single coronary artery. Numbers in parentheses are totals in each group.

Pathophysiological mechanisms of symptoms and death

These anomalies cause symptoms and death from myocardial ischaemia. In many older patients, the cause of ischaemia was atherosclerotic narrowing with or without thrombosis in the course of the anomalous artery and differs in no way from coronary atherosclerosis in normally attached arteries.[14] In some studies, there was less atheroma in anomalous than normally attached arteries, whereas in others the anomalous arteries appeared to have accelerated atheroma.[6] There was a tendency for more atherosclerosis in the anomalous left circumflex coronary artery arising from the right sinus of Valsalva than that arising normally.[8,24,25,56,57]

Even in the absence of coronary atheroma, some patients have classical angina pectoris, although older adults may have atypical chest pain. In a few patients, regional myocardial ischaemia has been shown by scintigraphic or computerised tomography studies. About 20% of autopsies have shown subendocardial scars or even a localised infarct.[58] Death may be due to ischaemia-induced ventricular fibrillation, as documented many times.[6] Almost all deaths occurred during or just after exercise, and frequently patients had no preceding symptoms.

There are four functional demonstrations of myocardial hypoperfusion and ischaemia. Brandt et al[59] studied a man with angina of effort who had an anomalous right coronary artery arising from the left sinus of Valsalva. During surgery, a graft was placed from the aorta to the right coronary artery after its emergence between the great arteries. Coronary flow

Table 5. Origin from posterior (non-aortic) sinus of Valsalva.

Reference	Age/gender	Symptoms due to anomaly	Anatomy
Left main coronary artery ectopic: cause of problem			
Anwar et al[92]	6F	Arrhythmia, chest pain	Intramural course, acute angulation at exit from aorta
Anwar et al[92]	11F	Arrhythmia, syncope	Intramural
Hamamichi et al[93]	12F	Sudden death after exertion	Slit-like orifice, acute angulation at exit from aorta
Ishikawa et al[94]	12F	Sudden death after exertion	Slit-like orifice, acute angulation at exit from aorta, flattened but not compressed by main pulmonary artery
Nishiyama et al[95]	13M	Cardiac arrest with running	Intramural course, acute angulation at exit from aorta
Nathan et al[96]	40F	Chest pain	Slit-like orifice, acute angulation at exit from aorta, probably intramural
Garg et al[97]	42M	Chest pain	Acute angulation at exit from aorta, passed between aortic root and left atrium
Zeina et al[98]	58M	?	Acute angulation at exit from aorta
Lo et al[99]	66M	?(Chest pain from CAD but abnormal origin)	Intramural course, acute angulation at exit from aorta
Left main coronary artery ectopic: not cause of problem			
Frescura et al[12]	1 day	No (perinatal asphyxia)	
Lawson et al[100]	52M	No (chest pain from CAD)	No angulation at exit from aorta
Cohen et al[101]	68F	No (probably due to CAD)	No angulation at exit from aorta
Morimoto et al[102]	72M	No (aortic valve disease and infective endocarditis)	Intramural course with acute angulation at exit
Left main coronary artery ectopic: cause of problem uncertain			
Liberman et al[103]	11M	Ventricular fibrillation	No abnormality detected
Datta et al[104]	?	?	?
Baduini[105]	?	?	No angulation at exit from aorta
Yang et al[77]	3 patients age?	?	All passed between aortic root and left atrium
Click et al[26]	?	?	?
Yamanaka and Hobbs[24]	?	?	?
Right coronary artery ectopic			
Candemir et al[106]	61F	No (chest pain from CAD)	?
Yamanaka and Hobbs[24]	4 patients, age ?	?	?
Both main coronary arteries ectopic			
Catanzaro et al[107]	16M	Sudden death after exertion	Intramural course, acute angulation at exit from aorta; No angulation described
Ectopic artery not described			
Ogden[108]	?	No (chest pain from CAD)	?

CAD = coronary artery disease; LMCA = left main coronary artery
Within each group, patients are arranged by ascending age

reserve as tested by reactive hyperaemia was normal when flow perfused the graft, but was much reduced when only the proximal right coronary artery conducted the flow. In a similar patient, the fractional flow reserve after injecting adenosine into the anomalous right coronary artery was reduced to 0.41.[60] In one patient with single right coronary artery, infusing adenosine reduced the fractional flow reserve in the left anterior descending coronary artery;[61] this patient had apical hypoperfusion abolished after surgery. Reduced fractional flow reserve after infusing adenosine or dobutamine was documented in a 14-year-old girl with the left main coronary artery attached to the right sinus of Valsalva, chest pain, and evidence of apical hypoperfusion on stress testing.[62] During surgery, a slit-like orifice was observed and corrected. The reduced myocardial fractional flow reserve indicates that the orifice obstruction was the major cause of the ischaemia.

A more elaborate study was performed by Bartoli et al[63] who took advantage of the incidental finding of a calf with an anomalous left coronary artery from the right sinus of Valsalva with inter-arterial passage. They increased myocardial metabolism and heart rate by infusing dobutamine and arterial blood pressure by infusing phenylephrine. During an increased heart rate, the resistance to flow increased in the left main coronary artery; its flow did not increase as much as the flow in the right coronary artery, and there was increasing ST depression. Elevating arterial blood pressure in normal calves increased the flow in normal left main coronary arteries but decreased it in the anomalous left main coronary artery. Histological changes of acute ischaemia were seen in the territory supplied by the anomalous left main coronary artery.

Schmidt et al[64] studied two adults with angina pectoris and a single right coronary artery. In one, the left main coronary artery passed anterior to the main pulmonary artery but ran deep in the ventricular muscle. In the other, the left main coronary artery passed between the two great arteries. A Doppler wire demonstrated the localised regions of flow acceleration in each abnormal left main coronary artery remote from its origin, suggesting narrowing and potential restriction to maximal flow. Dauty et al[65] observed a 22-year-old professional football player with a right coronary artery arising from the left sinus of Valsalva. The artery had a diameter of 3.5 mm at its origin that decreased to 1.6 mm as it passed between the great arteries. There are few reports on the absolute sizes of these abnormal coronary arteries, and no flow studies on them other than those cited above. It is possible that arteries may either become narrower over time or that patients might outgrow the vasodilator capability of these arteries, leading to late onset of symptoms.

Basso et al[58] postulated that the subendocardial scarring resulted from repetitive episodes of ischaemia, a conclusion that fits the patchy distribution of coronary flow reserve demonstrated in dogs by Coggins et al.[66] This probably explains the high number of sudden deaths during intensive exercise, but does not completely explain the age incidence of sudden death, which occurs predominantly between 10 and 20 years of age.[6,55] It may take several years before there is enough myocardial damage to make the heart vulnerable to ventricular fibrillation. Alternatively, the obstruction to coronary flow gradually increases because of differential growth of the anomalous coronary artery and the aorta so that the obstruction gradually increases in severity, and it is even possible for the flap that sometimes covers the coronary orifice to grow and become more obstructive with time. These considerations have a bearing on diagnosis, because tests for myocardial ischaemia may be normal at one time but abnormal some years later.

Mechanisms of ischaemia

Myocardial ischaemia suggests an obstruction to coronary blood flow that could be either distal, as the anomalous artery passes between the great arteries, peri-aortic due to kinking and angulation of the anomalous artery as it leaves the sinus of Valsalva, or proximal with respect to the abnormal coronary orifice and intramural course. A rarer possibility is diffuse spasm of the artery.

Early observations about the predominance of inter-arterial passage of the anomalous artery among patients who died suggested that during exercise the anomalous artery was compressed between the aorta and the main pulmonary artery or right ventricular outflow tract. One study of an anomalous right coronary artery with multidetector computed tomography reported a 35% decrease in the cross-sectional area of the origin of the right coronary artery in systole in a patient at rest.[67] Other investigators have demonstrated narrowing of the inter-arterial portion of the right coronary artery.[43,65,68–70]

During strenuous exercise in normal individuals, systolic and diastolic blood pressures increase in the aorta and pulmonary arteries. Aortic systolic arterial pressures may rise up to about 200 mmHg with severe exercise, and diastolic aortic pressure may increase by 10–20 mmHg.[71–73] Therefore, with exercise the coronary arteries should be exposed to these higher pressures and should dilate. The mean pulmonary arterial pressures can rise to 30 mmHg,[71,74–76] the increase being much less than in the aorta so that the pressure difference between the pulmonary and coronary artery increases during exercise, suggesting less ability of the pulmonary artery to compress the coronary artery.

Some deformation of the anomalous arteries in systole might occur because of stretching of the aortic root or tension or pressure changes in the dense connective tissue between the great arteries, but unfortunately there are no reports of the cyclic changes in diameter of these anomalous coronary arteries during exercise. Chaitman et al[77] described a case of a 49-year-old woman with mitral stenosis and pulmonary hypertension who had no evidence of myocardial ischaemia, despite inter-arterial passage of the left main coronary artery.

If because of some presently unknown anatomic factors the anomalous coronary artery is narrowed in systole, it is still not clear that this is of physiologic importance. As far as we know, almost all the systolic flow in the left coronary artery distends the extramural arteries and little if any perfuses the myocardium. If it does, it is confined to the superficial myocardium because the subendocardium is perfused only in diastole.[78] Furthermore, those anomalous arteries that run in the upper part of the septum and are always exposed to high pressures during systole have a very low incidence of symptoms and death. Add to this list the fact that some patients develop myocardial ischaemia and even die suddenly with anomalous arteries that do not pass between the great arteries, so that compression between the great arteries is an unlikely mechanism for the observed myocardial ischaemia in most patients.

An alternative mechanism is a proximal obstruction associated with the slit-like coronary orifice, sometimes an overlying tissue flap, or narrowing of the artery as it runs in the aortic wall. In one study,[79] patients were more likely to have symptoms if the intramural pathway was long (10 mm) than when it was short (5 mm). They did not, however, measure the luminal diameters.

It is possible that during exercise the increased systolic pressure in the aortic wall narrows the intramural artery further, or at least prevents the artery from dilating, thereby impeding the increased coronary blood flow that is required by the increased myocardial work.

The slit-like ostium, tissue flap, intramural course, and kinking of the artery as it leaves the sinus of Valsalva are found with the anomalous right coronary artery arising from the left sinus of Valsalva, with the left main coronary artery, which runs from the right sinus of Valsalva between the great arteries, or with the left main coronary artery arising from the posterior sinus of Valsalva.

Lipton et al[46] observed that in four patients with a single coronary artery the cross-sectional area of the single main coronary artery was about 46% of the combined cross-sectional area of two normally attached coronary arteries. It is possible that in some patients the diameter might be even smaller and restrictive at times when high coronary flows are needed.

Treatment

Medical treatment

Conservative treatment with beta-adrenergic blockers, nitrates, angiotensin-converting enzyme blockers, or calcium blockers, as well as limiting exercise, has been effective for some older patients with a right coronary artery arising from the left sinus of Valsalva. Kaku et al[28] described 44 patients with a mean age about 56 years, most of whom had symptoms including syncope and about half had scintigraphic evidence of local myocardial ischaemia. During follow-up for 2 months–14.5 years (mean 5.66 years), there were no deaths due to the anomaly. Ouali et al[36] treated 20 adults (mean age 53 years) for a mean of 34 months without complications, but there were only three patients with a right coronary artery from the left sinus of Valsalva. Berdoff et al[80] described seven patients with chest pain, all but one becoming asymptomatic on follow-up; the treatment was not described. No patient in these series had an anomalous left main coronary artery arising from the right sinus of Valsalva. Opolski et al[38] treated 21/24 symptomatic patients – 20 with an anomalous right coronary artery, two with an anomalous left main coronary artery, and one each with anomalous left circumflex coronary artery or left anterior descending coronary artery – conservatively for 5–44 months with no deaths due to the anomaly but with substantial residual symptoms including chest pain and syncope. A 45-year-old and a 61-year-old patient with a right coronary artery arising from left sinus of Valsalva became asymptomatic after treatment with beta-adrenergic blockers,[81,82] one such patient aged 68 years became asymptomatic with no anti-anginal treatment,[83] and a 51-year-old man with a left main coronary artery arising from the right sinus of Valsalva and taking a long intra-septal course became asymptomatic after slowing of his heart rate with Ivabradine (Procorolan®, Servier Laboratories, Neuilly-sur-Seine, France).[84]

Medical treatment is inappropriate for children or young adults who are usually managed by exercise restriction or surgical correction of the anomaly.[85]

Surgical treatment

Coronary artery bypass. Some of the earliest operations bypassed the potential obstructions by using a saphenous vein or internal thoracic artery graft,[86–89] but competition between the graft and the native flow path may lead to graft failure.[50,90–92]

Surgery on origin of anomalous artery. The type of surgery depends on the specific anatomy:

a. No intramural course; separate orifices in the sinus of Valsalva.
b. Slit-like orifice, intramural course, kinking, or narrowing at exit from aorta; these features are

typical of an anomalous coronary artery arising from the wrong sinus of Valsalva and taking an inter-arterial course.

c. Both right and left coronary arteries share a common orifice.
d. Single orifice and single main coronary artery that then divides outside the aorta.

Direct implantation. Direct implantation may be performed for group a, especially if the orifices are well separated.[93–97] It is usually unsuitable for the other anatomic types because of insufficient tissue to create a button around the orifice or the need to avoid kinking. However, it is not clear that this anatomy causes proximal obstruction.

Reconstruction of the orifice. The operation most often performed for group b is to remove any proximal obstruction by unroofing the intramural portion of the artery. In the large series reported by Poynter et al,[5] this operation was performed in 87% of the patients. Unroofing eliminates any flap and the slit-like orifice, widens the narrowed intramural artery and prevents its compression during systole, and eliminates kinking. The procedure is uncomplicated if the intramural artery is distal to the commissure. If it is not, then the commissure must be detached and later resuspended, and aortic regurgitation may result.[49,98,99] To avoid this complication, some surgeons create a neo-ostium between the distal portion of the intramural artery and the commissure and then obliterate the portion of the artery between the commissure and the original ostium.[100]

The operative mortality is virtually zero, but occasional short-term complications occur, as after any cardiotomy (see Table 3 by Peñalver et al[48]). Of more concern are long-term potential complications such as stenosis of the neo-orifice, loss of endothelial function, residual myocardial ischaemia,[101] and premature atherosclerosis in these arteries. Follow-up has not been very long, with the two longest series extending to 7 and 9 years.[49,102] In the Mayo Clinic experience,[50] the average follow-up was 1.1 years; one patient was doing well 14 years after surgery, and only 1/36 patients had symptoms. However, Wittlieb-Weber et al[102] followed 24 patients after surgery, with no late deaths. They noted, that 54% reported the same symptoms as pre-operatively, but with no signs of ischaemia, and that four patients developed mild aortic insufficiency. Long-term results remain to be evaluated.

Chest pain in children is less likely to be ischaemic in origin and more likely to be of non-specific chest wall origin than it is in adults. It is therefore possible that the anomalous coronary artery in children is often detected by echocardiography performed for non-specific chest pain that will not be relieved by surgery of the anomalous artery.

Similar relief of the proximal obstruction may be obtained by stenting the orifice. In the 1990s, interventional cardiologists learnt how to perform balloon angioplasty to insert a stent for atherosclerotic lesions of anomalous coronary arteries, and in 2000 Doorey et al[103] reported placing stents in the proximal portions of the coronary artery in four patients with a left main coronary artery arising from the right sinus of Valsalva and in nine patients with a right coronary artery arising from the left sinus of Valsalva. One stent implanted early in the series developed compression of its midsegment. In a short follow-up, all patients did well with normal perfusion scans. Since then, at least six other patients have had successful implantation of a stent into the anomalous right coronary artery.[68,70,104,105] Little follow-up information is available, and the long-term outlook for stents is uncertain; for this reason, stents are not currently indicated for children.

Surgically reconstructing the orifice of the anomalous coronary artery abolishes symptoms; hence, it strongly favours the concept that the obstruction to flow is proximal and not between the great arteries. The success of proximal stents does not have the same implications, because the stents are 10–20 mm long and hold open not only the region of the orifice, but also the inter-arterial portion of the anomalous artery.

Single ostium or single coronary artery. Sometimes the coronary artery with an anomalous origin shares a single orifice with the normal artery or common trunk and does not have an intramural course in the aortic wall (type c),[97] or else there is a single coronary artery that bifurcates outside the aorta (type d). Removing and reimplanting the ectopic artery into its appropriate sinus of Valsalva may be difficult because there may not be enough tissue to provide a large button for implantation.[98,106] The options are then to translocate the pulmonary artery (see below) or to perform a distal coronary artery bypass graft. In one patient,[107] the orifice of the single artery was narrowed, and enlarging this relieved the symptoms.

The role of distal obstruction was reconsidered after pulmonary artery translocation was introduced. Rodefeld et al[108] operated on an 11-year-old boy with right and left coronary arteries arising from a single ostium in the left sinus of Valsalva, the right coronary artery then passing between the great arteries. Reimplantation was not possible because there would not have been a large enough button of tissue after removing the right coronary artery from the common orifice. The main pulmonary artery was transected just below the pulmonary arterial bifurcation and then reanastomosed to the left pulmonary artery, thus opening up the space between the aorta and main pulmonary artery beyond their attachments to the heart; the right pulmonary artery was patched to

prevent stenosis. A variant of this technique is to transect the aortic root as well, widen the proximal part of the anomalous artery beyond the intramural segment with a patch, and then proceed with the pulmonary artery translocation.[109,110] With this technique, both proximal and perhaps distal obstructions will be relieved, although it is unclear whether the benefit is because of more than creating the neo-orifice.

Is the anomaly causing myocardial ischaemia?

These patients may come to medical attention for a number of symptoms: resuscitation after cardiac arrest, syncope or ventricular arrhythmias during or just after strenuous exercise, or angina of effort. Chest pain may be atypical but requires investigation if it is recurrent with exertion and no localised chest abnormalities are found. From the literature, atypical chest pain seems to be more common in older adults. Congestive heart failure is rare.

At other times, coronary anomalies may be found incidentally while the patient is being investigated by imaging techniques for other cardiac problems.

Symptomatic patients

In addition to a careful history and physical examination, the patients need an electrocardiogram to look for ST changes suggestive of myocardial ischaemia and for arrhythmogenic abnormalities such as the long or short QT interval, Brugada syndrome, or abnormalities consistent with arrhythmogenic right ventricular dysplasia.[111–113]

Imaging begins with an echocardiography–Doppler examination that has three objectives:

1. Exclude other cardiopulmonary pathology such as hypertrophic cardiomyopathy, aortic stenosis, or severe pulmonary hypertension.
2. Look for regional wall motion abnormalities.
3. Examine the origins of the coronary arteries. If these are ectopic the possibility of restrictive flow needs to be determined (see below). If they do not appear to be ectopic but the history is compatible with an ectopic coronary artery, further imaging with magnetic resonance imaging or fast computerised tomography is mandatory because of the known lack of sensitivity of echocardiography. Special care is needed for imaging intramural passage of the anomalous artery because most standard computerised tomography or magnetic resonance imaging sequences do not show intramural vessels well.[114] It may even be necessary to examine the origin of the artery by intravascular ultrasound, although relatively few cardiologists have expertise in this form of investigation.

The origins of the coronary arteries may be restrictive because of an ostial flap, slit-like orifice, narrowed and long intramural course in the aortic wall, narrowing or kinking as the artery leaves the aorta, or the tangential arterial exit that leaves the aorta at an acute angle. Such restrictions are associated with relative hypoperfusion, especially when myocardial flow needs to be increased markedly with exercise. Any site of localised flow acceleration in the coronary artery suggests a restriction that may cause hypoperfusion at maximal flow.

In the absence of visible restriction to flow, regional hypoperfusion should be assessed. This can be performed by single-photon emission computed tomography with $Thallium^{201}$ or $Technetium^{99m}$ or by positron emission tomography that has advantages over single-photon emission computed tomography.[115] The patient is examined during exercise and then while resting to look for redistribution. Alternatively, coronary flow reserve in the abnormal artery may be measured by echocardiography–Doppler examination at rest and then after exercise or after increasing myocardial blood flow by infusing dobutamine or dipyridamole. It is important to compare normal and ectopic arteries to show their difference. Farhad and Murphy[116] provided a detailed discussion of methods, mechanisms, and dosages.

Dobutamine increases myocardial contractility and heart rate, consequently increasing myocardial work and oxygen consumption. It is used as a substitute for exercise and has been shown to be free of serious complications when used in adults with myocardial ischaemia from coronary atheroma. It may, however, cause a coronary steal and regional myocardial ischaemia. Even without a steal, failure of flow to increase appropriately may lead to regional wall motion abnormalities. The agent is given by infusion at doses of 10–50 $\mu g\ kg^{-1} min^{-1}$.

Vasodilatation without exercise can be achieved by infusing adenosine at a dose of 140 $\mu g\ kg^{-1} min^{-1}$ for 4 min. Adenosine acts on all four purinergic receptors in the arterial wall to cause vasodilatation without an increase in myocardial work or oxygen consumption. Minor side effects are common, and the agent should be avoided in patients with reactive airway disease, sick sinus syndrome, or first- or second-degree heart block. Adenosine is rapidly metabolised. As an alternative, dipyridamole is infused at a rate of 0.14 $mg\ kg^{-1}\ min^{-1}$ for 4 min. This agent inhibits the reuptake of adenosine into cells and also inhibits its breakdown by adenosine deaminase.[117] In patients, it may cause a coronary steal and chest pain, and mild side effects are common, but this effect can be reversed immediately by 75 mg of intravenous aminophylline in adults. Regadenoson (Lexiscan®, AstellasPharma, Tokyo, Japan) has a much greater

affinity for A_{2A} receptors – the main receptors for coronary vasodilatation – than for the other adenosine receptors, and hence has fewer side effects. It is given as an intravenous bolus – 0.4 mg in 5 ml saline over 10 s – followed by a 5-ml saline flush.[117]

It is beneficial to use a combination of these tests, because an important large study of patients showed that any single test may not indicate ischaemia when the others do.[118] Furthermore, the stress electrocardiogram may show ischaemia at one time but not at another.[119]

If the ectopic artery is anatomically restrictive or shows a reduced coronary flow reserve, then treatment of the anomaly is required when the obstruction is severe enough (see below). If there is neither anatomic nor functional restriction of flow, then the patient may be observed with or without medical treatment such as nitrites, beta-adrenergic blockers, or calcium blockers.

Patients with incidental finding of an ectopic coronary artery

If an ectopic coronary is found incidentally, much the same course of investigation should be pursued. These patients will probably not have symptoms to suggest that the anomaly is causing myocardial ischaemia. Just as for symptomatic patients, the anatomy of the origin of the ectopic coronary artery must be defined, and if it is normal then the flow capacity of that ectopic artery must be evaluated. Either anatomic or functional flow restriction requires correction of the anomaly, but in their absence only observation is required.

Who should be treated?

Finding an anatomic site of flow restriction or reduced coronary flow reserve is by itself insufficient evidence to proceed to surgery, just as it is not absolute indication for treatment of coronary atheroma. It is the degree of obstruction and hypoperfusion that matters. If the severity of obstruction is not obvious to the naked eye, many cardiologists have determined myocardial fractional flow reserve or coronary flow reserve to assess the severity. The myocardial fractional flow reserve method involves measuring pressures with a pressure-sensitive wire in the proximal coronary or aorta (Pa), beyond the stenosis (Pc), and right atrial pressure as an estimate of coronary venous pressure (Pv). The measurements are made during maximal coronary vasodilatation.[120,121]

$$\text{Myocardial fractional flow reserve} = \frac{Pc - Pv}{Pa - Pv} \approx \frac{Pc}{Pa}$$

This method assumes normal microvascular function and linear relationships that are often absent.[122] Nevertheless, a myocardial fractional flow reserve ratio of less than 0.75 is a good predictor of the need for stenting a narrowed coronary artery.[123,124] This method has been applied successfully in children with Kawasaki disease,[125] and the cut-off values for myocardial fractional flow reserve in children were also 0.75. These authors also found that a coronary flow reserve of less than 2 had the same significance. Even if the coronary flow reserve can be measured non-invasively, the results are not independent of basal coronary flow. The rationale, values, and limitations of all these methods are described clearly by Canty.[126] Recent studies by Sen et al[127,128] have suggested that a ratio similar to the myocardial fractional flow reserve can be measured without the need for vasodilatation. It is even possible to measure stenosis resistance with a wire containing both pressure and flow sensors,[129] but good standards are not yet available.

With this background, any evidence of anatomic obstruction requires evaluation of its severity. Naturally, if there is associated evidence of regional ischaemia, then hypoperfusion has been confirmed.

Specific anomalies

If there is a left main coronary artery arising from the right sinus of Valsalva and passing between the great arteries in a young athlete, many physicians recommend surgical correction, especially if there is a slit-like orifice, intramural passage, or narrowing or kinking of the artery as it leaves the aorta. These features predict a high risk for sudden death during exercise, and warrant treatment.

If there is a left main coronary artery arising from the right sinus of Valsalva and not passing inter-arterially, then most physicians would look for evidence of significant anatomic obstruction to the coronary flow or evidence of hyoperfusion or myocardial ischaemia before recommending operation, because the risk of symptoms from these other courses is not high and because the long-term complications of the surgery are unknown. The same issue arises with a single coronary artery, although as pointed out above the flow restriction might be because of the size of the single coronary orifice. Should the patient be older, have vague symptoms, and not be involved in strenuous activity, medical treatment has been recommended. As mentioned above, no late deaths have occurred in a limited series of such patients.

If the anomaly is a right coronary artery arising from the left sinus of Valsalva, the decision is more difficult. If the data on the high incidence of asymptomatic anomalies are confirmed, then few of the anomalous right coronary arteries threaten health. Emphasis then must be placed on the anatomy of the orifice, with any signs of significant restriction, or on the functional tests of myocardial ischaemia. If these are present, then surgical correction is recommended. Once again, the more severe the symptoms and evidence of ischaemia, the more likely is it that surgery will be needed.

An ectopic left main coronary artery arising from the posterior sinus of Valsalva may often cause serious problems, and should be investigated as a potential cause of myocardial ischaemia. The risk is much less for a right coronary artery arising from the posterior sinus of Valsalva. Nevertheless, any anomaly of coronary arterial origin associated with symptoms related to myocardial ischaemia needs to be carefully assessed by expert imaging and if necessary by studies to detect hypoperfusion.

Physicians usually seek evidence of myocardial ischaemia by scintigraphic tests with and without exercise; hence, consideration should be given to the alternative of evaluating coronary flow reserve with transthoracic, trans-oesophageal, or intravascular Doppler techniques. The association of symptoms with a reduced flow reserve in the anomalous artery – coronary flow reserve <2 or myocardial fractional flow reserve <0.75 – might be taken to indicate the need for surgery.

Failure to find evidence of coronary flow restriction or myocardial ischaemia with any of the major anomalies suggests that surgery is not required at the time, but does not preclude the need for surgery in the future. One such patient with mild symptoms was followed with annual stress tests from the age of 8 years until she was 14 years when a positive stress test was first observed; surgery corrected the problem.[62] Anatomic abnormalities such as ostial flaps and narrowing or kinking of the artery might progress. After all, a patient who drops dead while exercising strenuously at the age of 18 years probably had no trouble performing the same strenuous exercise at the age of 17 years. Therefore, if one of these anomalies is identified in an asymptomatic patient, there should be follow-up with imaging and testing for regional myocardial ischaemia. This will result in many patients having unnecessary tests, but until we have better methods of detecting those at risk this will be the only way to reduce the death rate from these anomalies.

Conclusion

We can now detect in some patients an anomalous coronary artery that is causing ischaemia and is a threat to life; however, in many other patients the cause of the symptoms remains uncertain and our treatment is at best an educated guess. There is a need for extensive further study of these anomalies.

Acknowledgements

The author is grateful for helpful discussions with Dr David Teitel, Dr Paolo Angelini, and Dr Jane Newburger.

Financial support

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Conflict of interest

None

Supplementary Material

To view supplementary material for this article, please visit http://dx.doi.org/10.1017/S1047951114000250.

References

1. Roberts WC. Major anomalies of coronary arterial origin seen in adulthood. Am Heart J 1986; 111: 941–963.
2. Dodge-Khatami A, Mavroudis C, Backer CL. Congenital Heart Surgery Nomenclature and Database Project: anomalies of the coronary arteries. Ann Thorac Surg 2000; 69: S270–S297.
3. Angelini P. Coronary artery anomalies: an entity in search of an identity. Circulation 2007; 115: 1296–1305.
4. Brothers JA, Gaynor JW, Jacobs JP, Caldarone C, Jegatheeswaran A, Jacobs ML. The registry of anomalous aortic origin of the coronary artery of the Congenital Heart Surgeons' Society. Cardiol Young 2010; 20 (Suppl 3): 50–58.
5. Poynter JA, Williams WG, McIntyre S, Brothers JA, Jacobs ML, Congenital Heart Surgeons Society. Anomalous aortic origin of a coronary artery: a report from the congenital heart surgeons society registry. World J Pediatr Cong Heart Surg 2014; 5: 22–30.
6. Hoffman JIE. The Natural and Unnatural History of Congenital Heart Disease. Wiley/Blackwell, Oxford, 2009.
7. Patterson FK. Sudden death in a young adult with anomalous origin of the posterior circumflex artery. South Med J 1982; 75: 748–749.
8. Ueyama K, Ramchandani M, Beall AC Jr., Jones JW. Diagnosis and operation for anomalous circumflex coronary artery. Ann Thorac Surg 1997; 63: 377–381.
9. Surucu H, Tatly E, Deethirmenci A, Kurtoethlu N. Anomalous origin of coronary arteries from three separate ostiums in the right sinus of Valsalva: three case reports and review of the literature. Int J Cardiol 2006; 106: 264–267.
10. Tuncer C, Batyraliev T, Yilmaz R, Gokce M, Eryonucu B, Koroglu S. Origin and distribution anomalies of the left anterior descending artery in 70,850 adult patients: multicenter data collection. Catheter Cardiovasc Interv 2006; 68: 574–585.
11. Surana SP, Doddamani S, Swaminathan A, et al. Anomalous coronary circulation: left anterior descending and left circumflex coronary arteries arising from the right sinus of valsalva. Echocardiography 2012; 29: E102–E104.
12. Cheitlin MD, De Castro CM, McAllister HA. 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: 780–787.
13. 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: 689–695.
14. Alexander RW, Griffith GC. Anomalies of the coronary arteries and their clinical significance. Circulation 1956; 14: 800–805.
15. Lipsett J, Cohle SD, Berry PJ, Russell G, Byard RW. Anomalous coronary arteries: a multicenter pediatric autopsy study. Pediatr Pathol 1994; 14: 287–300.
16. Pelliccia A, Spataro A, Maron BJ. Prospective echocardiographic screening for coronary artery anomalies in 1360 elite competitive athletes. Am J Cardiol 1993; 72: 978–979.

17. 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: 89–93.
18. Davis JA, Cecchin F, Jones TK, Portman MA. Major coronary artery anomalies in a pediatric population: incidence and clinical importance. J Am Coll Cardiol 2001; 37: 593–597.
19. Lytrivi ID, Wong AH, Ko HH, et al. Echocardiographic diagnosis of clinically silent congenital coronary artery anomalies. Int J Cardiol 2008; 126: 386–393.
20. Werner B, Wroblewska-Kaluzewska M, Pleskot M, Tarnowska A, Potocka K. Anomalies of the coronary arteries in children. Med Sci Monit 2001; 7: 1285–1291.
21. Liberthson RR, Dinsmore RE, Bharati S, et al. Aberrant coronary artery origin from the aorta. Diagnosis and clinical significance. Circulation 1974; 50: 774–787.
22. Kimbiris D, Iskandrian AS, Segal BL, Bemis CE. Anomalous aortic origin of the coronary arteries. Circulation 1978; 58: 606–615.
23. Donaldson RM, Raphael M, Radley-Smith R, Yacoub MH, Ross DN. Angiographic identification of primary coronary anomalies causing impaired myocardial perfusion. Cathet Cardiovasc Diagn 1983; 9: 237–249.
24. Wilkins CE, Betancourt B, Mathur VS, et al. Coronary artery anomalies: a review of more than 10,000 patients from the Clayton Cardiovascular Laboratories. Texas Heart Inst J 1988; 15: 166–173.
25. Click RL, Holmes DR Jr., Vlietstra RE, Kosinski AS, Kronmal RA. Anomalous coronary arteries: location, degree of atherosclerosis and effect on survival – a report from the Coronary Artery Surgery Study. J Am Coll Cardiol 1989; 13: 531–537.
26. Yamanaka O, Hobbs RE. Coronary artery anomalies in 126,595 patients undergoing coronary arteriography. Cathet Cardiovasc Diagn 1990; 21: 28–40.
27. Topaz O, DeMarchena EJ, Perin E, Sommer LS, Mallon SM, Chahine RA. Anomalous coronary arteries: angiographic findings in 80 patients. Int J Cardiol 1992; 34: 129–138.
28. Kaku B, Shimizu M, Yoshio H, et al. Clinical features of prognosis of Japanese patients with anomalous origin of the coronary artery. Jpn Circ J 1996; 60: 731–741.
29. Kardos A, Babai L, Rudas L, et al. Epidemiology of congenital coronary artery anomalies: a coronary arteriography study on a central European population. Cathet Cardiovasc Diagn 1997; 42: 270–275.
30. Barriales Villa R, Moris C, Lopez Muniz A, et al. Adult congenital anomalies of the coronary arteries described over 31 years of angiographic studies in the Asturias Principality: main angiographic and clinical characteristics. Rev Esp Cardiol 2001; 54: 269–281.
31. Harikrishnan S, Jacob SP, Tharakan J, et al. Congenital coronary anomalies of origin and distribution in adults: a coronary arteriographic study. Indian Heart J 2002; 54: 271–275.
32. Gol MK, Ozatik MA, Kunt A, et al. Coronary artery anomalies in adult patients. Med Sci Monit 2002; 8: CR636–CR641.
33. Turkmen S, Cagliyan CE, Poyraz F, et al. Coronary arterial anomalies in a large group of patients undergoing coronary angiography in southeast Turkey. Folia Morphologia (Warsz) 2013; 72: 123–127.
34. Xu H, Zhu Y, Zhu X, Tang L, Xu Y. Anomalous coronary arteries: depiction at dual-source computed tomographic coronary angiography. J Thorac Cardiovasc Surg 2012; 143: 1286–1291.
35. Yildiz A, Okcun B, Peker T, Arslan C, Olcay A, Bulent Vatan M. Prevalence of coronary artery anomalies in 12,457 adult patients who underwent coronary angiography. Clin Cardiol 2010; 33: E60–E64.
36. Ouali S, Neffeti E, Sendid K, Elghoul K, Remedi F, Boughzela E. Congenital anomalous aortic origins of the coronary arteries in adults: a Tunisian coronary arteriography study. Arch Cardiovasc Dis 2009; 102: 201–208.
37. Aydinlar A, Cicek D, Senturk T, et al. Primary congenital anomalies of the coronary arteries: a coronary arteriographic study in Western Turkey. Int Heart J 2005; 46: 97–103.
38. Opolski MP, Pregowski J, Kruk M, et al. Prevalence and characteristics of coronary anomalies originating from the opposite sinus of Valsalva in 8,522 patients referred for coronary computed tomography angiography. Am J Cardiol 2013; 111: 1361–1367.
39. Tuo G, Marasini M, Brunelli C, Zannini L, Balbi M. Incidence and clinical relevance of primary congenital anomalies of the coronary arteries in children and adults. Cardiol Young 2013; 23: 381–386.
40. Aydar Y, Yazici HU, Birdane A, et al. Relationship between hypoplastic right coronary artery and coronary artery anomalies. Eur Rev Med Pharmacol Sci 2013; 17: 694–700.
41. Desmet W, Vanhaecke J, Vrolix M, et al. Isolated single coronary artery: a review of 50,000 consecutive coronary angiographies. Eur Heart J 1992; 13: 1637–1640.
42. Neuhaus R, Kober G. Single coronary artery with branching of the right coronary artery from the left atrioventricular ramus of the circumflex artery. Incidence and significance. Z Kardiol 1993; 82: 813–817.
43. Giroux SK, Cartier R. Atypical presentation of an anomalous origin of the right coronary artery with severe compression between the great vessels. Ann Thorac Surg 2002; 73: 1636–1638.
44. Angelini P. Coronary artery anomalies – current clinical issues: definitions, classification, incidence, clinical relevance, and treatment guidelines. Tex Heart Inst J 2002; 29: 271–278.
45. Ogden JA, Goodyer AVN. Patterns of distribution of the single coronary artery. Yale J Biol Med 1970; 43: 11–21.
46. Lipton MJ, Barry WH, Obrez I, Silverman JF, Wexler L. Isolated single coronary artery: diagnosis, angiographic classification, and clinical significance. Radiology 1979; 130: 39–47.
47. Shirani J, Roberts WC. Solitary coronary ostium in the aorta in the absence of other major congenital cardiovascular anomalies. J Am Coll Cardiol 1993; 21: 137–143.
48. Peñalver JM, Mosca RS, Weitz D, Phoon CK. Anomalous aortic origin of coronary arteries from the opposite sinus: a critical appraisal of risk. BMC Cardiovasc Disord 2012; 12: 83.
49. Mainwaring RD, Reddy VM, Reinhartz O, et al. Anomalous aortic origin of a coronary artery: medium-term results after surgical repair in 50 patients. Ann Thorac Surg 2011; 92: 691–697.
50. Davies JE, Burkhart HM, Dearani JA, et al. Surgical management of anomalous aortic origin of a coronary artery. Ann Thorac Surg 2009; 88: 844–847.
51. Brothers JA, McBride MG, Marino BS, et al. Exercise performance and quality of life following surgical repair of anomalous aortic origin of a coronary artery in the pediatric population. J Thorac Cardiovasc Surg 2009; 137: 380–384.
52. Azakie A, Russell JL, McCrindle BW, et al. Anatomic repair of anomalous left coronary artery from the pulmonary artery by aortic reimplantation: early survival, patterns of ventricular recovery and late outcome. Ann Thorac Surg 2003; 75: 1535–1541.
53. Alexi-Meskishvili V, Nasseri BA, Nordmeyer S, et al. Repair of anomalous origin of the left coronary artery from the pulmonary artery in infants and children. J Thorac Cardiovasc Surg 2011; 142: 868–874.
54. Eckart RE, Scoville SL, Campbell CL, et al. Sudden death in young adults: a 25-year review of autopsies in military recruits. Ann Intern Med 2004; 141: 829–834.
55. Moustafa SE, Zehr K, Mookadam M, Lorenz EC, Mookadam F. Anomalous interarterial left coronary artery: an evidence based systematic overview. Int J Cardiol 2008; 126: 13–20.
56. Leroy F, Germain S, Bauters C, Lablanche JM, Bertrand ME. Abnormal origin of the left circumflex coronary artery: clinical, angiographic and prognostic aspects. Apropos of 30 cases. Arch Mal Coeur Vaiss 1992; 85: 993–999.

57. Samarendra P, Kumari S, Hafeez M, Vasavada BC, Sacchi TJ. Anomalous circumflex coronary artery: benign or predisposed to selective atherosclerosis. Angiology 2001; 52: 521–526.
58. Basso C, Maron BJ, 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: 1493–1501.
59. Brandt B 3rd, Martins JB, Marcus ML. Anomalous origin of the right coronary artery from the left sinus of Valsalva. N Engl J Med 1983; 309: 596–598.
60. Naruse Y, Sato A, Kakefuda Y, et al. Anomalous origin of the right coronary artery from the left sinus of Valsalva in an elderly man: life-threatening worsening of angina after left lung lobectomy. Circulation 2012; 125: e1021–e1024.
61. Coceani M, Ciardetti M, Pasanisi E, et al. Surgical correction of left coronary artery origin from the right coronary artery. Ann Thorac Surg 2013; 95: e1–e2.
62. Lim MJ, Forsberg MJ, Lee R, Kern MJ. Hemodynamic abnormalities across an anomalous left main coronary artery assessment: evidence for a dynamic ostial obstruction. Catheter Cardiovasc Interv 2004; 63: 294–298.
63. Bartoli CR, Wead WB, Giridharan GA, Prabhu SD, Koenig SC, Dowling RD. Mechanism of myocardial ischemia with an anomalous left coronary artery from the right sinus of Valsalva. J Thorac Cardiovasc Surg 2012; 144: 402–408.
64. Schmidt MC, Klues HG, vom Dahl J, Brenn T, Hugel W, Hanrath P. Intracoronary Doppler flow velocity measurements in two patients with solitary coronary ostium: is there true obstruction? Coron Artery Dis 1996; 7: 761–765.
65. Dauty M, Piriou N, Laprerie AL, Menu P, Dubois C, Trochu JN. Congenital anomalous origin of a single coronary artery and high-level sporting competition. Clin J Sport Med 2012; 22: 371–373.
66. Coggins DL, Flynn AE, Austin RE Jr, et al. Nonuniform loss of regional flow reserve during myocardial ischemia in dogs. Circulation Research 1990; 67: 253–264.
67. Ghersin E, Litmanovich D, Ofer A, et al. Anomalous origin of right coronary artery: diagnosis and dynamic evaluation with multidetector computed tomography. J Comput Assist Tomogr 2004; 28: 293–294.
68. Bagur R, Gleeton O, Bataille Y, Bilodeau S, Rodes-Cabau J, Bertrand OF. Right coronary artery from the left sinus of Valsalva: Multislice CT and transradial PCI. World J Cardiol 2011; 3: 54–56.
69. Grollman JH Jr., Mao SS, Weinstein SR. Arteriographic demonstration of both kinking at the origin and compression between the great vessels of an anomalous right coronary artery arising in common with a left coronary artery from above the left sinus of Valsalva. Cathet Cardiovasc Diagn 1992; 25: 46–51.
70. Porto I, MacDonald ST, Selvanayagam JB, Banning AP. Intravascular ultrasound to guide stenting of an anomalous right coronary artery coursing between the aorta and pulmonary artery. J Invasive Cardiol 2005; 17: E33–E36.
71. Cumming GR. Hemodynamics of supine bicycle exercise in "normal" children. Am Heart J 1977; 93: 617–622.
72. Singh JP, Larson MG, Manolio TA, et al. Blood pressure response during treadmill testing as a risk factor for new-onset hypertension. The Framingham heart study. Circulation 1999; 99: 1831–1836.
73. Kurl S, Laukkanen JA, Rauramaa R, Lakka TA, Sivenius J, Salonen JT. Systolic blood pressure response to exercise stress test and risk of stroke. Stroke 2001; 32: 2036–2041.
74. Damato AN, Galante JG, Smith WM. Hemodynamic response to treadmill exercise in normal subjects. J Appl Physiol 1966; 21: 959–966.
75. Ekelund LG, Holmgren A. Central hemodynamics during exercise. Circ Res 1967; 20/21: 33–43.
76. Fowler NO. The normal pulmonary arterial pressure-flow relationships during exercise. Am J Med 1969; 47: 1–6.
77. Chaitman BR, Lesperance J, Saltiel J, Bourassa MG. Clinical, angiographic, and hemodynamic findings in patients with anomalous origin of the coronary arteries. Circulation 1976; 53: 122–131.
78. Flynn AE, Coggins DL, Goto M, et al. Does systolic subepicardial perfusion come from retrograde subendocardial flow? Am J Physiol (Heart Circ Physiol) 1992; 262: H 1759–H 1769.
79. Kaushal S, Backer CL, Popescu AR, et al. Intramural coronary length correlates with symptoms in patients with anomalous aortic origin of the coronary artery. Ann Thorac Surg 2011; 92: 986–991.
80. Berdoff R, Haimowitz A, Kupersmith J. Anomalous origin of the right coronary artery from the left sinus of Valsalva. Am J Cardiol 1986; 58: 656–657.
81. Barbou F, Schiano P, Lahutte M. Anomalous right coronary artery from the left coronary sinus, with an interarterial course. Arch Cardiovasc Dis 2010; 103: 626–628.
82. Sato Y, Matsumoto N, Komatsu S, et al. Anomalous origin of the right coronary artery: depiction at whole-heart coronary magnetic resonance angiography. Int J Cardiol 2008; 127: 274–275.
83. Bekedam MA, Vliegen HW, Doornbos J, Jukema JW, de Roos A, van der Wall EE. Diagnosis and management of anomalous origin of the right coronary artery from the left coronary sinus. Int J Card Imaging 1999; 15: 253–258.
84. Mogensen UM, Grande P, Kober L, Kofoed KF. Anomalous origin of the left main coronary artery from the right sinus of Valsalva with a septal course: an explanation to disabling angina? Int J Cardiol 2011; 151: e74–e76.
85. Brothers J, Gaynor JW, Paridon S, Lorber R, Jacobs M. Anomalous aortic origin of a coronary artery with an interarterial course: understanding current management strategies in children and young adults. Pediatr Cardiol 2009; 30: 911–921.
86. Bett JH, O'Brien MF, Murray PJ. Surgery for anomalous origin of the right coronary artery. Br Heart J 1985; 53: 459–461.
87. Thomas D, Salloum J, Montalescot G, Drobinski G, Artigou JY, Grosgogeat Y. Anomalous coronary arteries coursing between the aorta and pulmonary trunk: clinical indications for coronary artery bypass. Eur Heart J 1991; 12: 832–834.
88. Reul RM, Cooley DA, Hallman GL, Reul GJ. Surgical treatment of coronary artery anomalies: report of a 37 1/2-year experience at the Texas Heart Institute. Tex Heart Inst J 2002; 29: 299–307.
89. Reddy RC, Takahashi M, Beckles DL, Filsoufi F. Anomalous right coronary artery from the left sinus: a minimally invasive approach. Eur J Cardiothorac Surg 2012; 41: 287–290.
90. Fedoruk LM, Kern JA, Peeler BB, Kron IL. Anomalous origin of the right coronary artery: right internal thoracic artery to right coronary artery bypass is not the answer. J Thorac Cardiovasc Surg 2007; 133: 456–460.
91. Tavaf-Motamen H, Bannister SP, Corcoran PC, Stewart RW, Mulligan CR, DeVries WC. Repair of anomalous origin of right coronary artery from the left sinus of Valsalva. Ann Thorac Surg 2008; 85: 2135–2136.
92. Botman CJ, Schonberger J, Koolen S, et al. Does stenosis severity of native vessels influence bypass graft patency? A prospective fractional flow reserve-guided study. Ann Thorac Surg 2007; 83: 2093–2097.
93. Mustafa I, Gula G, Radley-Smith R, Durrer S, Yacoub M. Anomalous origin of the left coronary artery from the anterior aortic sinus: a potential cause of sudden death. J Thorac Cardiovasc Surg 1981; 82: 297–300.
94. Nelson-Piercy C, Rickards AF, Yacoub MH. Aberrant origin of the right coronary artery as a potential cause of sudden death: successful anatomical correction. Br Heart J 1990; 64: 208–210.
95. Erez E, Tam VK, Doublin NA, Stakes J. Anomalous coronary artery with aortic origin and course between the great arteries: improved diagnosis, anatomic findings, and surgical treatment. Ann Thorac Surg 2006; 82: 973–977.

96. Hamzeh G, Crespo A, Estaran R, Rodriguez MA, Voces R, Aramendi JI. Anomalous origin of right coronary artery from left coronary sinus. Asian Cardiovasc Thorac Ann 2008; 16: 305–308.
97. Desgue J, Cuttone F, Babatasi G, Labombarda F, Massetti M. Anomalous origin of the left main coronary artery. Surgical management. Asian Cardiovasc Thorac Ann 2013; 21: 61–63.
98. Kayalar N, Burkhart HM, Dearani JA, Cetta F, Schaff HV. Congenital coronary anomalies and surgical treatment. Congenit Heart Dis 2009; 4: 239–251.
99. Mumtaz MA, Lorber RE, Arruda J, Pettersson GB, Mavroudis C. Surgery for anomalous aortic origin of the coronary artery. Ann Thorac Surg 2011; 91: 811–814.
100. van Son JA, Mohr FW. Modified unroofing procedure in anomalous aortic origin of left or right coronary artery. Ann Thorac Surg 1997; 64: 568–569.
101. Brothers JA, McBride MG, Seliem MA, et al. Evaluation of myocardial ischemia after surgical repair of anomalous aortic origin of a coronary artery in a series of pediatric patients. J Am Coll Cardiol 2007; 50: 2078–2082.
102. Wittlieb-Weber CA, Paridon SM, Gaynor JW, Spray TL, Weber DR, Brothers JA. Medium-term outcome after anomalous aortic origin of a coronary artery repair in a pediatric cohort. J Thorac Cardiovasc Surg 2013, 7pp, http://dx.doi.org/10.1016/j.jtcvs.2013.07.022.
103. Doorey AJ, Pasquale MJ, Lally JF, Mintz GS, Marshall E, Ramos DA. Six-month success of intracoronary stenting for anomalous coronary arteries associated with myocardial ischemia. Am J Cardiol 2000; 86: A510.
104. Hariharan R, Kacere RD, Angelini P. Can stent-angioplasty be a valid alternative to surgery when revascularization is indicated for anomalous origination of a coronary artery from the opposite sinus? Tex Heart Inst J 2002; 29: 308–313.
105. Jennings BR, van Gaal WJ, Banning AP. Extrinsic compression of an anomalous right coronary artery causing cardiac arrest. Heart 2007; 93: 52.
106. Jaggers J, Lodge AJ. Surgical therapy for anomalous aortic origin of the coronary arteries. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 2005: 122–127.
107. Shah AR, Redmond M. Single coronary artery; extremely rare coronary anomaly successfully treated surgically in young adult male. Irish Med J 2010; 103: 150–151.
108. Rodefeld MD, Culbertson CB, Rosenfeld HM, Hanley FL, Thompson LD. Pulmonary artery translocation: a surgical option for complex anomalous coronary artery anatomy. Ann Thorac Surg 2001; 72: 2150–2152.
109. Alphonso N, Anagnostopoulos PV, Nolke L, et al. Anomalous coronary artery from the wrong sinus of Valsalva: a physiologic repair strategy. Ann Thorac Surg 2007; 83: 1472–1476.
110. Karl TR, Provenzano SC, Nunn GR. Anomalous aortic origin of a coronary artery: a universally applicable surgical strategy. Cardiol Young 2010; 20 (Suppl 3): 44–49.
111. Fontaine G, Fontaliran F, Hebert JL, et al. Arrhythmogenic right ventricular dysplasia. Annu Rev Med 1999; 50: 17–35.
112. Iyer VR, Chin AJ. Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D). Am J Med Genet Part C, Semin Med Genet 2013; 163: 185–197.
113. Romero J, Mejia-Lopez E, Manrique C, Lucariello R. Arrhythmogenic right ventricular cardiomyopathy (ARVC/D): a systematic literature review. Clin Med Insights Cardiol 2013; 7: 97–114.
114. Angelini P, Flamm SD. Newer concepts for imaging anomalous aortic origin of the coronary arteries in adults. Catheter Cardiovasc Interv 2007; 69: 942–954.
115. Bateman TM, Heller GV, McGhie AI, et al. Diagnostic accuracy of rest/stress ECG-gated Rb-82 myocardial perfusion PET: comparison with ECG-gated Tc-99 m sestamibi SPECT. J Nucl Cardiol 2006; 13: 24–33.
116. Farhad H, Murthy VL. Pharmacologic manipulation of coronary vascular physiology for the evaluation of coronary artery disease. Pharmacol Ther 2013; 40: 121–132.
117. Chen ML, Lo HS, Chao IM, Su HY. Dipyridamole Tl-201 myocardial single photon emission computed tomography in the functional assessment of anomalous left coronary artery from the pulmonary artery. Clin Nucl Med 2007; 32: 940–943.
118. Osaki M, McCrindle BW, Van Arsdell G, Dipchand AI. Anomalous origin of a coronary artery from the opposite sinus of Valsalva with an interarterial course: clinical profile and approach to management in the pediatric population. Pediatr Cardiol 2008; 29: 24–30.
119. Brothers J, Carter C, McBride M, Spray T, Paridon S. Anomalous left coronary artery origin from the opposite sinus of Valsalva: evidence of intermittent ischemia. J Thorac Cardiovasc Surg 2010; 140: e27–e29.
120. De Bruyne B, Paulus WJ, Pijls NH. Rationale and application of coronary transstenotic pressure gradient measurements. Cathet Cardiovasc Diagn 1994; 33: 250–261.
121. Pijls NH, van Son JA, Kirkeeide RL, De Bruyne B, Gould KL. Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty. Circulation 1993; 87: 1354–1367.
122. Spaan JA, Piek JJ, Hoffman JI, Siebes M. Physiological basis of clinically used coronary hemodynamic indices. Circulation 2006; 113: 446–455.
123. De Bruyne B, Pijls NH, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med 2012; 367: 991–1001.
124. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009; 360: 213–224.
125. Ogawa S, Ohkubo T, Fukazawa R, et al. Estimation of myocardial hemodynamics before and after intervention in children with Kawasaki disease. J Am Coll Cardiol 2004; 43: 653–661.
126. Canty JM Jr. Coronary blood flow and myocardial ischemia. In: Bonow RO, Mann DL, Zipes DP, Libby P (eds) Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. Elsevier/Saunders, Philadelphia, 2011: 1049–1075.
127. Sen S, Asrress KN, Nijjer S, et al. Diagnostic classification of the instantaneous wave-free ratio is equivalent to fractional flow reserve and is not improved with adenosine administration. Results of CLARIFY (Classification Accuracy of Pressure-Only Ratios Against Indices Using Flow Study). J Am Coll Cardiol 2013; 61: 1409–1420.
128. Sen S, Escaned J, Malik IS, et al. Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-intensity analysis: results of the ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation) study. J Am Coll Cardiol 2012; 59: 1392–1402.
129. Meuwissen M, Chamuleau SA, Siebes M, et al. The prognostic value of combined intracoronary pressure and blood flow velocity measurements after deferral of percutaneous coronary intervention. Catheter Cardiovasc Interv 2008; 71: 291–297.
130. Ay Y, Aydin C, Ay NK, Inan B, Başel H, Zeybek RH. Single coronary artetry anomaly causing ischemic motral insufficiency. Asian Cardiovasc Thorac Ann. Online Aug 22, 2013, doi:10.1177/0218492313475641 2013.