Prevalence and Spectrum of Coronary Artery Anomalies in Patients With an Isolated Congenital Left Ventricular Aneurysm or Diverticulum

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ABSTRACT

Background: Congenital left ventricular aneurysm (LVA) and diverticulum (LVD) are rare cardiac anomalies and frequently associated with other cardiac anomalies. The objective of our study was to investigate the prevalence and the spectrum of coronary anomalies in such patients.

Hypothesis: The incidence of coronary anomalies is increased in patients with LVA or LVD.

Methods: We assessed 117 patients with isolated LVA or LVD for the prevalence of coronary anomalies and compared the findings with an age- and sex-matched control group ($n = 117$) without the diagnosis of LVA or LVD.

Results: Coronary anomalies were present in 58.1% of the study population (68 of 117). The median age of affected patients was 64 years, and 45 (38.5%) were male. Coronary anomalies were more prevalent in patients with LVA or LVD (58.1% vs 6.8%, $P < 0.001$), male patients (89% vs 57%, $P = 0.0002$), and in patients with nonapical location of LVA or LVD (24% vs 45%, $P = 0.02$) compared with control, whereas age and type (LVA vs LVD) had no influence (57% vs 57.6%, $P = 0.4$; and 58.8% vs 57.6%, $P = 0.87$, respectively). The number of adverse cardiac events was similar in both groups during a 4.2-year follow-up period (29% vs 19%, $P = 0.09$). None of the patients in our series had major coronary anomalies with potential lethal consequences.

Conclusions: This large single-center study suggests that the prevalence of abnormal coronary-artery anatomy in patients with isolated LVA or LVD is as high as 58.1%. However, we did not identify major coronary anomalies with potential lethal consequences, and the clinical course during follow-up was not influenced by the presence or absence of coronary anomalies.

Introduction

Congenital left ventricular aneurysm (LVA) and diverticulum (LVD) are rare malformations, with approximately 500 published cases in the literature since the first description in 1816.¹ A recent publication demonstrated a prevalence of 0.76% in patients undergoing coronary angiography.² Although most investigators distinguish between LVA and LVD, the cause, histopathology, and clinical implications remain controversial.^{3–8} The advent of echocardiography and magnetic resonance imaging has led to earlier diagnosis, including prenatal detection.^{7–10} Other than 1 large single-center study,² the published research on these anomalies consists of case reports and small case series, including mostly infants and young children with large aneurysms and poor clinical outcome.^{10–16} High morbidity and mortality rates due to heart failure, aneurysm rupture, thromboembolism, and sudden death of unclear cause have been reported.^{3,4} More recently published data demonstrated a more favorable course with no cardiac mortality in adults with LVA and LVD.^{2,8}

Interest in coronary anatomy and variability was cautiously aroused in the 16th century when Renaissance physicians began to perform anatomic investigations in the early European medical schools. When considering the spectrum of coronary morphologies, the terms abnormal or anomalous should be used for any form observed in $<1\%$ of the general human population and should be distinguished from normal variants.¹⁷ Many different coronary anomalies have been described in the literature over the past decades, mainly involving anomalies of origination and course, anomalies of intrinsic coronary arterial anatomy, and anomalies of coronary termination (Table 1).

We hypothesized that the development of the coronary arteries might be affected as well during the phase of early embryonic development when the development of isolated LVA or LVD occurs. The purpose of this study was to assess the prevalence and the spectrum of coronary anomalies detected in a large group of patients with isolated LVA or LVD.

Methods

Definition

The diagnosis of LVA or LVD in our series was established after angiographic exclusion of coronary artery disease,

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Table 1. Classification of Coronary Anomalies in Human Hearts¹⁸

Anomalies of origination and course
Absent left main trunk (split origination of LCA)
Anomalous location of coronary ostium within aortic root or near proper aortic sinus of Valsalva (for each artery)
High
Low
Commissural
Anomalous location of coronary ostium outside normal “coronary” aortic sinuses
Right posterior aortic sinus
Ascending aorta
Left ventricle
Right ventricle
Pulmonary artery
LCA that arises from posterior facing sinus
Cx that arises from posterior facing sinus
LAD that arises from posterior facing sinus
RCA that arises from anterior right facing sinus
Ectopic location (outside facing sinuses) of any coronary artery from pulmonary artery
From anterior left sinus
From pulmonary trunk
From pulmonary branch
Aortic arch
Innominate artery
Right carotid artery
Internal mammary artery
Bronchial artery
Subclavian artery
Descending thoracic aorta
Anomalous location of coronary ostium at improper sinus (which may involve joint origination or “single” coronary pattern)
RCA that arises from left anterior sinus, with anomalous course
Posterior atrioventricular groove or retrocardiac
Retroaortic
Between aorta and pulmonary artery (intramural)
Intraseptal
Anterior to pulmonary outflow
Posteroanterior interventricular groove (wraparound)
LAD that arises from right anterior sinus, with anomalous course

Table 1. *Continued*

Between aorta and pulmonary artery (intramural)
Intraseptal
Anterior to pulmonary outflow
Posteroanterior interventricular groove (wraparound)
Cx that arises from right anterior sinus, with anomalous course
Posterior atrioventricular groove
Retroaortic
LCA that arises from right anterior sinus, with anomalous course
Posterior atrioventricular groove
Retroaortic
Between aorta and pulmonary artery
Intraseptal
Anterior to pulmonary outflow
Posteroanterior interventricular groove
Single coronary artery
Anomalies of intrinsic coronary arterial anatomy
Congenital ostial stenosis or atresia
Coronary ostial dimple
Coronary ectasia or aneurysm
Absent coronary artery
Coronary hypoplasia
Intramural coronary artery (muscular bridge)
Subendocardial coronary course
Coronary crossing
Anomalous origination of posterior descending artery from the anterior descending branch or a septal penetrating branch
Split RCA
Proximal + distal PDs that both arise from RCA
Proximal PD that arises from RCA, distal PD that arises from LAD
Parallel PDs × 2 (arising from RCA, Cx) or “codominant”
Split LAD
LAD + first large septal branch
LAD, double (parallel LADs)
Ectopic origination of first septal branch
RCA
Right sinus
Diagonal
Ramus
Cx

Table 1. Continued

Anomalies of coronary termination
Inadequate arteriolar/capillary ramifications
Fistulas from RCA, LCA, or infundibular artery to:
Right ventricle
Right atrium
Coronary sinus
Superior vena cava
Pulmonary artery
Pulmonary vein
Left atrium
Left ventricle
Multiple, right + left ventricles
Anomalous anastomotic vessels
Abbreviations: Cx, circumflex artery; LAD, left anterior descending artery; LCA, left coronary artery; PD, posterior descending artery; RCA, right coronary artery.

and clinical exclusion of local or systemic inflammation or traumatic causes as well as cardiomyopathies. Definition of an LVA included akinetic or dyskinetic structures with the ratio of the connection to the left ventricular cavity compared with the maximum diameter of the body of the anomaly being >1 (Figure 1, panel A). In LVD this ratio is <1 in a structure with normal systolic contraction (Figure 1, panel B).

Study Population

Between January 1, 2001, and December 31, 2003, 17 257 consecutive patients underwent diagnostic coronary angiography at our institution. During this period, 125 patients with angiographically proven isolated LVA or LVD were identified. Eight angiograms were excluded because they either were nonselectively performed or did not adequately show all of the coronary vessels. The baseline characteristics of the study population and the control group are presented in Table 2.

Control Group

The control group was established by collecting data of 117 age- and sex-matched individuals without the diagnosis of isolated congenital LVA or LVD and without evidence of coronary artery disease, previous noncoronary cardiac surgery, local or systemic inflammation, or cardiomyopathies. The patients underwent coronary angiography for various reasons at our institution between January 1, 2001, and December 31, 2003 (Table 2).

Coronary Angiography

All coronary angiographies were performed with biplane angiographic equipment in the cardiac catheterization laboratory of the Zentralklinik Bad Berka and were prospectively reviewed according to the criteria described below. In the vast majority of cases, multiple projections had been obtained by means of the Judkins technique, using preformed right and left coronary catheters. In a minority of cases, alternative catheters were used after the primary catheters failed to allow selective visualization (mainly multipurpose catheters or Amplatz right or left preformed curves). Although the radial approach has gained increased interest in recent years, during the study period this approach was used in $<5\%$ of the cases.

We specifically and systematically studied the following coronary angiographic features as proposed by Angelini et al (Table 1).¹⁸

Origin: To elucidate the relationship between the coronary ostia and the aortic sinuses, we examined the morphology of the coronary sinuses; the vertical level of the coronary ostia in the aortic root, with respect to the bottom of the aortic sinus and to the sinotubular junction or ridge; and the orientation of the proximal coronary stems (variants: normal, tangential).

Course: The relationship between the coronary arteries and other cardiac structures (mainly the atrioventricular and semilunar valves) was studied by inference, and the coronary courses were observed in different angiographic projections to reconstruct their 3-dimensional anatomy. In some cases, a catheter was positioned in the pulmonary artery for reference.

Major Coronary Anomalies: "Major coronary anomalies" mainly include anomalous left coronary artery from the right sinus of Valsalva, especially the interarterial type (ALCA);

Figure 1. Left ventricular angiography. (A) Congenital left ventricular aneurysm (black arrow). (B) Congenital left ventricular diverticulum (white arrow).

Table 2. Baseline Characteristics and Clinical Presentation of Patients With LVA or LVD and Controls

	LVA/LVD Group (n = 117)	Control Group (n = 117)	P Value
Age, y			1
Median	64	64	
IQR	48–72	48–72	
Male sex, n (%)	45 (38.5)	45 (38.5)	1
Hypertension, n (%)	79 (68)	71 (61)	0.7
DM, n (%)	15 (13)	19 (16)	0.6
Hypercholesterolemia, n (%)	30 (26)	34 (29)	0.7
BMI (kg/m ²)			0.3
Median	26 ± 2.4	27 ± 4	
IQR	24–28	25–29	
Angina, n (%)	67 (57)	56 (48)	0.4
Rhythm disturbances, n (%)	33 (28)	14 (5)	0.02
Valvular pathology, n (%)	25 (21)	35 (30)	0.3
Dyspnea, n (%)	19 (16)	23 (26)	0.6
Syncope, n (%)	7 (6)	2 (2)	0.2
Stroke, n (%)	6 (5)	4 (3)	0.8
Echocardiographic suspicion for LVA by referring physician, n (%)	2 (2)	0 (0)	0.5
Abbreviations: BMI, body mass index; DM, diabetes mellitus; IQR, interquartile range; LVA, left ventricular aneurysm; LVD, left ventricular diverticulum.			

anomalous right coronary artery (RCA) from the left sinus of Valsalva (ARCA); and anomalous left coronary artery arising from the pulmonary artery (ALCAPA).

Follow-Up

All clinical data were obtained by retrospective review of the patient records. At the end of the data-collection period, all identified patients were followed up by a standardized telephone call with special emphasis on survival, arrhythmic events (patients were considered to have an arrhythmic event if sudden cardiac death occurred, or sustained ventricular tachycardia or appropriate implantable cardioverter-defibrillator shocks were documented), syncope, need for pacemaker or defibrillator implantation, and recurrent hospitalizations. In case of recurrent hospitalizations between the index coronary angiogram and the follow-up telephone call, we additionally reviewed the medical record of this particular hospital stay.

Statistical Analysis

The prevalence of coronary anomalies is given as percentage of all included patients. The data of continuous variables (age, body mass index) are presented as median and interquartile range (IQR) because age showed an asymmetrical distribution. Categorical variables were analyzed by 2-tailed Fisher exact test for univariate analysis. All probability values were 2-tailed, and a value of <0.05 was considered significant.

Results

Prevalence and Pattern of Coronary Abnormalities

The prevalence of various abnormalities of the coronary arteries and the coronary dominance pattern are summarized in Table 3. We found LVAs in 51 patients (43.6%), and LVDs were diagnosed in 66 patients (56.4%). The median age was 64 years (IQR, 48–72 years), and 45 (38.5%) were male.

Abnormal coronary anatomy was identified in 68 patients (58.1%) with a total of 81 coronary anomalies, resulting in a statistically significant difference as compared with

Table 3. Prevalence of Coronary Abnormalities in Patients With LVA or LVD and Controls

Anomaly, n (%)	LVA/LVD Group (n = 117)	Control Group (n = 117)	P Value
Coronary anomalies (total)	68 (58.1)	8 (6.8)	<0.001
Split RCA	28 (24)	2 (1.7)	<0.0001
Ectopic RCA (right cusp)	14 (12)	3 (2.5)	
Ectopic RCA (left cusp)	1 (0.9)	1 (0.9)	
Fistulas	9 (7.7)	1 (0.9)	0.02
Absent left main coronary artery	4 (3.4)	1 (0.9)	0.4
Cx arising from the right cusp	2 (1.8)	1 (0.0)	1
LCA arising from the right cusp	0 (0)	0 (0)	1
Low origination of RCA	3 (2.7)	0 (0)	0.2
Other anomalies	7 (6)	3 (2.5)	0.3
Coronary dominance patterns			
Dominant RCA	97 (82.9)	104 (89)	0.3
Dominant LCA	9 (7.7)	10 (8.5)	1
Codominant arteries	11 (9.4)	3 (2.5)	0.05
Abbreviations: Cx, circumflex artery; LCA, left coronary artery; LVA, left ventricular aneurysm; LVD, left ventricular diverticulum; RCA, right coronary artery.			

patients without LVA or LVD. The pattern of coronary anomalies mainly involved abnormal anatomy of the RCA and anomalies of coronary termination (mainly coronary fistulas). None of the patients in our series had major coronary anomalies.

Coronary Anomalies in Relation to Age and Sex

Coronary-anomaly patterns were different with respect to sex, as a larger proportion of male patients than female patients had anomalies (89% vs 57%, $P = 0.0002$). Not surprisingly, advanced age was not associated with a significant increase of the prevalence of coronary anomalies compared with younger patients (57% vs 57.6%, $P = 0.4$).

Coronary Anomalies in Relation to Type and Location of LVA or LVD

Coronary-anomaly patterns did not differ with respect to type of anomaly (LVA or LVD). The proportion of patients with LVA and of patients with LVD having coronary anomalies was similar (58.8% vs 57.6%, respectively, $P = 0.87$).

The coronary-anomaly patterns differed with respect to the location of the LVA or LVD. We arbitrarily classified the location of LVA or LVD into 4 subgroups: anterior ($n = 13$, 11%), inferior ($n = 30$, 25.6%), apical ($n = 67$, 57.4%), and other location ($n = 7$, 6%). A larger proportion of coronary anomalies was encountered in the group with a nonapical location of the anomaly compared with apical location (45% vs 24%, respectively, $P = 0.02$).

Clinical Course

The mean follow-up period for the entire study population was 50 ± 6 months (range, 12–59; cumulative follow-up, 5850 months). The incidence of cardiac events during follow-up was not influenced by the presence or absence of abnormal coronary-artery anatomy. During follow-up, 34 of 117 patients (29%) from the study population and 22 of 117 patients (19%) from the control group had ≥ 1 cardiac event ($P = 0.09$). The 5 deaths during follow-up (2.1%) were all attributable to noncardiac causes.

Discussion

The results of our study suggest that the prevalence of coronary anomalies in patients with LVA and LVD is as high as 58%. This is an almost 9-fold higher prevalence as observed in our control group, and as reported in a cohort of 1950 patients without LVA and LVD undergoing coronary angiography, who were analyzed using the same diagnostic criteria as we did in our patients.¹⁸ However, in one of the largest angiographic reviews, by Yamanaka and Hobbs,¹⁹ the incidence of coronary-artery anomalies in 126 595 American patients undergoing coronary angiography was reported as 1.3%. This surprisingly low prevalence compared with our data and with the data of Angelini et al¹⁸ might be attributable to at least 2 facts: Yamanaka and coworkers were using a much less sophisticated classification system for coronary anomalies, as discussions of this topic are far more detailed than would have been several decades ago; and their coronary angiograms were obtained mainly in the early 1960s and 1970s, a period of time when the

diagnostic equipment was not as highly developed as it is today. The pattern of coronary anomalies in our series mainly involved abnormal anatomy of the RCA ($P < 0.0001$ compared with the control group) and anomalies of coronary termination (eg, coronary fistulas). In general, the RCA is the most common anomalous vessel, being involved in about 50%–70% of all cases in the literature.^{20,21} The incidence of anomalous RCA in the normal population varies greatly in different reports, ranging from approximately 0.04% to 2%.^{18,20,22,23} Prevalence of coronary fistulas was reported in a large series in only 125 patients (0.4%) out of 28 210 coronary angiograms.²⁴

Coronary anomaly patterns in our series were significantly different with respect to sex, as a larger proportion of male patients had coronary anomalies compared with female patients. This is in contrast with other publications, where the incidence of coronary artery anomalies was more common in women than in men.^{18,24} However, there are also several studies from other groups reporting a higher incidence of coronary anomalies in men.^{20,22}

We also could demonstrate in our cohort a higher incidence of coronary anomalies in patients with nonapical location of the LVA or LVD. Both LVA and LVD are thought to be developmental anomalies, starting in the fourth embryonic³ week, and can be explained by a partial stop in the development of the embryonic ventricle.²⁵ Before this, a development disturbance of the primitive paramidline mesoderm occurs between the 14th and 18th day of the embryonic phase, shortly after the differentiation into a ventral and parietal part.^{26,27} However, by the beginning of the third week, as the heart wall increases in thickness, a dedicated vascular system develops over the surface of the myocardium as a result of a precisely orchestrated series of molecular and morphogenetic events.²⁸ Considering all this, the development of the coronary arteries might be affected as well during the early phase of embryonic LVA or LVD development. Another theory assumed that the early embryonic coronary arteries were already present in the common undivided truncus, before any subdivision occurred, and that abnormal spiral septation of the truncus would cause ectopic origination.²⁹ Unfortunately, a morphogenetic explanation may not be so conveniently available in the absence of basic facts of normal descriptive embryology.³⁰ More recent research elucidated basic mechanisms of coronary vasculogenesis,³¹ angiogenesis,^{31–33} and embryonic arteriogenesis,³⁴ and the role of cellular progenitors such as epicardium-derived cells, cardiac neural crest cells, and cells of the peripheral conduction system. Different groups discuss the role of growth factors (such as platelet-derived growth factor β ,^{32,33} transforming growth factor $\beta 1$,^{32,33} hypoxia-inducible factor-1 α ,^{35,36} and vascular endothelial growth factor)^{31,37} and genes (such as friend of GATA-2,^{38,39} vascular cell adhesion molecule 1,³⁹ blood vessel epicardial substance,⁴⁰ and retinoic acid synthetic enzyme)⁴¹ at different stages of coronary artery development, providing a multiplicity of options and mechanisms that may give rise to coronary anomaly.²⁸

Nonhuman models of coronary anomalies also do exist; many mammals and birds, for example, have muscular

bridges,¹⁸ and anomalous coronary origination is frequently seen in inbred Syrian hamsters.⁴²

None of the patients in our series had major coronary anomalies, a term some researchers have suggested to classify coronary anomalies depending on their pathologic consequences. In a study done from the Minneapolis Heart Institute Foundation Registry, the second most frequent cause of sudden cardiac death in young athletes was major coronary anomalies, in 17%.⁴³ The lack of major coronary anomalies in our cohort might be attributable to 2 facts. First, the overall prevalence of major coronary anomalies in the general population is very low (0.107% ARCA, 0.017% ALCA, and 0.003% ALCAPA, respectively),^{19,44} and therefore the number of patients included in our series was maybe just too small. Second, as the median age of our patients was 64 years, patients with major coronary anomalies, and therefore potential lethal complications, already may have died.

Study Limitations

Several limitations of the study merit further discussion. First, this study is subject to limitations inherent in retrospective studies. Second, as the incidence of coronary anomalies is usually in the range of <1%, large study populations (>1000) would be advantageous. Unfortunately, our series of 117 patients is much smaller, and the true incidence of coronary anomalies in patients with LVA or LVD might be over- or underestimated. However, LVA or LVD are very rare entities, and our series is the largest group of patients with LVA or LVD to date.

Conclusion

This study suggests that the prevalence of coronary anomalies in adult patients with isolated LVA and LVD is almost 9-fold higher compared with the control group. The prevalence of coronary anomalies in our series was influenced by male sex and location of the anomaly. However, we did not identify major coronary anomalies with potential lethal consequences, and the clinical course of the study group during a 4.2-year follow-up period was not influenced by the presence or absence of coronary anomalies.

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