Characteristics of Congenital Coronary Artery Fistulas Complicated with Infective Endocarditis: Analysis of 25 Reported Cases

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ABSTRACT

Congenital coronary artery fistulas (CAFs) are infrequent congenital coronary artery anomalies. Complications such as left-to-right shunt, congestive heart failure, myocardial infarction, pericardial effusion, aneurysm formation, rupture, hemopericardium, pulmonary hypertension, infective endocarditis (IE), syncope, stroke, and sudden death may occur with a variable low frequency. To describe the clinical characteristics of patients with CAFs complicated by IE. A search was conducted through PubMed using the terms “CAFs” and “IE.” Papers with a full description of the fistula characteristics and detailed data regarding bacterial endocarditis were included for evaluation. In the overall group of reviewed subjects (n=25, 9 females), the mean patient age was 42.5 years (range: 16 and 87). The right coronary artery (RCA) and left coronary artery (LCA) contributed equally to fistula formation. Terminations into the right heart side occurred in 19 (76%) fistulas. The majority of the fistulas (92%) were unilateral. The cultured microorganism was Streptococcus in 14 (56%) and Staphylococcus in 4 (16%) of the reviewed subjects. Echocardiographic single or multiple valvular regurgitation was found in 8 (32%) of the reviewed subjects. Small and large intracardiac vegetations were detected in 18 patients (72%). Antibiotic therapy was initiated in 20 (80%) subjects and 16 fistulas were treated surgically. During surgery, spontaneous closure of the fistula was observed in one patient. Percutaneous therapeutic embolization (PTE) was successfully performed in two subjects. CAFs complicated by IE may affect all age groups with a slight male preponderance. Unilateral fistulas, either arising from the right or left coronary artery, are predominant, draining mainly into the right heart side. It is emphasized that antibiotic prophylaxis is strongly advised for pediatric and adult patients with congenital CAFs.

Key Words. Congenital Coronary Artery Fistulas; Congenital Anomaly; Infective Endocarditis; Fistula Characteristics; Valvular Heart Disease; Surgical Closure

Introduction

Congenital coronary artery fistulas (CAFs) are associated with a risk of complications such as infective endocarditis (IE), rupture, and sudden death. Congenital CAFs have been associated with IE in children1 and adults.2 The fistulas may originate from the right coronary artery (RCA) or left coronary artery (LCA) and may terminate into any right or left cardiac chamber or any thoracic venous or arterial vessel. IE may involve unilateral3 as well as bilateral4 fistulas. The pathogenic microorganisms may invade the semilunar5,6 or atrioventricular3,7,8 valvular structures.

Both Streptococci9-12 and to a lesser extent Staphylococci13,14 species have been isolated from CAFs patients with IE. Valvular15 and nonvalvular4,9 infection and vegetation may occur. A literature review describing the clinical characteristics of congenital CAFs complicated by IE in 25 reported cases is presented.

This review aimed to summarize the clinical characteristics of patients and features of the CAFs complicated by IE.

Methods

A search was conducted through PubMed using the terms “CAFs” and “IE.” For a paper to be included, it had to contain a full and detailed description of the fistula accompanied by data regarding IE. This resulted in a total of 60 papers.
Twenty-four were not included because of irrelevance and 15 were excluded due to incompleteness and a lack of detail. Reference lists were scrutinized for relevant publications, resulting in the identification of an additional two papers. Therefore, 23 papers were eligible for analysis and evaluation. Other congenital coronary artery anomalies were excluded. The following items for evaluation of coronary artery fistulas complicated by IE were stipulated: age, gender, involved microorganism, diagnostic modalities (echocardiography, coronary angiography, and cardiac catheterization), fistula characteristics (origin, termination, number of donor vessels “unilateral, bilateral or multilateral,” and mode of termination [cameral “CCFs” vs. vascular “CVFs”]), details regarding IE (blood culture when available, vegetation, valvular, and nonvalvular involvement) and surgical or nonsurgical management.

**Statistical Analysis**

Values were expressed as means, averages, and percentages.

**Results**

Overall, 25 (9 females and 16 males) reviewed subjects were included in the analysis. The mean patient age was 42.5 years (range: 16 and 87). Clinical presentations included fever (15 subjects), fatigue (5 subjects), bacterial endocarditis (4 subjects), congestive heart failure (2 subjects), weight loss and nocturnal sweats (2 subjects each), hemoptysis (1 subject), and stroke (1 subject) (Table 1).

There was an equal distribution of the RCA (n = 14) and the LCA (n = 13) in the fistula formation. There were 23 (92%) unilateral fistulas, with bilateral fistulas being found in only two patients. None of the subjects presented multilateral fistulas. Terminations into the left heart side were found in six patients and into the right heart side in 19 (76%) patients. Regarding mode of termination, 14 patients (56%) had coronary-cameral fistulas and 11 possessed coronary-vascular fistulas (CVFs). The cultured microorganism was *Streptococcus* in 14 subjects (*viridans* n = 7, *mitis* n = 1, *pneumoniae* n = 1, and unspecified n = 5), *Staphylococcus aureus* in four, negative culture in two, *HACEK* (Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, and Kingella) in one and not reported in four of the reviewed subjects.

Small and large vegetations, which were confirmed echocardiographically and/or surgically, occurred in 18 patients. Of those, sterile culture was found in two, another eight were caused by *Streptococcus* infection, *HACEK* was responsible for the infection in one, by *S. aureus* in four and the microorganism was not reported in three. Echocardiographic evaluation revealed single or multiple valvular involvement, including regurgitation in eight of the reviewed subjects. Valvular vegetations were demonstrated in 12 subjects (single n = 9 and multiple n = 3 producing 15 valvular lesions) including involvement of the aortic (AV n = 4), mitral (MV n = 7), tricuspid (TV n = 3), and pulmonary valve (PV n = 1) (Table 2).

Among the reviewed subjects, 20 received antibiotic therapy and 16 were treated surgically (6 isolated and 10 combined with coronary artery bypass grafting (n = 4) and/or valvular correction (n = 10)). Six subjects received antibiotic therapy alone.

Percutaneous therapeutic embolization (PTE) was successfully performed in two subjects. During surgery, spontaneous closure of the fistula by thrombus and debris was observed in one patient. Aortic valve replacement was performed in four patients and four underwent mitral valve replacement. Furthermore, mitral valve repair in one and combined with tricuspid valve plasty in another patient.

**Laboratory Data: Echocardiographic/Angiographic/ Hemodynamic/Microbiologic/Septic Embolization and Associated Coronary Artery Disease**

**Echocardiographic Data**

Valvular vegetations were demonstrated in 12 subjects (single n = 9 and multiple n = 3 valvular lesions) including involvement of the aortic (AV n = 4), mitral (MV n = 7), tricuspid (TV n = 3), and pulmonary valve (PV n = 1). The size of vegetation was variable (mean 6.9–13 mm, range 3 × 6 to 12 × 18 mm). Echocardiographic evaluation revealed single or multiple valvular involvement, including (mild, moderate, and severe) regurgitation in eight of the reviewed subjects. None of the reviewed subjects had preexistent significant valvular disease.

**Angiographic Data: (Fistula Characteristics: Origin/Pathway/Termination/Diameter)**

There was an equal distribution of the RCA (n = 14) and LCA (n = 13) in the fistula formation. The unilateral fistulas accounted for 92% of cases (23 patients) and the bilateral fistulas were found in only two patients. None of the subjects presented multilateral fistulas. Terminations into the left
<table>
<thead>
<tr>
<th>Case/Age/Gender</th>
<th>Year/Reference/ Clinical Presentation</th>
<th>Pathogenic Microorganism/ Septic Embolization</th>
<th>Vegetations/ Involved Valves</th>
<th>Fistula Characteristics L-R Shunt</th>
<th>Pharmacological and Nonpharmacological Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>35F</td>
<td>1964(17)/intermittent fever, dyspnea, fatigue</td>
<td>Streptococcus viridans</td>
<td>None</td>
<td>Cx → PLSVC</td>
<td>AB/SL</td>
</tr>
<tr>
<td>31M</td>
<td>1992(41)/intermittent fever after dental procedure</td>
<td>Streptococcus viridans</td>
<td>None</td>
<td>RCA → LV Dilated RCA</td>
<td>AB (4 weeks)</td>
</tr>
<tr>
<td>17F</td>
<td>1993(45)/intermittent fever, hemoptysis/weight loss</td>
<td>Streptococcus viridans Septic pulmonary embolism</td>
<td>Vegetations on the edges of TV</td>
<td>RCA → CS Aneurysm RCA</td>
<td>AB/CABG/SL</td>
</tr>
<tr>
<td>41M</td>
<td>1995(11)/fatigue</td>
<td>Streptococcus viridans</td>
<td>None</td>
<td>RCA → CS (1.4:1) Aneurysm RCA Cx → CS (1:21) Aneurysm Cx</td>
<td>AB/CABG/SL</td>
</tr>
<tr>
<td>72F</td>
<td>1995(11)/fever, nocturnal sweats, weight loss</td>
<td>Streptococcus viridans</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30M</td>
<td>1998(35)/nocturnal sweats</td>
<td>Streptococcus viridans</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>61M</td>
<td>1999(49)/fever, nocturnal sweats, general malaise</td>
<td>Streptococcus</td>
<td>None</td>
<td>Cx → CS (25%)</td>
<td>AB</td>
</tr>
<tr>
<td>31M</td>
<td>2004(14)/fever, myalgias, neck stiffness, nausea, vomiting</td>
<td>Staphylococcus aureus Septic pulmonary embolism</td>
<td>Vegetations in RA. Normal heart valves Vegetations on the LCC and the inferior atriocaval junction. Normal heart valves with mild AR and TR</td>
<td>Cx → CS Aneurysm Cx Left sinus of Valsalva → RA (2.0:1)</td>
<td>AB (10 days)/SL/debridement AB (2 months)/SL</td>
</tr>
<tr>
<td>30M</td>
<td>2004(9)/fever</td>
<td>Streptococcus</td>
<td>Vegetation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23M</td>
<td>2004(16)/fever</td>
<td>NR</td>
<td>Vegetations with RVOT obstruction. Destruction of pMLV Severe AR</td>
<td>LAD → RV (SCA) (2.09:1) Bilateral LAD, RCA → LA (1.13:1)</td>
<td>SL/MVR/SL</td>
</tr>
<tr>
<td>65F</td>
<td>2004(16)/fever</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>37M</td>
<td>2005(4)/intermittent fever, weight loss</td>
<td>Streptococcus mitis</td>
<td>Vegetations within the CS normal cardiac valves</td>
<td>Cx, RCA → CS RCA → RA (1:3:1)</td>
<td>AB (&gt;6 weeks)/SL</td>
</tr>
<tr>
<td>16F</td>
<td>2005(7)/fever, chest pain</td>
<td>Staphylococcus aureus Septic pulmonary embolism</td>
<td>Vegetation over TV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>32F</td>
<td>2007(5)/acute pulmonary edema, low-grade fever</td>
<td>Culture negative</td>
<td>Vegetation AV</td>
<td>LM-RV</td>
<td>AVR/Spontaneous closure</td>
</tr>
<tr>
<td>65F</td>
<td>2009(15)/severe congestive heart failure</td>
<td>Streptococcus pneumoniae</td>
<td>Vegetation over AV, MV and CS. Destruction of MV and AV</td>
<td>RCA → CS Aneurysm RCA Cx → CS</td>
<td>AB/AVR/MVR/CABG/SL</td>
</tr>
<tr>
<td>61M</td>
<td>2009(3)/bacterial endocarditis</td>
<td>NR</td>
<td>Small vegetations on the edges of MV and TV with TR and MR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65F</td>
<td>2010(6)/constitutional symptoms</td>
<td>HACEK</td>
<td>Vegetation PV</td>
<td>LCS → PA</td>
<td>SL</td>
</tr>
<tr>
<td>45M</td>
<td>2011(51)/sepsis</td>
<td>NR</td>
<td>Vegetation RA</td>
<td>RCA → RA</td>
<td>AB (2 months)/PTE</td>
</tr>
<tr>
<td>23M</td>
<td>2012(6)/bacterial endocarditis</td>
<td>Streptococcus</td>
<td>Vegetation MV Moderate MR</td>
<td>RCA → LV Dilated RCA Aneurysm Cx</td>
<td>AB/MVR/SL</td>
</tr>
<tr>
<td>27M</td>
<td>2013(10)/bacterial endocarditis</td>
<td>Streptococcus viridans</td>
<td>MV perforation. No vegetation Severe MR</td>
<td>RCA → LV Aneurysm RCA</td>
<td>AB (6 weeks)/SL/valve repair (MVP)</td>
</tr>
<tr>
<td>Case/Age/ Gender</td>
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<tr>
<td>31M 2014(47)/fever, fatigue</td>
<td>Streptococcus Septic renal embolism</td>
<td>Vegetation MV and AV</td>
<td>Cx → LV</td>
<td>Dilated Cx</td>
<td>AB (5 weeks)/AVR/MVR/SL</td>
</tr>
<tr>
<td>53F 2014(48)/fever, headache, vomiting</td>
<td>Staphylococcus aureus Septic pulmonary embolism</td>
<td>Vegetation MV</td>
<td>RCA → RA Aneurysm RCA</td>
<td>AB (6 weeks)</td>
<td></td>
</tr>
<tr>
<td>49M 2015(12)/intermittent fever, fatigue, headache, anorexia, dizziness, cough</td>
<td>Streptococcus</td>
<td>Vegetation at the junction between CAF and the SVC</td>
<td>RCA → SVC Dilated RCA</td>
<td>AB (6 weeks)/PTE</td>
<td></td>
</tr>
<tr>
<td>38M 2015(34)/acute biventricular failure, fever, dyspnea on exertion, cough, decreased exercise tolerance</td>
<td>Culture negative</td>
<td>Vegetation AV Severe AR</td>
<td>Cx → RA Dilated Cx</td>
<td>SL/AVR</td>
<td></td>
</tr>
<tr>
<td>87M 2015(13)/fatigue, lethargy</td>
<td>Staphylococcus aureus History of pulmonary embolism</td>
<td>Vegetation at drainage point RV free wall</td>
<td>RCA → RV Aneurysm RCA</td>
<td>AB/CMM</td>
<td></td>
</tr>
</tbody>
</table>

AB, antibiotic; AR, aortic regurgitation; AV, aortic valve; AVR, aortic valve replacement; CABG, coronary artery bypass grafting; CAF, coronary artery fistula; CMM, conservative medical management; CS, coronary sinus; Cx, circumflex coronary artery; F, female; HACEK, Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, and Kingella; LA, left atrium; LCC, left coronary cusp; LM, left main coronary artery; L-R shunt, left-to-right shunt; LV, left ventricle; M, male; MR, mitral regurgitation; MV, mitral valve; MVR, mitral valve replacement; NR, not reported; PTE, percutaneous therapeutic embolization; pMVL, posterior mitral valve leaflet; PLSVC, persistent left superior vena cava; PV, pulmonary valve; RCA, right coronary artery; RA, right atrium; RV, right ventricle; RVOT, right ventricle outflow tract; SCA, single coronary artery; SL, surgical ligation; SVC, superior vena cava; TR, tricuspid regurgitation; TV, tricuspid valve.
heart side were found in six patients and into the right heart side in 19 (76%) patients. Regarding the mode of termination, 14 patients (56%) had coronary-cameral fistulas and 11 possessed CVFs. Dilatation of the donor vessel was present in 88% of subjects (22/25). The mean diameter of the donor-vessel (n = 11) was 21.2 mm (range 8–50 mm). Aneurysm formation of the vessels was prevalent (36%), besides elongation and tortuosity of its pathway. In contrast, dilatation of the termination site was only found in 16% of the subjects.

Hemodynamic Data

Qp:Qs was performed in 10 patients. Variable shunt size with the left to right shunt with a pulmonary to systemic flow ratio was small (<1.5, n = 5), moderate (1.5–2.0, n = 2) and severe (>2.0, n = 3). Symptoms occurred irrespective of the shunt size.2,7,11,16,17 Aneurysm formation was noticed in two subjects with limited (<1.5) left-to-right shunt.11 Spontaneous partial closure was not reported in any of the reviewed subjects. Spontaneous total closure by debris and thrombi was seen during surgery in one subject.5

Cultured Pathogenic Microorganisms

The cultured microorganism was Streptococcus in 14 subjects (Viridans n = 7, mitis n = 1, pneumoniae n = 1 and unspecified n = 5), S. aureus in four, HACEK (Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, and Kingella) in one, there was a negative culture in two and the result was not reported in four of the reviewed subjects. Small and large vegetations confirmed echocardiographically and/or surgically occurred in 18 patients. Of those, sterile culture was found in two, eight were caused by Streptococcus infection, HACEK was responsible for the infection in one, the microorganism was not reported in three and by S. aureus in four.

Septic Embolization

Septic emboli to the lungs (four subjects and one with a past history of pulmonary embolism) and the kidney (one subject) were reported in 6/25 (24%) (three females and three males, mean age of 39.2 (range 16–87 years)) of the reviewed subjects. The cultured pathogenic microorganisms were S. aureus (4×) and Streptococci (2×). Dilatation and aneurysm formation of the vessels were present in five of them. The fistula originated from the RCA in four and from the Cx in two of the subjects. In case of septic renal emboli (Streptococci), the fistula terminated into the LV and regarding the pulmonary septic emboli (S. aureus (4×) and Streptococci (1×)), the fistula ended at the right heart side (right atrium (RA) 2×, coronary sinus (CS) 2×, and right ventricle (RV) 1×) in all. The majority of the septic pulmonary emboli were caused by S. aureus (4/5 = 80%).

Associated Coronary Disorders

In 21 subjects, CAFs were isolated defects, while the fistula was associated with acquired obstructive coronary artery disease in four of the reviewed subjects. Single coronary artery was reported in one subject.16

Time between Diagnosis, Prior Antibiotic Treatment, and Intervention

A prior course of intravenous antibiotics was reported in 20 subjects. The time between diagnosis and intervention was documented in 10 subjects, not reported in another 10 subjects and the time lasting from diagnosis until surgical intervention was not mentioned at all in five subjects. The time between establishing the diagnosis, initiating antibiotic course, and start of surgical intervention varied from days (one subject), 2–6 weeks (8 subjects) to 6 months (one subject).
IE may occur not only in patients with coronary-cameral fistulas but also in patients with CVFs. IE is not only reported in congenital fistulas but also has been described with acquired accidental fistulas.

In the beginning of the last century, vegetation complicating IE was reported in postmortem pediatric cases of coronary-cameral fistulas. Nowadays, antemortem diagnosis is easily established due to the increased awareness and widespread and early use of noninvasive diagnostic modalities.

The estimated incidence of IE has been reported to be associated with other congenital cardiac defects. In 1992, Fernandes et al. reported recurrent IE in 1 out of the 93 patients studied. On the other hand, in 2015, Kaminska et al. identified 18 reports of patients with CAFs complicated with IE in the period from 2000 to 2015. IE may be present as an initial manifestation of CAFs or may develop during the course of disease. IE may occur in isolated CAFs or fistulas associated with other congenital cardiac defects. Accordingly, in the current review, fever was the most common symptom occurring in 60% of subjects followed by fatigue and sepsis.

In 2006, upon reviewing the worldwide literature, IE was reported in 2% of pediatric subjects. The subacute presentation of bacterial endocarditis has been reported in both pediatric subjects with coronary-cameral fistula and adult patients with CVF. In 1984, Slater et al. reported recurrent IE in a middle-aged man with a coronary-cameral fistula.

It has been reported that the most common microorganisms causing IE include: *Streptococci*, *S. aureus*, *Enterococcus* species, *HACEK* organisms, and *fungi*. The rate of subsequent bacteremia (*Streptococcus* species) following transesophageal echocardiography is estimated at 0–25% and after dental extractions at 30–100%. *Streptococci* accounted for the majority of IE associated with CAFs, with *Streptococcus viridans* being the most commonly involved microorganism. In the current review, *S. viridans* accounted for 50% of *Streptococci* species. The majority of published reports did not include the focus of infection and no predisposing factors for bacterial endocarditis were acquainted. Dental procedure preceded the occurrence of IE in the case reported by Tsai et al. *Staphylococci* have been isolated in a few cases, but *Streptococcus* species are the most commonly isolated microorganisms from blood cultures. This was the case in the present review, as *Streptococcus* species were predominant (56%). In coronary-cameral fistula associated with IE, *S. aureus* or *Streptococcus mitis* were isolated and vegetations were found in pediatric subjects.

In patients with CAFs complicated by IE, valvular and nonvalvular involvement has been reported. It was noted in a coronary-cameral (RCA to RV) fistula, in a surgically treated child and in a conservatively treated elderly patient caused by *S. viridans* and *S. aureus*, respectively, that IE was associated with nonvalvular vegetations protruding at the drainage point into the right ventricle.

Small or large nonvalvular vegetations, as well as small or large valvular vegetations at the atrioventricular valves or semilunar valves, have been observed. Destruction of the right or left atrioventricular valve and semilunar valves occurred secondary to IE. In 1993, Ong reported a case of CVF which presented as a recurrent pulmonary embolism secondary to septic embolism originating from vegetations on the edges of the tricuspid valve. Furthermore, echocardiographic evaluation revealed a large vegetation of the right ventricle without valvular vegetation, causing obstruction of the right ventricle outflow tract; in another patient, the posterior mitral valve leaflet was totally destroyed.

Earlier reports have indicated that congenital coronary-cameral fistulas (CCFs) are more prone for the development of IE than CVFs. The reason for this is that it is believed that the high-speed jet lesion may cause damage to the endothelial lining of the myocardium, leading to local vulnerable nidus near the drainage site of the fistula. Furthermore, it is assumed that vegetation and perforation occur because of the increased and abnormal turbulent flow (Figure 1 and supporting information video 1) related to fistulas near the cardiac valves.

Additional complications of IE associated with CAFs include septic pulmonary embolism as well as septic embolization to the renal region.
Septic Embolization

Septic emboli to the lungs and the kidney were reported in 6/25 (24%) of the reviewed subjects. The majority of the septic pulmonary emboli were caused by *S. aureus* (4/5 = 80%). Dilatation and aneurysm formation of the vessels were present in five of them. Termination was coronary-cameral in four and coronary-vascular in two of the subjects. Termination into the left ventricle occurred in the fistula causing septic renal emboli (*Streptococci*) and regarding the pulmonary septic emboli (*S. aureus* (4×) and *Streptococci* (1×)), the fistula ended at the right heart side in all. These findings emphasize that aggressive pharmacological and nonpharmacological treatment strategies are highly recommended to prevent such complications.

Mechanism of Left-Sided Valve Involvement in Right-Sided Origin of CAFs

Right-sided origin of the fistula with left-sided valve involvement was found in five reports. On the other hand, right-sided origin of the fistula with right-sided valve involvement were present in four fistula with left-sided pathway causing left-sided endocarditis were detected in four of the reviewed subjects.

It is postulated that jet-related lesions at the site of entry of CAF may cause damage to the intimal wall that may be the site of endocarditis. Furthermore, the turbulent and usually continuous flow related with CAF near the cardiac valves may be responsible for the damage. Congenital CAF may cause endocarditis of the valves on the left and right side of the heart. In case of right-sided origin of CAF with left-sided endocarditis, infectious emboli may migrate via the pulmonary vasculature to the left-sided cardiac valves. Septic pulmonary embolism giving rise to left-sided valvular endocarditis has been reported in few CAF cases with right-sided origin. In some cases, infectious pulmonary emboli may remain unnoticed and may be reported as a medical history. Some authors declared that it was unclear which was the first focus of infection the CAF itself or the infected valve lesion. In our current review, none of the subjects had preexistent important valvular disease.

In the current review, the applied treatment modalities included intravenous antibiotics, surgical ligation of the fistulas combined with CABG and valve repair and single or multiple valve replacement. In our current review, surgical closure of the fistula was frequently performed (64%), after completing effective antibiotic treatment, but PTE was successfully performed in some selected cases (8%).

Time between Diagnosis, Prior Antibiotic Treatment, and Intervention

A prior course of intravenous antibiotics, of variable length from days to months, was reported in 20 subjects. However, the time between diagnosis and intervention was documented in a limited number of the reviewed reports (10 subjects). The outcome was favorable in all reported subjects.

Spontaneous obliteration of small fistulas without significant left-to-right shunt in the absence of IE have been reported. Spontaneous closure of the fistula (4%) has occurred via the formation of thrombotic materials and debris following an episode of IE. Spontaneous closure, not associated with IE, has been observed in pediatric and adult subjects caused by atherosclerotic and thrombotic changes. In addition, turbulence-induced shearing force resulting from high flow through the fistulous vessels might lead to excessive endothelial damage and intraluminal atherosclerotic changes. Slater et al. found old healed vegetations surrounding the terminal portion of the fistula during surgery. Furthermore, spontaneous complete occlusion by debris and clots was found in the case reported by Sethuratnam and colleagues. In patients who have been operated upon, IE remains a real danger as long as residual or recurrent fistulas, with or without dilatation of the donor vessel, exist.

Figure 1. Fistulous jet (*) of a fistula (F) arising from the left anterior descending coronary artery (LAD) and terminating into pulmonary artery (PA) may cause lesion of the endothelial wall of the vessel and may act as a nidus (*).
postoperatively. Cheung et al. reported a relatively high incidence (19%) of residual or recurrent fistulas. A residual fistula may manifest growth and increase in size, resulting in the formation of an aneurysm. It has been reported that proximal coronary artery dilatation persists after surgical procedures and sometimes thromboses. As early as 1966, Araya and associates noticed the fatal rupture of the dilated proximal artery after closure of a coronary fistula. Consequently, Cheung et al. suggested a reduction aneurysmectomy to prevent postoperative fatal rupture of the dilated proximal coronary artery.

It is widely accepted that onset of symptoms including typical or atypical chest pain, dyspnea or palpitation due to left-to-right shunt may occur with Qp:Qs ratio of >1.5. In the current review, although the shunt size was variable with pulmonary to systemic flow ratios (Qp:Qs) of small (<1.5, n = 5), moderate (1.5–2.0, n = 2), and severe (>2.0, n = 3), symptoms and IE occurred irrespective of the shunt magnitude. It should be emphasized that antibiotic prophylaxis is strongly advised for pediatric and adult patients with congenital CAFs.

Conclusions
IE as sequelae of CAFs is an important complication. Slightly more males (60%) than female subjects are affected by IE, with an equal contribution of the fistula-donor right and left coronary arteries. Streptococcus species were predominant. The majority of fistulas were unilateral with the overwhelming majority ending into the right heart side, producing valvular and nonvalvular vegetations. Distal septic embolization to the lungs and kidney may also occur. Antibiotic therapy and surgical treatment were the most commonly applied interventions in the majority of the subjects reviewed.

Limitations of the Study
First, there is a data collection bias over a time period which ranged from 1964 until 2015 and second, there is publication bias, as only papers with abnormal and interesting findings are accepted for publication. The results of the current literature review are intended to be indicative and require interpretation with some caution. Further studies on a larger number of patients with congenital CAFs, treated or untreated, complicated by IE are warranted to delineate other characteristics. We are encouraged to initiate an international survey on coronary artery fistulas (Euro-CAF.care).

Summary of Features of Patients with Congenital CAFs Complicated by IE Based on Findings of the Current Review
1. IE may complicate the course in patients of all age groups with congenital CAFs.
2. There is an equal distribution of RCA and LCA with regard to the fistula formation.
3. High incidence of unilateral fistulas with a high percentage of drainage into the RH side.
4. Significantly high rate of culture of Streptococci as a causative pathogenic microorganism.
5. All four cardiac valves, chambers and great venous vessels are affected. Valvular and nonvalvular vegetation may evolve with a variable size of vegetation (mean 6.9–13 mm, range 3 × 6 to 12 × 18 mm), and spontaneous closure, secondary to debris and thrombotic changes, is infrequently observed (4%).
6. A slight difference was found between CCFs (56%) and CVFs (44%).
7. The shunt magnitude was variable and IE may occur irrespective of shunt size.
8. Dilatation of the involved vessel is predominant (88%), with aneurysm formation in 36% of the reviewed subjects. In contrast, dilatation of the termination site was only found in 16% of the subjects.
9. Septic pulmonary and renal emboli were reported in 6/25 (24%) of the reviewed subjects.

Characteristics of Congenital CAFs Complicated with IE
1. In coronary-cameral and to a lesser extent coronary-vascular fistulas, IE caused by Streptococci or Staphylococci may affect all age groups with a slight male preponderance (64%).
2. Unilateral fistulas are predominant (92%) and drainage to the right heart side (76%) is prevalent.

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