Predictors of Long-Term Adverse Outcomes in Patients With Congenital Coronary Artery Fistulae

Anne Marie Valente, MD; James E. Lock, MD; Kimberlee Gauvreau, ScD; Elizabeth Rodriguez-Huertas, BS; Caitlyn Joyce, MHP, PA-C; Laurie Armsby, MD; Emile A. Bacha, MD; Michael J. Landzberg, MD

Background—Significant morbidities, including angina, symptomatic heart failure, and myocardial infarction, have been reported after coronary artery fistula (CAF) closure; however, predictors that may be associated with adverse outcomes have not been established. The goal of this investigation is to describe the long-term outcomes witnessed in patients with either treated or untreated CAF at our institution and to investigate whether certain features predicted adverse outcomes.

Methods and Results—The records and angiograms of patients with CAF who underwent a diagnostic cardiac catheterization at Children’s Hospital Boston from 1959 through 2008 were reviewed. Of 76 patients identified, 20% were associated with additional congenital heart disease. Forty-four underwent transcatheter closure, 20 underwent surgical repair, and no intervention was performed in the remaining 12 subjects. Three patients who had initially undergone surgical closure had a second intervention, 1 underwent repeat surgery, and 2 underwent transcatheter closure. One patient who had undergone transcatheter closure underwent a second transcatheter closure for residual fistula. Major complications, including myocardial infarction, angina with coronary thrombosis, and symptomatic cardiomyopathy, occurred in 11 (15%) patients. The sole angiographic feature that was predictive of adverse outcome was drainage of the CAF into the coronary sinus (P<0.001). Clinical predictors associated with adverse outcomes included older age at diagnosis (P<0.001), tobacco use (P=0.006), diabetes (P=0.05), systemic hypertension (P<0.001), and hyperlipidemia (P<0.001).

Conclusions—Long-term complications of CAF closure may include coronary thrombosis, myocardial infarction, and cardiomyopathy. CAF that drain into the coronary sinus are at particularly high-risk of long-term morbidities after closure, and strategies including long-term anticoagulation should be considered. (Circ Cardiovasc Interv. 2010;3:134-139.)

Key Words: fistula ■ coronary disease ■ complication ■ congenital

Coronary artery fistulae (CAF) are rare anomalies, and management remains controversial. Elective ligation in childhood has been recommended because of increasing incidence of late symptoms and complications in older patients. Despite passage of 50 and 25 years from first incidence of late symptoms and complications in older childhood has been recommended because of increasing awareness and availability of surgical and transcatheter repair of congenital lesions have led to greater potential to perform intervention on CAF. As the incidence of long-term complications of CAF and CAF-related interventions is largely unknown, the goal of this investigation is to describe surgical ligation had a greater mortality (7% versus 1%) and increased postoperative complications (23% versus 7%). Several other institutions have reported their series of CAF management, although long-term follow-up, some of which includes occurrences of myocardial ischemia or infarction and cardiac-related death, is sparse. Cheung et al reported postsurgical coronary arterial angiographic abnormalities as nearly universal at a mean follow-up of 9.1 years after surgical fistula closure; nearly half of examined surgically treated distal vessels were threadlike or completely occluded. Widespread use of echocardiography coupled with increased awareness and availability of surgical and transcatheter repair of congenital lesions have led to greater potential to perform intervention on CAF. As the incidence of long-term complications of CAF and CAF-related interventions is largely unknown, the goal of this investigation is to describe surgical ligation had a greater mortality (7% versus 1%) and increased postoperative complications (23% versus 7%). Several other institutions have reported their series of CAF management, although long-term follow-up, some of which includes occurrences of myocardial ischemia or infarction and cardiac-related death, is sparse. Cheung et al reported postsurgical coronary arterial angiographic abnormalities as nearly universal at a mean follow-up of 9.1 years after surgical fistula closure; nearly half of examined surgically treated distal vessels were threadlike or completely occluded. Widespread use of echocardiography coupled with increased awareness and availability of surgical and transcatheter repair of congenital lesions have led to greater potential to perform intervention on CAF. As the incidence of long-term complications of CAF and CAF-related interventions is largely unknown, the goal of this investigation is to describe

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the history of treated and untreated CAF at our institution and to investigate whether certain patient and CAF features predicted adverse outcomes.

Methods

Patient Selection
All patients with presumed congenital CAF who underwent a diagnostic cardiac catheterization from 1959 to 2008 at the Children’s Hospital Boston (Boston, Mass) were identified from medical, surgical, and imaging databases. Criteria for exclusion from data collection included history of traumatic thoracic injury or cardiac transplantation, identification of CAF after surgical repair in patients with complex congenital heart disease, or presence of coronary sinusoids associated with pulmonary atresia with intact ventricular septum or hypoplastic left heart syndrome. Hospital and office records as well as angiograms from catheterizations and subsequent CAF imaging studies were reviewed for patient demographics, clinical presentation, diagnostic testing, findings at cardiac catheterization or surgery, and follow-up. No autopsy data were available.

Procedural Technique
The TCC techniques used were performed as previously described. Varieties of surgical repairs were used. Epicardial repair involved either on-pump or off-pump identification of coronary fistulae and suture ligation without use of cardioplegic arrest or aortic cross-clamping. Endocardial repair involved cardioplegic arrest and aortic cross-clamping, entry into the right atrium, location of the fistula entry, and subsequent ligation from the inside the heart.

Angiogram Review
Angiograms were independently reviewed by 2 investigators blinded to subject history and outcomes. Specific characteristics of the coronary vessels, including coronary arterial dominance and maximal dimensions and number and location of CAF origin and drainage sites, as well as specific fistula characteristics, including maximal fistulae dimensions, were described.

Follow-Up Data
Postoperative follow-up information was collected through February 15, 2009. The occurrence of a major late complication was defined as presence of myocardial infarction, coronary thrombosis documented by imaging study, newly recognized ventricular tachycardia warranting investigation, or symptomatic heart failure associated with newly recognized decreased myocardial contractility and warranting change in therapy. Presence of residual fistula was documented by imaging at least 1 month after the procedure. The date of last clinical visit and last documented contact information at Children’s Hospital Boston were recorded. Each successfully contacted patient provided verbal consent for telephone interview, which included an approved standardized follow-up questionnaire regarding clinical outcomes. The National Death Index was searched for additional mortality data.

Data Analysis
Continuous variables were summarized as median (range) and compared for patients with and without major complications using the Wilcoxon rank sum test. Categorical variables were expressed as number (percent) and compared using Fisher exact test. When statistically significant differences were found between patients with and without a complication, logistic regression analysis was used to examine the association between complication and the risk factor, adjusting for length of follow-up. Analyses were performed using the Stata statistical package version 10. This investigation was reviewed and approved by the institutional review board.

Results
CAF were identified in 76 patients; no gender predominance existed. At their initial presentation, 88% had an audible murmur, and none had baseline electrocardiographic evidence of previous myocardial infarction. The clinical baseline characteristics of the cohort are listed in Table 1. Sixty-one (80%) patients had an isolated CAF; 20% were associated with congenital heart disease (6 with single coronary artery disease, 2 with ventricular septal defect, 1 with atrial septal defect, 2 with patent ductus arteriosus, 1 with coarctation of the aorta, 1 with bicuspid aortic valve, 1 with tetralogy of Fallot, and 1 with transposition of the great arteries).

Diagnostic angiography at a median age of catheterization of 7 years (5 days to 74 years) was available for review for 64 patients. One patient underwent 2 separate diagnostic catheterizations. More than 1 CAF was identified in 12 (19%) patients. The median pulmonary-to-systemic blood flow ratio was 1.3 (range, 1.0 to 2.3). Angiographic features are listed in Table 2. Twelve subjects with CAF did not undergo any intervention. TCC was pursued in 44 patients; 20 additional patients underwent surgical CAF repair. Three patients who had initially undergone surgical closure had a second intervention, 1 had repeat surgery, and 2 had percutaneous interventions. One patient who had undergone TCC underwent a second TCC for residual fistula.

TCC Patient Group
The median age of the patients at the time of percutaneous intervention was 11 years (range, 10 months to 74 years); 9 (20%) were symptomatic with chest discomfort or symptoms of heart failure at the time of intervention. At the 47 catheterizations (46 patients), intravascular coils (Occluding Spring Emboli) were placed in 40 procedures, umbrella devices (Rashkind Umbrella Occluder, Bard Clamshell Septal Umbrella, CardioSEAL Septal Occluder) in 7, and Grifka vascular occlusion devices (Cook Cardiology) in 3.

Procedural complications included transient ST-T wave changes in 5 patients; atrial arrhythmias in 7; device mobilization in 11; and coronary dissection in 2, which, in both instances, occurred at the site of coil implantation followed by thrombosis and were without acute sequelae. There were no immediate deaths, strokes, or infections.
Surgical Intervention Group

The median age of patients who underwent surgical closure was 5.5 years (range, 3 days to 48 years); 6 (28%) were symptomatic with chest discomfort or symptoms of heart failure at the time of intervention. No major surgical procedural complications were reported. One patient had a significant postsurgical residual fistula and underwent a second surgical procedure. At the 21 surgeries (20 patients), an endocardial approach was performed in 6, epicardial approach in 7, and a combined epicardial and endocardial approach in 7. One patient did not have the surgical report available for confirmation of surgical approach.

Follow-Up

Of the 76 patients studied, 71 had information available for follow-up. The median time from intervention to follow-up was 12.2 years (range, 0.3 years to 47.6 years), with the median age at last documented contact with Children’s Hospital Boston being 14 years (range, 17 days to 74 years). Median follow-up is 4.2 years in the patients with a complication, and 14.6 years in the patients without a complication, P<0.001.

Of the 64 patients who had undergone either TCC or surgical closure of CAF, 85% had documentation of subsequent imaging at least 1 month after the procedure. Of those patients, 16 (30%) had documented residual fistula. Three who had initially undergone surgical closure had a second intervention, 1 had repeat surgery, and 2 had percutaneous interventions. One patient who had undergone TCC underwent a second TCC for residual fistula. There was no significant association between residual fistula and risk of late complication. Three of the 16 (19%) patients with residual fistula leaks experienced a complication versus 8 of the 48 (17%) without a residual leak (P=1.0).

At follow-up, 2 patients died at ages 32 and 47 years. The cause of death could not be determined, although neither had reports of earlier complication in available records. Of the remaining 74 patients, 11 (15%) had major complications (Table 3). Seven had myocardial infarctions, 1 of which

Surgical Intervention Group

<table>
<thead>
<tr>
<th></th>
<th>Overall (n=64)</th>
<th>Patients Without Major Complications (n=53)*</th>
<th>Patients With Major Complications (n=11)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right coronary dominance</td>
<td>58 (91)</td>
<td>49 (92)</td>
<td>9 (82)</td>
<td>0.27</td>
</tr>
<tr>
<td>Fistula origin</td>
<td></td>
<td></td>
<td></td>
<td>0.41</td>
</tr>
<tr>
<td>LMCA</td>
<td>3 (5)</td>
<td>3 (6)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>12 (19)</td>
<td>11 (21)</td>
<td>1 (9)</td>
<td></td>
</tr>
<tr>
<td>Circumflex</td>
<td>21 (33)</td>
<td>15 (28)</td>
<td>6 (55)</td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>28 (44)</td>
<td>24 (45)</td>
<td>4 (36)</td>
<td></td>
</tr>
<tr>
<td>Fistula drainage site</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Right atrium</td>
<td>19 (30)</td>
<td>19 (36)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>CS</td>
<td>19 (30)</td>
<td>9 (17)</td>
<td>10 (91)</td>
<td></td>
</tr>
<tr>
<td>Right ventricle</td>
<td>15 (23)</td>
<td>15 (28)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>5 (8)</td>
<td>5 (9)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>6 (9)</td>
<td>5 (9)</td>
<td>1 (9)</td>
<td></td>
</tr>
<tr>
<td>Maximum coronary diameter, mm</td>
<td>8.0 (1.2–20)</td>
<td>8.0 (2.5–20)</td>
<td>10.5 (1.2–20)</td>
<td>0.29</td>
</tr>
<tr>
<td>Proximal coronary diameter, mm</td>
<td>8.0 (1.2–20)</td>
<td>8.0 (1.2–20)</td>
<td>9.0 (1.2–20)</td>
<td>0.36</td>
</tr>
<tr>
<td>Maximal fistula diameter, mm</td>
<td>10 (0.5–60)</td>
<td>9.8 (1.5–33)</td>
<td>12 (0.5–60)</td>
<td>0.29</td>
</tr>
<tr>
<td>Narrowest segment of fistula, mm</td>
<td>3.0 (0.5–14)</td>
<td>3.0 (0.5–14)</td>
<td>4.0 (0.5–7.0)</td>
<td>0.71</td>
</tr>
<tr>
<td>Length of coronary involvement, cm</td>
<td>3.0 (0.15–30)</td>
<td>3.0 (0.15–30)</td>
<td>3.0 (1.0–13)</td>
<td>0.08</td>
</tr>
<tr>
<td>Presence of visible thrombus</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Values are presented as n (%) or median (range).

LMCA indicates left main coronary artery; LAD, left anterior descending coronary artery; Circumflex, left circumflex coronary artery; RCA, right coronary artery; CS, coronary sinus.

*Two subjects underwent 2 separate percutaneous interventions.

Table 2. Angiographic Features of the Cohort

Table 3. Patient Clinical Features by Complication Status (n=74)

<table>
<thead>
<tr>
<th></th>
<th>Major Complication (n=11)</th>
<th>No Complication (n=63)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>43 (17–59)</td>
<td>5 (0.1–74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>0.75</td>
</tr>
<tr>
<td>Male</td>
<td>6 (55)</td>
<td>30 (48)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>5 (45)</td>
<td>33 (52)</td>
<td></td>
</tr>
<tr>
<td>Event risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tobacco use</td>
<td>3 (38)</td>
<td>1 (2)</td>
<td>0.006</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>4 (50)</td>
<td>2 (4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>5 (56)</td>
<td>0 (0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2 (22)</td>
<td>1 (2)</td>
<td>0.05</td>
</tr>
<tr>
<td>Fistula drainage site</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CS</td>
<td>10 (91)</td>
<td>10 (17)</td>
<td></td>
</tr>
<tr>
<td>All other sites</td>
<td>1 (9)</td>
<td>53 (83)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as n (%) or median (range).
eventuated in urgent coronary artery bypass grafting and 2 led to automatic defibrillator placement. Two patients had angina with subsequent documentation of intracoronary thrombus; 1 had thrombus recognized while taking warfarin at therapeutic levels 4 years after CAF intervention (Figure). Two patients developed cardiomyopathy and significant heart failure symptoms. At the time of recognition of major complication, 5 patients were taking some form of antithrombotic medicine (aspirin in 3, clopidogrel in 2, and warfarin in 2).

The single angiographic feature that was significantly associated with occurrence of major complication was drainage of the CAF into the coronary sinus (CS) \((P<0.001)\) (Table 2). Clinical factors associated with complications included older age at diagnosis \((P<0.001)\), tobacco use \((P=0.006)\), diabetes \((P=0.05)\), systemic hypertension \((P<0.001)\), and hyperlipidemia \((P<0.001)\). Each factor remained significantly associated with the occurrence of a major complication after adjusting for length of follow-up.

**Discussion**

Elective closure of CAF has been advocated to prevent complications later in life. However, little is known about the history of CAF and the possible late complications that occur after TCC or surgical interventions. Our investigation revealed that major complications occur late after closure of CAF, with an incidence of 15%. The etiology of the complications is most likely multifactorial.

Increased age at the time of intervention was associated with major adverse outcomes. Certain modifiable coronary risk factors, such as continued tobacco use, systemic hypertension, diabetes, and hyperlipidemia, also correlated with an increased risk of such long-term morbidity. It is remarkable to note that these events occurred over relatively short follow-up in relatively few patients in this study cohort who demonstrated freedom of angiographic epicardial coronary atherosclerotic obstruction at the time of procedure. The role of atherosclerotic risk factors in this accelerated thrombosis seen after rapid reduction of blood flow remains to be defined.

The only angiographic feature that was associated with major complications was drainage of the fistula into the CS. In fact, 10 of the 11 patients identified with major complications had a CAF that drained into the CS. The median age is higher for patients with fistula drainage to the CS versus all other drainage sites (46.5 years versus 20.6 years, respectively; \(P<0.001)\). However, within the CS subgroup, the median ages for patients with and without complications do not differ significantly (33.9 years versus 47.6 years, respectively; \(P=0.17)\). Interestingly, in the Mayo clinic series, both patients who developed ischemic symptoms after surgical closure had large right coronary artery fistulae draining into the CS.7

Myocardial ischemia or infarction in patients with current or past CAF seem to have multiple potential determinants, including flow-mediated inflammatory vascular changes, vascular trauma or dissection, coronary compression, abnormal myocardial perfusion pressure due to intravascular stenoses or to abnormal drainage compartments, micro- or macrovascular venous thrombosis, and micro- or macrovascular arte-
Mechanisms contributing to the development of coronary thrombosis in persons affected by CAF segregate into several categories, including conduit and resistance vessel sequelae of abnormal flow patterns associated with vascular ectasia, coronary tortuosity, abrupt changes in vessel caliber, and abnormal vascular connections; potential for congenitally intrinsic local or circulating changes in the clotting or fibrinolytic cascade; and effects of direct vascular trauma. The greater fistula length, diameter, and degree of tortuosity noted in past reports of CAF draining to the CS, coupled with both the abrupt cessation of high volume coronary arterial and venous flow occurring after surgical or transcatheter CAF occlusion and any underrecognized differences in procedural technique used to close these more complex CAF, may further exacerbate this prothrombotic tendency.

The presence of a “blind pouch” with limited flow due to lack of distal egress has been demonstrated to carry a risk of thrombosis in other congenital heart disease; such occurrences have been demonstrated to carry a risk of thrombotic tendency.

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**CLINICAL PERSPECTIVE**

Current cardiovascular practice includes closure of all identified audible congenital coronary arterial fistulae. This study describes the long-term follow-up of coronary arterial fistulae at a single referral institution and identifies certain predictors that are associated with adverse outcomes. We raise significant question about this intervention in particular subsets of affected patients due to identification of increased risk of early and late thrombosis and myocardial infarction. We show that coronary fistulae that drain into the coronary sinuses are at particularly high risk of adverse outcomes (early and late thrombosis and myocardial infarction) when closure is performed. As well, we found that older patient age and certain modifiable cardiac risk factors, such as tobacco use, diabetes, systemic hypertension, and hyperlipidemia, were associated with similar adverse patient outcomes. Improved registry assessment of such interventions may lead to greater understanding of outcomes in patients with coronary arterial fistulae.

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