Coronary-cameral fistulas in adults (first of two parts)

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Abstract
This is a case series and review of the literature adding 11 new cases. Coronary-cameral fistulas (CCFs) are infrequent anomalies which are in general co-incidentally found during diagnostic coronary angiography (CAG). To delineate the characteristics of congenital and acquired CCFs in adults, we performed a PubMed search for papers dealing with congenital or acquired CCFs in adults. Publications on coronary-vascular fistulas or paediatric subjects were not included. From the world literature, a total of 243 adult patients were identified who had congenital (65%) or acquired (35%) CCFs. In this review, which is part one of a two-part series on CCFs, we describe and discuss the congenital fistulas, give an overview on the published literature and report details of our own series of 11 patients with MMFs and solitary macro CCFs. Of the congenital group, 85% were small or large solitary macro CCFs (cut-off 1.5 mm) and 15% were coronary artery-ventricular multiple micro-fistulas (MMFs). Apical hypertrophic cardiomyopathy was reported in some of the reviewed subjects with MMFs (3/24 = 13%) but not was seen in our own series. Conservative medical management was generally the treatment of choice in congenital MMFs; prophylactic implantable cardioverter defibrillators (ICD) were implanted in 2/24 (8%) of subjects, especially when extensive micro-fistulisations were involved. None of the patients of our own series required an ICD, as the MMFs were of limited size. Congenital or acquired CCFs in adults are infrequent anomalies having a wide spectrum of clinical presentation may vary from asymptomatic to severely devastating states requiring different treatment modalities.

Core tip: A case series and review of the literature adding 11 new cases. A total of 243 adult patients were identified who had congenital (65%) or acquired (35%) coronary-cameral fistulas. Of the congenital group, 56% were small or large solitary macro CCFs (cut-off 1.5 mm) and 9% were coronary artery-ventricular multiple micro-fistulas (MMFs). T-waves were inverted in the anterior precordial leads in 38% and apical hypertrophic cardiomyopathy was reported in 13% of the subjects. Conservative medical management was generally the treatment of choice in congenital MMFs; prophylactic implantable cardioverter defibrillators were implanted in 8% of subjects, especially when extensive micro-fistulisations were involved.

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INTRODUCTION

Coronary-cameral fistulas (CCFs) are defined as single or multiple, small or large direct communications that arise from one or more coronary arteries and enter into one of the four cardiac chambers (right atrium (RA) and ventricle (RV) and left atrium (LA) and ventricle (LV)). These arterio-venous or arterio-arterial connection, giving rise to left-right or left-left shunts, respectively. In general, CCFs are invariably congenital, but they may also have an acquired etiology which will be addressed in the second part of this review. The congenital entity can be distinguished into coronary artery-ventricular multiple micro-fistulas or small or large solitary macro fistulas, the latter making up the vast majority.

Eleven adult patients with congenital multiple micro-fistulas (MMFs) and solitary macro CCFs from our own patient population are presented and discussed. The present part of the review is confined to congenital CCFs discusses development, clinical presentation, diagnosis and therapy of this infrequent entity and finally review the published literature.

LITERATURE RESEARCH

PubMed was searched for the terms "CCFs", "congenital" and "acquired" combined with "adult". English and non-English publications were screened for both types of congenital and acquired CCFs in an adult population. The definitions used for congenital and acquired traumatic accidental or iatrogenic CCFs were adopted from previous publications. The following criteria were stipulated to include homogenous subsets for analysis: congenital solitary macro (small and large) coronary cameral fistulas or coronary artery-ventricular multiple micro-fistulas MMFs (first part) and acquired traumatic accidental, iatrogenic or spontaneous CCFs (second part). Manuscripts were checked for completeness and a meticulous search was performed for fistula termination into any of the cardiac chambers. Review subjects were tabulated according to the etiology, age, gender, clinical presentations, complications and management. Patients with coronary-vascular fistulas (CVFs) and publications considering a paediatric population were not included. Data of 11 adult patients with congenital MMFs and solitary macro CCFs are presented (Table 1).

Definitions

The definitions offered by Chiu et al and Gupta-Malhotra were applied.

Congenital coronary-cameral fistulas: Small or large, single or multiple fistulous connections originating from any of the coronary arteries and terminating into any of the cardiac chambers (RA, RV, LA and LV).

Solitary macro-fistulas: These are single or multiple, small (< 1.5 mm) or large fistulas (> 1.5 mm), originating mainly from the proximal segment of a coronary artery and entering into a cardiac chamber.

Coronary artery-left: Ventricular MMFs: These are multiple small channels originating from the mid or distal part of one or more coronary arteries fistulating more often into the left than the right ventricular cavity.

Statistical analysis

Continuous variables are expressed as means and ranges and categorical variables were presented as percentages.

RESULTS

From the published literature, 243 adult patients were selected with 65% congenital (159/243) and 35% acquired (84/243) CCFs. Of the congenital group, 56% (135/243) were solitary macro (large or small) coronary artery-cameral fistulas and 9% (24/243) coronary artery-ventricular multiple micro-fistulas. The congenital subgroup will be presented here (first part). This review focuses on and pertains to different aspects with regard to etiology, clinical presentation and management (Tables 2 and 3).

Literature review

Congenital coronary artery-cameral fistulas: Sixty-five percent (n = 159) of the 243 CCFs were congenital. Fifteen percent (24/159) of whom, (15 females, 63%) had multiple micro-fistulas (MMFs). The mean age was 62.7 years (range 39-85); 9 patients had known hypertension and 2 diabetes mellitus. The origin of the fistulas was the left coronary artery (LCA) in 23, the right coronary artery (RCA) in 8 and from the left sinus of Valsalva in 1 of the fistulas. Unilateral fistulas were present in 15, bilateral fistulas in 8 and multipolar fistulas in 1 of the patients. Origin from the distal segment of the involved coronary artery was documented in 5 of the subjects. The fistulas terminated into the LV in 24 patients and into the RV in 1 patient.

The main clinical presentations were angina pectoris (n = 10), chest pain (n = 10), dyspnoea (n = 4), supraventricular tachycardia (n = 3), acute coronary syndrome (n = 3), ventricular fibrillation (n = 1), syncope (n = 3), fatigue (n = 1), congestive heart failure (n = 1), family history of sudden death (n = 1) and abnormal ECG (n = 1). Among the diagnostic modalities implemented were besides ECG and conventional coronary angiography, ambulatory Holter ECG monitoring (n = 4), exercise tolerance testing (n = 7) (1 was non-diagnostic and 6 were positive for ischemia), transthoracic echocardiography (n = 17), cardiovascular magnetic resonance (CMR) (n = 4), myocardial perfusion test (n = 11) (5 were negative and 6 were positive for ischemia) and multi-detector computed tomography (MDCT) (n = 1). Sinus rhythm was demonstrated in 22, atrial flutter in 1 and supraventricular tachycardia in 2 of the patients. Significant coronary artery disease was present in only 2 patients. Dilated and tortuous coronary arteries were reported in 6 (25%) subjects.

The major treatment modality was conservative medi-
Solitary macro-fistulas CCFs\textsuperscript{[11,33-35]}: A total of 135 patients with solitary congenital small or large CCFs (135/159; 85\%) were reviewed and included. They were part of a previous publication\textsuperscript{[11]}. Mean age of these patients was 46.2 years (range 18-85), and 50\% were females. CCFs with single (unilateral) origin were 87\% and CCFs with multiple (bilateral and multilateral) in 13\% of subjects. In fistulas with single or multiple origins, the share from the RCA or LCA to the fistula formation was equally distributed.

Fistula-related complications such as aneurysmal formation (18.2\%), infective endocarditis (8\%) and pericardial effusion (2.9\%) were reported. None of the patients with CCFs developed a myocardial infarction (MI). It was observed that the presence of CCFs predisposed to the development of infective endocarditis as compared to the patients with CVFs.

Current own series
There were 11 patients with congenital MMF's mean age of 61.5 years (range 44-79) (6 females) having 16 MMFs (Figure 1A and B) and 1 patient with congenital solitary macro CCF (Table 1) (Figure 2). The clinical presentations were chest pain (n = 4), angina pectoris (n = 4), non-ST elevation MI (n = 1) and dyspnoea on exertion (n = 2). None of the patients had an infective endocarditis. The concomitant disorders and risk factors were transient ischemic attack (n = 2), sick sinus syndrome (n = 1), aortic and mitral regurgitation (n = 2), previous MI (n = 3), diabetes mellitus (n = 1), chronic obstructive pulmonary disease (n = 2), arterial hypertension (n = 3), obstructive sleep apnoea syndrome (n = 1), glomerulonephritis (n = 1), coronary artery disease (n = 3) [coronary artery bypass grafting (n = 1), percutaneous coronary intervention (n = 1)] and aortic or mitral valve replacement (n = 2). The ECG depicted sinus rhythm in 10 and atrial fibrillation in 1 patient without T wave inversion in the anterior chest leads.

Transthoracic (n = 10) and transesophageal (n = 2) echocardiography were performed. Of these, 6 were normal, 1 showed left ventricular hypertrophy, 1 demonstrated moderate LV systolic function, 1 had severe mitral regurgitation and 1 showed hypokinesia of the inferior wall. Three patients underwent myocardial perfusion tests (1 was negative and 2 were positive for ischemic changes). MDCT was performed in 1 patient and revealed normal coronary arteries without identification of the MMFs. Bilateral fistulas were seen in 6 and unilateral fistulas in 5 patients. They originated from the RCA (n = 7) and from the left coronary artery (n = 9) and terminated into the left ventricle in 15 and the right ventricle in 1 of the fistulas. In 1 patient the CCF originated from the RCA and terminated into the right atrium. He underwent mitral valve repair and surgical ligation of the fistula. Significant coronary artery disease was found in 3 subjects, of whom 2 had one vessel disease (VD) and 1 had 3-VD, while 8 were free of atherosclerotic lesions.

Conservative medical management was applied in all
patients, which consisted of aspirin (n = 9), lipid lowering drug (n = 6), β-blocker (n = 5), angiotensin-receptor blocker (n = 5), calcium channel blocker (n = 2), angiotensin-converting enzyme inhibitor (n = 3) and an oral anticoagulant (n = 1).

**COMMENTS**

Congenital coronary cameral fistulas encompass a group of solitary macro (small or large) or multiple micro coronary cameral communications that are increasingly recognized due to sophistication and wide spread application of non-invasive and invasive angiographic imaging modalities.[9,38] Both entities, solitary macro and multiple micro coronary cameral fistulas, have rarely been reported in a single asymptomatic patient.[17] Congenital CCFs may develop due to a disturbance of embryonic development with partial persistence of the embryonic intertrabecular vascular network.[19,34] Congenital MMFs terminate mainly into the LV, and in congenital solitary macro CCFs the outflow sites are the right atrium, coronary sinus, right ventricle, left atrium and left ventricle.[11] Congenital coronary cameral fistulas vary widely in their clinical presentation. While most patients are asymptomatic or have non-specific complaints, bilateral MMFs draining into the LV may remain clinically silent[69] or may produce diastolic murmur[40] and diastolic volume overload, mimicking aortic valve insufficiency.

**Congenital coronary artery-ventricular multiple micro-fistulas**

Among the reviewed subjects, only a single asymptomatic patient with (silent MMFs) was assessed because of an abnormal ECG at rest (1/24; 4%). Moreover, the clinical diagnosis of congenital MMFs can be difficult because as laboratory tests and ECG manifestations are non-specific and the imaging modalities may sometimes be non-interpretable. Moreover, the diagnostic capabilities of CMR and MDCT have failed to demonstrate congenital MMFs.[22,24]. On the contrary, MDCT is a readily valuable tool for the detection of congenital solitary macro CCFs.[41].

**ECG findings**

Of great interest are the ECG findings in the 24 literature review subjects, of whom sinus rhythm was depicted in the majority of cases (23/24; 96%) and atrial flutter in a single patient (4%). T-waves were inverted in the anterior...
precordial leads in 9 (38%) subjects, and 3 of them had LVH and apical hypertrophic cardiomyopathy (AHCM). Therefore, congenital MMFs may be included in the differential diagnosis of anterior precordial T-wave inversion. Reversible or permanent T-wave inversions either associated with multilateral or unilateral congenital MMFs have been reported. However, in our own series, none of the patients showed T-wave inversion in the precordial leads and T-wave inversions in the anterior chest wall leads were absent in patients with solitary macro CCFs.

**Shunt characteristics**

The magnitude of the shunt of MMFs may be considerable. In MMFs, Cottier et al. measured a reduction of 28% of total coronary blood flow during recumbent bicycle exercise whereas greater cardiac vein flow increased by 66% in the presence of typical anginal pain and ischemic LV dysfunction. Furthermore, Meissner et al. measured coronary artery flow velocity with intravascular Doppler guide wire for hemodynamic quantification of shunt flow, which revealed a left-to-left shunt of 23% of the total LV output. Oh et al. assessed the hemodynamic significance of unilateral MMFs by fractional flow reserve (FFR) and found no evidence of hemodynamic compromise. These investigations may provide interesting data but were not performed either in the reviewed subjects (n = 24) or in our own current series (n = 11).

Non-invasive, myocardial perfusion tests may, incidental-
ly, demonstrate reversible perfusion defects in congenital MMFs\(^4\) as was depicted in 2 patients of our own series and in 6 of the reviewed subjects.

**Incidence of congenital MMFs**

The angiographic incidence of congenital MMFs in the Chinese adult population is estimated at 0.09% with slight female predominance (58%) as was found in the review subjects (63%) and in our own series (60%). Origin from mid or distal segment of the LAD is highly prevalent, occurring in 88% of patients. Symptoms ensued in the 6th decade of life. Our findings were similar and in accordance with the findings of others\(^6\). The mean age in the reviewed subjects was 62.7 years and in our own series of 10 patients with MMFs, it was 69.1 years.

**Associated disorders**

Concomitant AHCM was detected in 13% of the reviewed MMFs subjects and was not observed in any of the solitary CCFs patients\(^23,28\). AHCM, a variant of hypertrophic cardiomyopathy, is rare among Caucasians but more common in the Asian population, especially in the Japanese\(^20\). This association between MMFs has recently been observed not only with AHCM\(^47,48\) but also with non-compaction cardiomyopathy (NCCM)\(^49\). Alternatively, one can assume and may speculate that an early common pathway may exist, yet not detected, for their development. In addition, pre-existent congenital multilateral fistulas (from all 3 epicardial coronary arteries) have been reported in a heart transplant recipient, which were detected after transplantation during routine coronary angiography\(^9\).

**Autopsy findings**

Autopsy of patients with congenital multilateral MMFs to both ventricles depicted insignificant atherosclerotic coronary artery disease, cardiac dilatation and hypertrophy, and dilated coronary arteries with histologically, numerous small vessels of various diameters across the myocardium with patchy subendocardial fibrosis\(^11,32\). This was in accordance with the necropsy findings of Honey and Lau in solitary macro congenital CCFs\(^35,34\), the only difference being the presence of a single fistulous vessel.

**Congenital solitary macro coronary-cameral fistulas**

On the other hand, congenital solitary macro coronary-cameral fistulas (small and large)\(^11,33-35\) showed an incidence of 0.07%. Of these, 0.03% were large and 0.04% were small CCFs\(^1\). CCFs with (unilateral) origin presented 87% and CCFs with multiple (bilateral and multilateral) origin 13% of subjects. Fistula-related complications such as aneurysmal formation (18.2%), infective endocarditis (8%) and pericardial effusion (2.9%) were reported. None of the CCFs patients developed MI, however, and subjects with CCFs were susceptible for the development of infective endocarditis compared to the group presented with coronary-vascular fistulas\(^11\). In bilateral CCFs, hemodynamic significance was assessed by FFR and ischemia was ruled out\(^43\). In our patient with congenital solitary macro fistula from RCA to RA, the fistulous vessel was surgically ligated during redo of mitral valve repair for mitral valve prolapse accompanied with symptomatic severe mitral regurgitation.

Supraventricular (SV) and ventricular arrhythmias have been associated with coronary cameral fistulas (solitary or MMFs). In our own series (\(n = 11\)), atrial fibrillation/flutter (AF) was present in only 1 patient (10%), and AF and supraventricular tachycardia were present in 2 of the MMFs reviewed subjects (8%). However, neither ventricular arrhythmias nor infective endocarditis were reported in the MMFs subjects.

**Myocardial infarction**

In the absence of atherosclerosis, MI may develop in the presence of MMFs originating from all 3 coronary arteries terminating into both ventricles\(^83\). One patient of our own series (1/10; 10%) sustained inferior wall MI, in which the fistula-bearing RCA was involved.

**Management**

In all 24 reviewed subjects, conservative medical management was conducted including \(\beta\)-blockers\(^17\), calcium channel blockers\(^21\) and ivabradine\(^21\) as was previously reported\(^3\). While congenital MMFs are generally treated conservatively, congenital solitary CCFs may undergo percutaneous occlusion or surgical ligation in the presence of substantial significant shunts. Only in few of the reviewed subjects, having morphologically extensive MMFs, a prophylactic ICD was implanted (8%). None of the patients in our own series required an ICD as the MMFs were not widespread.

**CONCLUSION**

In almost 40% of the reviewed subjects with congenital coronary artery-ventricular multiple micro-fistulas, T-wave inversion was present in the precordial leads of the electrocardiogram in association with or without apical hypertrophic cardiomyopathy. For adult patients with congenital coronary artery-ventricular multiple micro-fistulas, conservative medical management is the treatment of choice. Due to the multiplicity of the fistulas, they are inaccessible for percutaneous or surgical intervention which may be considered in large solitary coronary-cameral macro fistulas with hemodynamically significant shunts. Limited data were reported on adult patients with solitary CCFs. Within the entity of CCFs, each subtype has its own specific characteristics such as origin, termination of fistulas and treatment options. In addition, there were few reports on the implantation of an ICD in patients with extensive congenital MMFs in association with syncope.
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