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ORIGINAL ARTICLE

Retrospective Study

Congenital coronary artery fistulas complicated with pulmonary hypertension: Analysis of 211 cases

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Abstract

AIM

To compare the behavior of pulmonary hypertension (PHT) associated with coronary artery fistulas (CAFs) between the Asian and Caucasian subjects.

METHODS

CAFs may be complicated with PHT secondary to left-to-right shunt. Literature review limited to the English language. A total of 211 reviewed patients were collected. Of those, 111 were of Asian and 100 were of Caucasian ethnic origin. The mean age of the Asian and the Caucasian groups of patients were 48.9 (range 19-83) and 49.9 years (range 16-85), respectively. In both groups, right heart catheterization was the most commonly (95%) used method for determining pulmonary artery pressure.

RESULTS

From all of the reviewed subjects, PHT was found in 49 patients (23%), of which 15 were Asian and 34 were Caucasian. In 75% of PHT subjects, mild to moderate PHT was reported and 76% of the fistulas had a vascular mode of termination. Treatment was surgical in 61%, followed by percutaneous therapeutic embolization (27%) and finally conservative medical management in 12% of PHT subjects. PHT was associated with a slight female gender predominance. The majority demonstrated mild to moderate PHT. PHT was reported more frequent in the Caucasian compared with the Asian ethnicity group. The majority of fistulas in patients with PHT had a vascular mode of termination. The results of this review are intended to be indicative and require cautious interpretation.

CONCLUSION

The likelihood for a CAF patient to develop PHT is presented when possessing the following features, with a Caucasian female having a fistula with a vascular mode of termination.

Key words: Congenital coronary artery fistulas; Congenital anomaly; Pulmonary hypertension; Asian population; Caucasian population

Core tip: Congenital coronary artery fistulas (CAFs) are infrequent but hemodynamically important anomalies which may evolve a myriad of complications, such as myocardial infarction, congestive heart failure, infective endocarditis, aneurysm, rupture, pericardial effusion, arrhythmias and sudden death. In addition, secondary pulmonary hypertension (PHT) may complicate the course of CAFs. Moreover, when monitoring CAF patients, the clinicians responsible for the management of patients with congenital CAFs should be aware of the development of PHT during the course of the disease.

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INTRODUCTION

Congenital coronary artery fistulas (CAFs) are uncommon anomalies. Most CAFs are small and hemodynamically inconsequential with a negligible shunt. However, some can be sizeable and lead to shunting of blood from the coronary circulation to low-pressure pulmonary vascular bed, resulting in pulmonary hypertension (PHT)[1]. CAFs may be associated with normal[2-4] pulmonary artery pressure (PAP) in unilateral[5-8] or bilateral[9,10] fistulas, or may sometimes be accompanied with elevated PAP[11-14]. Rarely, in octogenarians with bilateral CAFs, PAP may remain normal[15].

The hemodynamic consequences of CAFs varies, depending on their magnitude and the cardiac chamber or vascular site involved. Fistulas terminating into the right heart chambers may produce left-to-right shunt and volume overload of the pulmonary circulation, whereas fistulas to the left heart side cause left ventricular volume overload.

In a literature review, 211 subjects were included and a comparison was made between the Asian (*n* = 111) and Caucasian (*n* = 100) subjects regarding the behavior of PAP associated with CAFs.

MATERIALS AND METHODS

The data source was based on an extensive literature review of the English literature in the PubMed database regarding congenital CAFs and PAP. The search was conducted using the terms "congenital coronary artery fistulas" and "pulmonary artery pressure". Inclusion of a paper occurred when full data on PAP either using right heart catheterization (RHC) (direct measurement) or Doppler echocardiography [calculation of estimated PAP based on tricuspid regurgitation (TR) peak velocity] were provided.

This retrieval resulted in a collection of 133 papers which included 49 of Asian (*n* = 111 patients) and 84 of Caucasian (*n* = 100 patients) reports. Three were excluded because of duplication. Reference lists from selected papers were manually searched for potentially relevant publications. Whenever available, the most recent data were included. Another seven papers were therefore added, meaning that the final retrieval result was 137 papers. Congenital multiple micro-fistulas were not included and patients with acquired fistulas were excluded.

Definition of PHT[16-18]

Invasive method: PHT is defined as the systolic PAP (sPAP) or mean PAP, exceeding 35 mmHg or 25 mmHg, respectively. Furthermore, the mean PAP rises above 30 mmHg with exercise, occurring secondary to either a pulmonary or a cardiac disorder[16].

Non-invasive method: In accordance with the European Society of Cardiology criteria for detecting the presence of PHT, based on the TR peak velocity and Doppler-calculated sPAP at rest (assuming a normal right atrial pressure of 5 mmHg), additional echocardiographic variables suggestive of PHT were used to determine the sPAP[19,20]. PHT was defined by an estimate of right ventricular systolic pressure of greater than 40 mmHg. sPAP is estimated using TR jet velocity based on the simplified Bernoulli's equation [4 × (TRV)^2 + RA pressure][19,21,22] (TRV: TR velocity; RA: Right atrium). PHT was classified into three categories: Mild (40-49 mmHg), moderate (50-59 mmHg) and severe (> 59 mmHg).

Statistical analysis

Values were expressed as means, averages, and percentages.

RESULTS

Total group

A total of 211 (M: 87 = 41% and F: 124 = 59%) reviewed patients were collected from the world literature. The mean age was 49.4 years (range 16-85). The reported method of assessment of PAP was RHC (*n* = 201, Caucasian *n* = 94 and Asian *n* = 107) and Doppler echocardiography (*n* = 10, Caucasian *n* = 6 and Asian *n* = 4) in 95% and 5% of the subjects, respectively. The congenital CAFs were unilateral in 118 (56%), bilateral in 87 (41%) and multilateral in 6 (3%) of the subjects. The CAFs arose from the right (133/268 = 49.6%) and left (135/268 = 50.4%) coronary artery, respectively. The mode of termination was either vascular (90/211 =

Table 1 Reviewed Asian (*n* = 111) and Caucasian (*n* = 100) group of patients

	Total reviewed subjects	Asian group	Caucasian group
n	211	111 (53%)	100 (47%)
Gender	F 124 (59%)	F 63 (57%)	F 61 (61%)
	M 87 (41%)	M 48 (43%)	M 39 (39%)
Mean age (range)[1], yr	49.4 (16-85)	48.9 (19-83)	49.9 (16-85)
CAF characteristics			
Unilateral	118 (56%)	42 (38%)	76 (76%)
Bilateral	87 (41%)	63 (57%)	24 (24%)
Multilateral	6 (3%)	6 (5%)	-
Mode of termination			
CVFs	90 (43%)	43 (39%)	47 (47%)
CCFs	121 (57%)	68 (61%)	53 (53%)
RHC	201 (95%)	107 (96%)	94 (94%)
sPAP/RVSP	10 (5%)	4 (4%)	6 (6%)
Management			
CMM	38	20	18
PTE[2]	29	9 (8%)	20 (20%)
SL	124 (59%)	82 (74%)	42 (42%)
WW	2	-	2
Death	2	-	2
Not mentioned	16	-	16

[1]Subjects (*n* = 41) from ref. [35] were not included in calculation of mean age (*n* = 170, 70 Asian and 100 Caucasian). [2]In one patient, PTE failed followed by SL treatment (ref. [147]) and another treated with hybrid procedures (ref. [133]). CAF: Coronary artery fistula; CCFs: Coronary-cameral fistulas; CVFs: Coronary-vascular fistulas; CMM: Conservative medical management; F: Female; M: Male; PTE: Percutaneous therapeutic embolization; RHC: Right heart catheterization; SL: Surgical ligation; sPAP: Systolic pulmonary artery pressure; RVSP: Right ventricular systolic pressure.

43%) or cameral (121/211 = 57%) (Table 1).

Among the applied therapeutic modalities, surgical ligation (SL) was performed in 124 (59%), conservative medical management (CMM) in 38 (18%), percutaneous therapeutic embolization (PTE) in 29 (13%) and watchful waiting in 2 (1%). There were 2 mortalities (1%) and treatment options were not mentioned in 16 (8%) of the subjects. Among the whole group, 23% (49/211) were found to have elevated PAP.

Asian population: n = 111

The reviewed patients of Asian ethnicity [*n* = 111, Male *n* = 48 (43%) and Female *n* = 63 (57%)] had a mean age of 48.9 years (range 19-83).

Between 1986 and 2014, papers published describing Asian population with congenital CAFS and reported data on PAP were included: from 1986-1993[23-28], 1994-1999[29-33], 2001-2004[34-39], 2005[40-42], 2006[43-49], 2007[50-55], 2009-2011[56-61] and 2012-2014[62-69]. PAP was measured by RHC in 107 and by Doppler echocardiography in 4.

Ninety-six subjects (86%) had normal PAP. Among the CAFs, 42 were unilateral (38%), 63 bilateral (57%) and 6 multilateral (5%). The treatment modalities were SL [82 = (74%)], CMM [20 = (18%)] and PTE [9 = (8%)]. No watchful waiting strategy was conducted and death did not occur in any of the subjects.

Table 2 Asian and Caucasian group of patients (*n* = 49) with pulmonary hypertension

	Total group	Asian group	Caucasian group
n	49	15 (31%)	34 (69%)
Age[1]	56 (16-80)	54.4 (24-77)	56.8 (16-80)
Gender	F 34 (69%)	F 12 (80%)	F 22 (65%)
	M 15 (31%)	M 3 (20%)	M 12(35%)
CAF			
Unilateral	37 (76%)	9 (60%)	28 (82%)
Bilateral	12 (24%)	6 (40%)	6 (18%)
PHT			
Mild	26 (53%)	8/15 (53%)	18/34 (53%)
Moderate	11 (22%)	2/15 (13%)	9/34 (26%)
Severe	12 (25%)	5/15 (33%)	7/34 (21%)
Mean PAP (mmHg)	35.6 (range 26-60)	36.9 (range 27-49)	34.3 (range 26-60)
Mean Qp:Qs ratio	1.9 (range 1.13-2.75)	1.9 (range 1.13-2.75)	1.9 (range 1.3-2.7)
RHC	43 (88%)	13 (87%)	30 (88%)
Doppler (sPAP)	6 (12%)	2 (13%)	4 (12%)
CAF characteristics			
Origin	R 8, L 30, bilateral 11	R 2, L 8, bilateral 5	R 6, L 22, bilateral 6
Termination	RH side 45 LH side 4	RH side 13 LH side 2	RH side 32 LH side 2
Mode of termination			
CVFs	37 (76%)	9/15 (60%)	28/34 (82%)
CCFs	12 (24%)	6/15 (40%)	6/34 (18%)
Associated disorders	17/49 (35%)	5/15 (33%)	12/34 (35%)
Management			
SL	30 (61%)	9	21
PTE	13 (27%)	4	9[2]
CMM	6 (12%)	2	4

[1]Subjects from ref. [35] were not included in calculation of mean age. Mean age was calculated from 170 (70 Asian and 100 Caucasian) subjects. [2]One PTE failed (from ref. [147]) followed by SL treatment and another treated with hybrid procedures (from ref. [133]). CAF: Coronary artery fistula; CCFs: Coronary-cameral fistulas; CVFs: Coronary-vascular fistulas; CMM: Conservative medical management; F: Female; R: Right coronary artery; L: Left coronary artery; LH: Left heart side; M: Male; PAP: Pulmonary artery pressure; PHT: Pulmonary hypertension; PTE: Percutaneous therapeutic embolization; RH: Right heart side; RHC: Right heart catheterization; SL: Surgical ligation; sPAP: Systolic pulmonary artery pressure.

PHT was found in 15 Asian (14%) (M, *n* = 3; F, *n* = 12) subjects with a mean age 54.4 years (range 24-77). Among the 15 subjects, mild, moderate and severe PHT was detected in 8, 2 and 5, respectively.

Caucasian population: n = 100

The mean age (*n* = 100, Male 39 and Female 61) was 49.9 years (range 18-85). Published papers on Caucasian population regarding CAFs and PAP between 1955 and 2014 were included for evaluation: 1955-1961[70-75], 1964-1967[5,76-78], 1971-1976[2,79-82], 1981-1989[11,83-85], 1990-1991[3,6,10,86,87], 1992-1994[88-92], 1995-1997[4,9,31,93-95], 2000-2002[12,13,96-101], 2003-2004[102-106], 2005-2006[7,15,107-113], 2007-2009[14,114-124], 2010-2012[8,125-130], and 2013-2014[131-134]. PAP was evaluated by RHC in 94% (*n* = 94) and in 6 by Doppler echocardiography method. The CAFs were unilateral in 76 (76%) and bilateral in 24 (24%) of the subjects. No multilateral fistulas were

reported. Sixty-six subjects (66%) had normal PAP.

Treatment modalities included SL (42), PTE (20), CMM (18), and watchful waiting (2), and were not mentioned in 16 cases. There were 2 mortalities (2). PHT was found in 34 subjects (34%) [M: *n* = 12 (35%) and F: *n* = 22 (65%)], with a mean age of 56.8 years (range 16-80).

PHT population: n = 49

PHT was found in 49 patients (49/211 = 23%), with a mean age of 56 years (range 16-80). There were 34 females (69%) and 15 males (31%), with 15 Asian (mean age 54.4, range 24-77 years) and 34 (mean age 56.8, range 16-80 years) of Caucasian patients. The fistulas were unilateral in 37 (76%) and bilateral in 12 (24%) of the subjects. Measurement of PAP was achieved by RHC in 43 subjects (13 Asian and 30 Caucasian) and by Doppler echocardiography in 6 (2 Asian and 4 Caucasian) subjects. Mild, moderate and severe PHT was reported in 26 (53%), 11 (23%) and 12 (24%) subjects, respectively (Table 2).

The following features were detected among PHT group of patients: A female predominance (34/49 = 69%), unilateral origin (37/49 = 76%) from the left coronary artery (30/49 = 61%) and termination into the right heart side (45/49 = 92%) were the major findings of the PHT group of patients.

The percentage of unilateral and CVFs was higher in the Caucasian group (82% and 82%) compared to the Asian group (60% and 60%), respectively (Table 3).

DISCUSSION

CAFs may remain silent, co-existing with longevity for years and emerging as a coincidental finding during non-invasive or invasive[135] investigation for the analysis of suspected cardiac disorder.

CAFs are an uncommon congenital anomaly which may be associated with several complications (Table 4). These complications may have coronary vascular, pericardial or myocardial origin. Furthermore, they may have a valvular source or may originate from an atrial or ventricular arrhythmic substrate. Such complications may include myocardial infarction (MI) (4%)[136,137], congestive heart failure (20%)[136], infective endocarditis (reported in 4%-12% in different series)[81,136], atrial[138] and ventricular[139] arrhythmias, aneurysm (reported in 20% of cases)[96,140], rarely ruptured aneurysm with hemopericardium[141] and unruptured aneurysm[139,142], pericardial effusion[143], syncope[142,144] and sudden death[145]. It has been postulated that fistula-related complications increase with age[136]. Secondary PHT is an infrequent complication of congenital CAFs. As early as 1955, Davison reported PHT in patients with CAFs[70].

Most CAFs are small and hemodynamically inconsequential with a negligible left-to-right shunt. However, some can be sizeable and lead to shunting of blood from the coronary circulation to low-pressure pulmonary vascular bed, resulting in PHT[1].

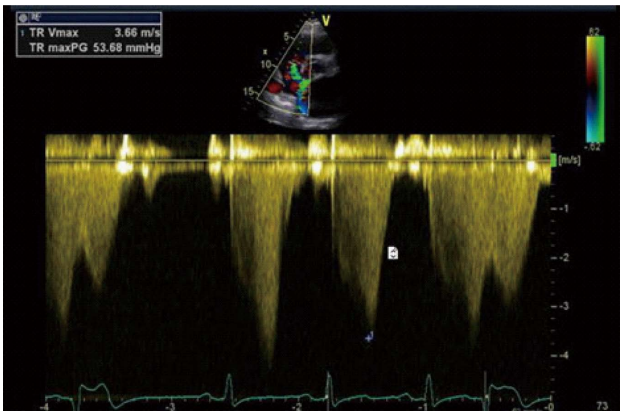

Figure 1 Continuous wave Doppler demonstrating blood flow velocity (3.66 m/c) across the tricuspid valve.

In congenital CAFs, although PHT may occur when sizeable left-to-right shunt exists; in the current review, the mean Qp:Qs was modest, with moderate magnitude 1.9:1.0.

It has been stated that severe PHT is not frequently observed in isolated CAFs[87]. Mild to moderate PHT[5] has sporadically been reported in unilateral[39,45,107,124,146,147] and bilateral fistulas[42,103,112,118]. Indeed, in the current literature review, only 25% were found to have severe PHT, with the majority (75%) having mild or moderate PHT. No reports of multilateral CAFs associated with PHT were found. It is noteworthy that CAFs may be associated with longevity[96] and PHT has been reported in septuagenarians[11] and octogenarians[107].

Although PAP can be measured on Doppler echocardiography, the gold standard for diagnosis is RHC. In the current review, 95% were direct calculation of PAP using RHC and only 5% as an estimate of right ventricular systolic pressure by Doppler echocardiography using TR jet velocity based on the simplified Bernoulli's equation (Figure 1). It is widely accepted that pulmonary artery systolic pressure (sPAP) can be considered normal until 40 mmHg in the elderly and obese subjects. Moreover, tricuspid regurgitant jet velocity is a parameter that has been widely applied to estimate sPAP[22].

In comparison with the Caucasian group of patients (65%) with PHT, female gender accounted for 80% in the Asian group and was almost equally associated (35% *vs* 33%) with concomitant congenital and acquired coronary and valvular heart defects.

In the total group of patients (*n* = 49) with PHT, female gender accounted for (69%), unilateral fistulas was present in (76%) and mild to moderate PHT (75%) was predominant. RHC was performed in 88% of patients and in 12% Doppler echocardiography was used for estimation of the sPAP. Coronary vascular fistulas as a mode of termination were found in the overwhelming majority (76%) of patients. SL was performed in 61% of

Table 3 Mode of termination coronary-vascular fistulas *vs* coronary-cameral fistulas in the pulmonary hypertension (*n* = 49) and all reviewed (*n* = 211) subjects

	CVFs	CCFs	Mean age and range (yr)
Total *n* = 211	90/211 (43%)	121/211(57%)	38.3 (26-67)
Asian 15/111 (14%)	9/15 (60%)	6/15 (40%)	39.7 (27-67)
Caucasian 34/100 (34%)	28/34 (82%)	6/34 (18%)	36.8 (26-60)

CCFs: Coronary-cameral fistulas; CVFs: Coronary-vascular fistulas.

patients with PHT.

In the present review of all 49 subjects, possible common features of CAFs associated with PHT were unilateral fistula (37/49 = 76%) originating from the left coronary artery (30/49 = 61%) with a vascular termination (76%) into the right heart side (45/49 = 92%). These findings have to be investigated in a future international survey or prospective study.

A significant difference was noted in the percentages of coronary-cameral fistulas between Asian (40%) and Caucasian (18%) groups of patients with PHT. There was no difference in associated cardiac defects, congenital or acquired, in both the Asian and Caucasian groups (33% and 35%, respectively).

Limitations of the study

Among the Asian population reported by Cheung *et al*[35] in 2001, among the 41 subjects, there were children included in their study. The time span for data collection spread from 1955 to 2014 due to period collection bias.

Publication bias, only subjects with abnormal findings are accepted for publication. Although the data were of high quality and were collected from the world literature, the results of this review are intended to be indicative and require cautious interpretation.

It is clear that more research and studies are warranted for the identification and registration of congenital CAFs associated with PHT; the cause seems to be more multi-factorial (gender, fistula origin and outflow) and dependent on the fistula characteristics itself. We are encouraged to initiate an international survey on CAFs (Euro-CAF.care).

In conclusion, among the whole population, 23% were found to have elevated PAP. In the Asian group of patients 14% demonstrated PHT compared to 34% among the Caucasian group. Among the patients (*n* = 49) with PHT, 69% were female. The majority of fistulas (76%) in patients (*n* = 49) with PHT were of CVFs type in contrast to CCFs who accounted for 24% of subjects. The likelihood for a CAF patient to develop PHT is presented when possessing the following features, with a Caucasian female having a fistula with a vascular mode of termination. The findings of this review need to be confirmed in a larger multicenter international registry, preferably with a longer follow-up.

Table 4 Possible complications of coronary artery fistulas

Complication	Features
Cardiovascular	Myocardial infarction, stroke, aneurysm, rupture
Infectious	Bacterial endocarditis, septic pulmonary and septic renal embolism
Valvular	Incompetence, dysfunction, perforation
Pericardial	Hemopericardium, pericardial effusion, tamponade
Myocardial	Congestive heart failure
Arrhythmic	Supraventricular arrhythmias, ventricular arrhythmias and sudden death

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COMMENTS

Background

Congenital coronary artery fistulas (CAFs) are uncommon anomalies. Most CAFs are small and hemodynamically inconsequential with a negligible shunt. However, some can be sizeable and lead to shunting of blood from the coronary circulation to low-pressure pulmonary vascular bed, resulting in pulmonary hypertension (PHT).

Research frontiers

CAFs may be associated with normal pulmonary artery pressure (PAP) in unilateral or bilateral fistulas, or may sometimes be accompanied with elevated PAP. Rarely, in octogenarians with bilateral CAFs, PAP may remain normal.

Innovations and breakthroughs

The likelihood for a CAF patient to develop PHT is presented when possessing the following features, with a Caucasian female having a fistula with a vascular mode of termination.

Applications

The findings of this review need to be confirmed in a larger multicenter international registry, preferably with a longer follow-up.

Peer-review

This paper is interesting review concerning association PAH and CAF. Therefore, this article should be published.

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