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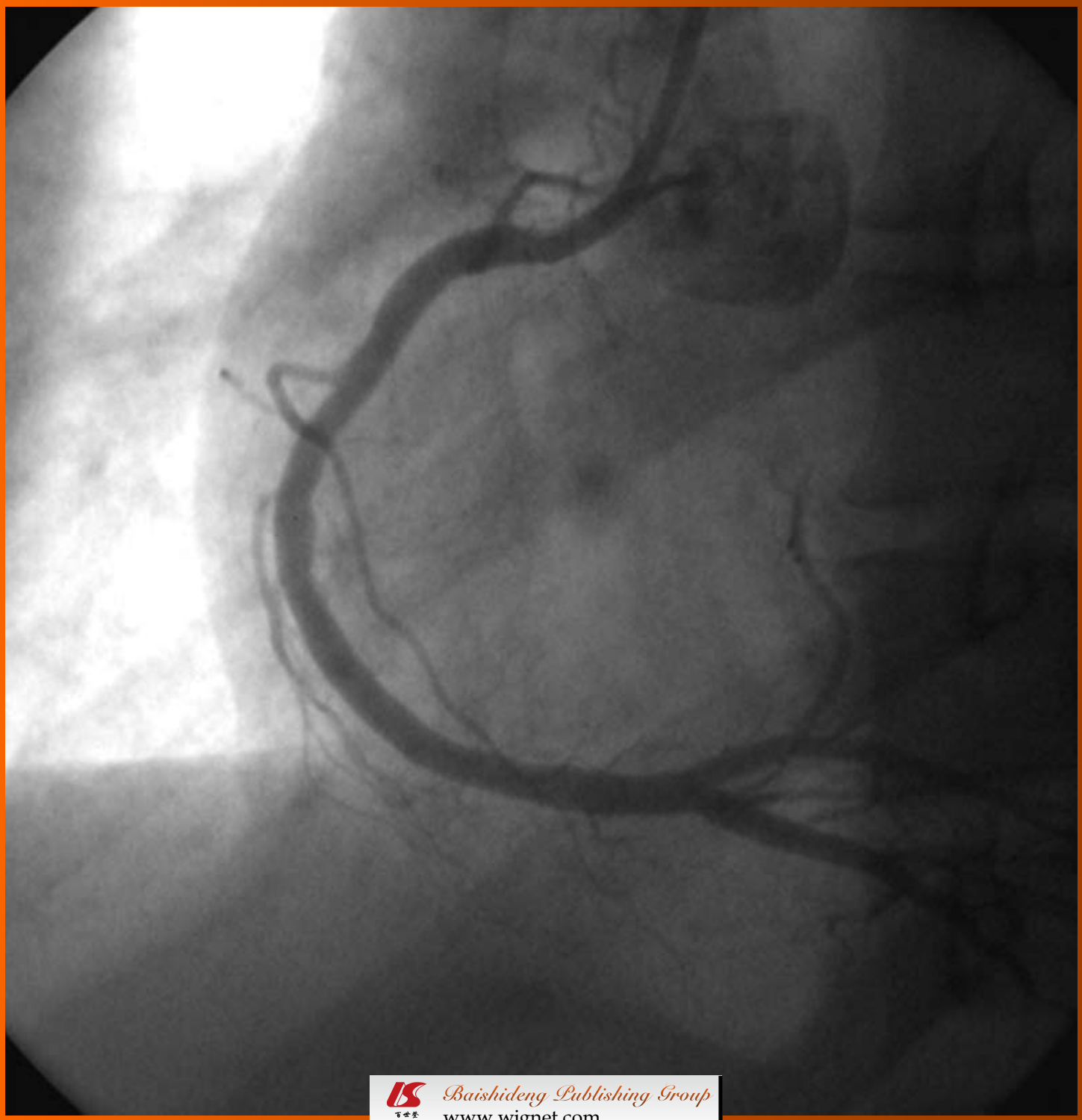

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EDITORIAL

Hypertension in the elderly: Are we all on the same wavelength?

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Abstract

Hypertension is of frequent occurrence in the elderly population. Isolated systolic hypertension (ISH) accounts for the majority of cases of hypertension in the elderly. ISH is associated with a 2-4-fold increase in the risk of myocardial infarction, left ventricular hypertrophy, renal dysfunction, stroke, and cardiovascular mortality. There have been many studies to determine the optimal treatment for hypertension in the elderly. Why, when and how to treat hypertension in the elderly was the scope of the majority of these trials. Despite countless efforts many aspects remain obscure. While a number of novel drugs are being developed, the issue of whether all antihypertensive drugs bestow parallel benefits or whether some agents offer a therapeutic advantage beyond blood pressure control remains of crucial importance. Furthermore, the response of the elderly to different antihypertensive agents also differs from that of younger patients and may explain some of the disparities in outcomes of trials conducted in elderly patients with hypertension.

Key words: Hypertension; Myocardial infarction; Left ventricular hypertrophy; Antihypertensive agents

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INTRODUCTION

Hypertension is of frequent occurrence in the elderly (age greater than 60 to 65 years), with prevalence as high as 60%-80%[1,2]. Isolated systolic hypertension (ISH) accounts for 60%-75% of cases of hypertension in the elderly[3,4]. It is defined as a systolic blood pressure (BP) above 160 mmHg, with a diastolic BP below 90 mmHg[5,6]. ISH is associated with a 2-4-fold increase in the risk of myocardial infarction (MI), left ventricular hypertrophy, renal dysfunction, stroke, and cardiovascular mortality[7,8]. Elevated systolic BP is a more important risk factor for cardiovascular and renal disease than elevated diastolic BP[9,10]. Studies have clearly pointed out that lowering systolic BP to < 160 mmHg is markedly beneficial in terms of reducing the risk, however no trial has directly measured the degree of added benefit that would occur at a

systolic BP target < 140 mmHg[11,12]. While a number of novel drugs are being developed, an issue of whether all antihypertensive drugs bestow parallel benefit or whether some agents offer a therapeutic advantage beyond BP control remains of crucial importance. Furthermore, the response of the elderly to different antihypertensive agents also differs and may explain some of the disparities in outcomes of trials conducted in elderly patients with hypertension.

WHY TO TREAT?

As late as the 1970s, the customary belief was to disregard elevated BP in the elderly, despite the fact that the age-related risk of coronary heart disease (CHD) as a consequence of hypertension was evident in various epidemiologic data[13]. Now, there is robust evidence that treatment of hypertension in the elderly has a multitude of benefits in terms of morbidity and mortality. Two meta analyses performed in 1994 clearly demonstrated significant reductions in stroke (35%), stroke deaths (34%), CHD events (including MI, 15%), CHD deaths (25%), all cardiovascular events (29%), cardiovascular deaths (25%), and even all-cause mortality (12%)[14,15]. Even more striking was the 5-year number needed to treat (NNT) estimate (which indicates the number of patients needed to treat in order to prevent one event in question and is a means of assessing effectiveness of health care intervention), indicated that fewer than 100 older people required to be treated to prevent one event. These numbers were nearly 10-fold lower than estimates based on the first Medical Research Council Study which involved 35-60-year-old hypertensives[15]. Since NNT estimates are inversely proportional to the cost-effectiveness ratio, these meta-analyses inferred that hypertension treatment in the elderly is much more rewarding in terms of cost-effectiveness compared to treatment of the same level of BP in younger individuals. According to an older meta-analysis in both elderly and younger hypertensives, drug treatment largely reduces the number of individuals progressing to higher stages of hypertension, which is not only more difficult and expensive to treat, but also increases cardiovascular risk[16]. Data from the Multiple Risk Factor Intervention Trial clearly showed the importance of hypertension as a risk factor for end-stage renal disease[17]. Furthermore, a meta analysis has also shown a 42% reduction in heart failure in elderly patients receiving antihypertensive therapy[18]. Finally, left ventricular hypertrophy, an important subclinical disease marker that may be the most powerful of all cardiovascular risk factors, can be substantially improved by antihypertensive therapy: some meta-analyses, based on detection by (admittedly imperfect) electrocardiograms have placed the estimate of effectiveness as high as 35%[16].

WHEN TO TREAT?

The trials in the 1996 meta-analysis all had baseline mean systolic pressures of 160 mmHg or more[19]. No trials have been performed in patients with ISH with baseline systolic pressure of 140 to 149 mmHg[20]. The recommendation to treat such patients is based upon observational studies that show a graded relationship between increasing systolic BP and cardiovascular risk[21]. Among elderly patients younger than 80 years of age, antihypertensive therapy is initiated among those with systolic pressures greater than 140 mmHg and/or diastolic pressures greater than 90 mmHg[22]. However, there is disagreement as to the threshold systolic BP warranting therapy among elderly patients older than 80 years of age with ISH. Some would initiate antihypertensive therapy at a systolic pressure between 150 and 159 mmHg, while others would only treat patients with a systolic pressure of 160 mmHg or greater[23].

HOW TO TREAT?

All patients should receive non pharmacologic therapy, particularly dietary salt restriction and weight loss in obese patients. Drug therapy should be started if lifestyle changes fail after trying for at least 3 to 6 mo, unless compelling evidence for treatment exists[22]. A potential limiting factor to the use of antihypertensive drugs is that orthostatic (postural) and/or postprandial hypotension is common among elderly hypertensive patients[24,25]. The 2007 American Heart Association statement on the treatment of BP in ischemic heart disease, the 2007 European Society of Hypertension/European Society of Cardiology guidelines on the management of hypertension, and meta-analyses from 2008 and 2009 concluded that the amount of BP reduction and not the choice of antihypertensive drug is the key determinant of reduction in cardiovascular risk in both younger and older patients with hypertension[26-29].In general, three classes of drugs are considered first-line therapy for the treatment of hypertension in elderly patients: low-dose thiazide diuretics (e.g. 12.5-25 mg/d chlorthalidone), long-acting calcium channel blockers (most often dihydropyridines), and angiotensin converting enzyme inhibitors or angiotensin Ⅱ receptor blockers[30-32]. A long-acting dihydropyridine or a thiazide diuretic is generally preferred in elderly patients because of increased efficacy in BP lowering[30]. There is evidence that, in the absence of a specific indication for use, β-blockers should not be considered for primary therapy of hypertension, particularly in elderly patients[33]. They may be worse than other agents for the prevention of stroke, particularly among smokers, and perhaps for mortality[33-36]. With all drugs, orthostatic hypotension should be avoided because of the increased risk of falling in older patients. If the initial dose of an antihypertensive drug does not control the BP, the dose may be increased or a second drug may be added to reduce the risk of dose-related adverse effects of the first drug[22]. Most elderly patients ultimately require two or more antihypertensive agents. If the BP is 20/10 mmHg above the goal, combination drug therapy with drugs from two different

classes is indicated as initial therapy[22].

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BRIEF ARTICLE

Current characteristics of congenital coronary artery fistulas in adults: A decade of global experience

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Abstract

AIM: To describe the characteristics of coronary artery fistulas (CAFs) in adults, including donor vessels and whether termination was cameral or vascular.

METHODS: A PubMed search was performed for articles between 2000 and 2010 to describe the current characteristics of congenital CAFs in adults. A group of 304 adults was collected. Clinical data, presentations, diagnostic modalities, angiographic fistula findings and treatment strategies were gathered and analyzed. With regard to CAF origin, the subjects were tabulated into unilateral, bilateral or multilateral fistulas and compared. The group was stratified into two major subsets according to the mode of termination; coronary-cameral fistulas (CCFs) and coronary-vascular fistulas (CVFs). A comparison was made between the two subsets. Fistula-related major complications [aneurysm formation, infective endocarditis (IE), myocardial infarction (MI), rupture, pericardial effusion (PE) and tamponade] were described. Coronary artery-ventricular multiple micro-fistulas and acquired CAFs were excluded as well as anomalous origin of the coronary arteries from the pulmonary artery (PA).

RESULTS: A total of 304 adult subjects (47% male) with congenital CAFs were included. The mean age was 51.4 years (range, 18-86 years), with 20% older than 65 years of age. Dyspnea (31%), chest pain (23%) and angina pectoris (21%) were the prevalent clinical presentations. Continuous cardiac murmur was heard in 82% of the subjects. Of the applied diagnostic modalities, chest X-ray showed an abnormal shadow in 4% of the subjects. The cornerstone in establishing the diagnosis was echocardiography (68%), and conventional contrast coronary angiography (97%). However, multislice detector computed tomography was performed in 16%. The unilateral fistula originated from the left in 69% and from the right coronary artery in 31% of the subjects. Most patients (80%) had unilateral fistulas, 18% presented with bilateral fistulas and 2% with multilateral fistulas. Termination into the PA was reported in unilateral (44%), bilateral (73%) and multilateral (75%) fistulas. Fistulas with multiple origins (bilateral and multilateral) terminated more frequently into the PA (29%) than into other sites (10.6%) (P = 0.000). Aneurysmal formation was found in 14% of all subjects. Spontaneous rupture, PE and tamponade were reported in 2% of all subjects. In CCFs, the mean age was 46.2 years whereas in CVFs mean age was 55.6 years (P = 0.003). IE (4%) was exclusively associated with CCFs, while MI (2%) was only found in subjects with CVFs. Surgical ligation was frequently chosen for unilateral (57%), bilateral (51%) and multilateral fistulas (66%), but percutaneous therapeutic embolization (PTE) was increasingly reported (23%, 17% and 17%, respectively).

CONCLUSION: Congenital CAFs are currently detected in elderly patients. Bilateral fistulas are more frequently reported and PTE is more frequently applied as a therapeutic strategy in adults.

Key words: Coronary artery fistulas; Congenital heart defect; Coronary angiography; Multi-detector computed tomography angiography

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INTRODUCTION

Nowadays congenital coronary artery fistulas (CAFs) in adults are frequently non-invasively[1-4], semi-invasively[5-8] and invasively[9] detected because of the rapid advent of various imaging modalities. With these advanced diagnostic techniques many unilateral[10-15], bilateral[16-20] and multilateral[21] fistulas have been diagnosed. Many reports from various parts of the world recording congenital CAFs in adults have been published during the last decade[22-28]. The pertinent diagnosis of congenital CAFs in adults has been published from different regions of the world[29-36]. A review of the world literature resulting in 304 patients between 2000 and 2010 to identify the current characteristics of congenital CAFs in adults is presented, and the important findings are discussed.

MATERIALS AND METHODS

PubMed was searched for terms "coronary artery" and "fistulas" combined with "congenital" and "adult". From the English and non-English medical literature, only relevant publications regarding congenital CAFs in adults were chosen and considered for analysis and evaluation. The search was conducted for the period from 2000 to 2010. Coronary artery-ventricular multiple micro-fistulas and acquired CAFs, as well as cases of anomalous origin of the coronary arteries from the pulmonary artery (PA) were excluded. Papers with a mixed population (pediatric and adult) or with pediatric subjects alone were excluded. Papers and data were carefully examined for completeness. The following criteria for CAFs were stipulated to include homogenous subsets for analysis: origin and number of donor vessels (unilateral, bilateral and multilateral) and mode of termination [coronary-cameral fistula (CCF) *vs* coronary-vascular fistula (CVF)]. Patients were tabulated according to the origin from the right or left coronary arteries or their branches, or from the right or left sinus of Valsalva and number of the fistulas with regard to their characteristics [from the left main trunk (LMT), left anterior descending (LAD), circumflex coronary artery (Cx), right coronary artery (RCA), left coronary artery (LCA), unilateral, bilateral or multilateral fistulas]. A number of parameters were examined for comparison, such as mean age, gender, clinical presentation, fistula characteristics and complications. The following question was addressed in this review: do different age groups in the adult population with congenital CAFs differ in clinical presentation, fistula characteristics and treatment modalities?

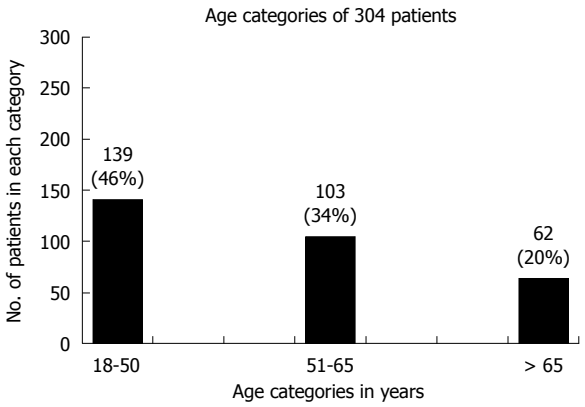

Figure 1 Age categories in years of 304 adults with congenital coronary artery fistulas. Septuagenarians represented (20%) of the cohort. The majority (46%) was in the age category 18-50 years.

Definitions

CCFs: The fistula terminates into a cardiac chamber (right atrium (RA)/coronary sinus (CS), right ventricle (RV), left atrium (LA) and left ventricle (LV).

CVFs: The fistula terminates into a thoracic vessel [PA, superior vena cava (SVC), pulmonary veins (PV), bronchial and cardiac veins and right ventricular outflow tract (RVOT)].

These definitions were adopted and modified from Gupta-Malhotra[37].

Statistical analysis

Data and categorical variables are presented as counts and percentages and continuous variables are expressed as mean. Statistical analysis was performed by using the two-tailed paired Student *t*-test and Chi-square test. A P value < 0.05 was considered significant. Statistical analyses were performed using SPSS version 18.0 (SPSS Inc., USA).

RESULTS

Review subjects

Characteristics of 304 patients between 2000 and 2010 were collected. Of this group, 47% were male, mean age was 51.4 years (range, 18-86 years). The majority (46%) of patients were aged 18-50 years but a considerable proportion (20%) were older than 65 years (Figure 1). The fistulas were multilateral in 6 (2%) patients, bilateral in 55 (18%) and unilateral in 243 (80%). The origin of the unilateral fistulas was from the LCA in 69% [LMT (7%), LAD (42%), Cx (20%)] and RCA in 31% (Table 1).

Table 1 Origin, termination, pathway and management of unilateral fistulas in adult patients with congenital coronary artery fistulas (n = 243)

Origin	LMT (n = 17) (7%)	LAD (n = 102) (42%)	Cx (n = 48) (20%)	RCA (n = 76) (31%)
Termination				
PA	47%	75%	23%	16%
RA/CS	29%	7%	52%	37%
RV	6%	9%	4%	25%
SVC	12%	none	6%	5%
LV	none	3%	4%	12%
Aneurysm	18%	7%	17%	17%
Management				
SL	47%	63%	52%	54%
CMM	41%	13%	31%	17%
PTE	12%	24%	17%	29%

LMT: Left main trunk; LAD: Left anterior descending coronary artery; Cx: Circumflex coronary artery; RCA: Right coronary artery; PA: Pulmonary artery; CS/RA: Coronary sinus/right atrium; RV: Right ventricle; SCV: Superior vena cava; LV: Left ventricle; SL: Surgical ligation; CMM: Conservative medical management; PTE: Percutaneous therapeutic embolization.

Major clinical presentations and complications

Thirty-five patients (11%) were asymptomatic. In 11 (4%) patients, the clinical presentation was not recorded and 85% of patients were symptomatic. The major presentations were composed of a single symptom in 63% and 37% presented with multiple symptoms. These were, in decreasing order of frequency, dyspnea (31%), chest pain (23%) and angina pectoris (21%). Moreover, palpitation was a commonly reported symptom occurring in 13%, congestive heart failure (CHF) in 8%, infective endocarditis (IE) in 4%, and abnormal shadow on chest X-ray in 4% of patients. Furthermore, fatigue was reported in 6% of patients, atrial fibrillation in 5%, syncope in 4%, pericardial effusion (PE) in 2% and myocardial infarction (MI) in 2%. Ventricular and supra-ventricular tachycardia were very rarely seen.

CHF: Overt CHF was reported in 8% of patients, 70% of whom were female. The mean age was 60.6 years (range, 27-86 years). In these patients, the mean ratio of the left-to-right shunt (Qp:Qs) was 1.8 (range, 1.2-2.7). The mean systolic PA pressure was elevated at 47 mmHg (varying from 25/9 to 61/24 mmHg), compatible with mild pulmonary hypertension. Unilateral fistulas were predominant, being present in 19/23 (83%) of patients, and bilateral in 4/23 (17%). The origin was the LCA in 21/27 (78%) and the RCA in 6/27 (22%) of the fistulas. The therapeutic management of this sub-group was surgical ligation (SL) in 14 patients, percutaneous therapeutic embolization (PTE) in 5 patients and conservative medical management (CMM) in 4 patients.

IE: IE was reported in 11/304 patients (4%), 36% of whom were female. All had CCFs where fistulas arose from right or left coronary arteries having a unilateral[1,38-41] or bilateral[1,42] origin. The termination site was always a cardiac chamber either right- or left-sided: RA[38,41], RV[1], CS[39,40,42,43] or LA[1]. *Streptococcus*[38,42,44] and *Staphylococcus* species[40] were isolated from blood cultures. Echocardiography demonstrated aneurysmal dilatation of the donor vessels[43-45], and recipient chamber[42,45], and valvular[44,45] and non-valvular[42,44] vegetation. Furthermore, there was moderate and severe valvular regurgitation with ruptured chordae[1,39]. Non-valvular vegetation was located in the inferior atriocaval junction[38] and CS[40,42,44]. Turbulent flow in the recipient chamber was noted by color Doppler[40,45]. Associated congenital and acquired heart defects (single coronary artery, bicuspid aortic valve and atrio-ventricular valvular heart disease) were also visualized[1,2,41]. All patients were treated surgically, but two were managed conservatively. IE has been reported to occur in the clinical history of patients with CAFs[46].

MI: Both ipsilateral (4 ×) and contralateral (1 ×) to the shunt, infarctions (2%) were reported only in patients with CVFs where the fistulas communicated to the right or left side of the vascular system; PA[9,27,47-49], SVC[10,50], RVOT[12,51] and PV[52]. The mean age was 60.8 years (range, 51-78 years). They were 2 females and 3 males. Significant coronary artery disease was present in 2 patients and 3 were free of atherosclerotic lesions. A unilateral fistula was found in 2 and bilateral fistulas in 3 patients. Of the 3 patients with bilateral fistulas (LAD-RCA), one had inferolateral MI, one developed inferior MI and the third presented with anterior MI. A myocardial perfusion test revealed reversible ischemia in 2 and was negative in one. Medical treatment of the fistula was conducted in 3, PTE in one and SL in one of the patients. PCI was performed in a non-fistula vessel in 2 patients. No infarct-related complications were described.

Diagnostic work-up

Cardiac murmur: Cardiac murmur was reported in (47%) of patients. Of those, continuous heart murmur was heard in (82%), systolic murmur in (11%) and diastolic murmur in (7%). No murmur was heard in (53%). Only few patients had two different cardiac murmurs.

Abnormal shadow on chest X-ray: The chest X-ray demonstrated a marked abnormal shadow in 11/304 (4%) patients; unilateral in 8 (5 LCA, 3 RCA) and bilateral in 4 (LAD-RCA). The LCA participated in the formation of the fistula in the majority of fistulas (9/16) with an abnormal shadow on the chest X-ray on either unilateral[53,54] or bilateral fistulas[55-58]. The RCA was involved in fistula formation in 7/16 (44%) patients. Termination occurred into the PA in 9/12 (75%) patients, into the CS in one (8%), into the RA in one (8%) and into the LA in one (8%). All fistulas were associated with an aneurysm. Three-quarters of the patients (9/12) were treated surgically, (8%) PTE was performed in one and 2 (17%) were followed with CMM.

For the morphological, anatomical visualization, and

functional assessment of CAFs, different diagnostic modalities separately or combined were applied to confirm the presence of unilateral[12,13,59-61], bilateral[16,19,30,48,62], or multilateral[6,21,63] CAFs. In the reviewed group, the cornerstone in establishing the diagnosis was conventional coronary angiography (CAG) (97%) and echocardiography (68%). However, multi-slice detector computed tomography (MDCT) is slowly gaining popularity, and was applied in (16%) of reviewed patients. In the current review, associated congenital and acquired heart disease was present in 22% compared with 13% in a previous review in 2006[64].

Doppler echocardiography remains of great diagnostic value in the detection, intra-operative imaging and follow-up of patients with CAFs[2,22]. CAFs could be suspected[7,8] and confirmed[51,65,66] by echocardiography, as well as demonstration of dilatation and aneurysm of the donor vessel[34,36,67-70] and dilatation of the recipient chamber[3,4,71-73]. Thrombotic or vascular masses have been visualized by echocardiography[72]. Abnormal flow by color Doppler imaging provided a direct clue in the diagnosis of fistulous communication[74-79]. Furthermore, turbulent blood flow may be seen in the dilated recipient cardiac chamber[2]. In cases of IE associated with CAFs, valvular[44,45] and non-valvular[42,44] vegetations have been described. Echocardiographic examination showed a variety of associated congenital and acquired heart defects[2,3,51,80]. By means of echocardiography, right-sided pressure could be estimated and the left-to-right shunt (ratio of pulmonary to systemic blood flow) could be calculated[24,47,51,81,82]. Rupture of an aneurysm associated with CAFs causing PE and tamponade was easily illustrated by echocardiography[15,83,84].

Angiographic fistula characteristics related to the origin and number of donor vessels: Unilateral fistulas were found in 80% of subjects (Table 1). An origin from the LMT was reported infrequently in 17 patients in total (7%). The fistulas terminated mostly into the right heart side[10-15,85]. Outflow was mostly into the main PA (47%)[2,61,86], with distribution to the left[80] or right PA branch[87]. Only a few ended in the left heart side[75]. Mild[14,75], moderate[71] to severe[11] pulmonary hypertension was recorded. Dilatation[10,12,14] of the LMT was not frequently observed. In only 3 reports, aneurysmal formation of the LMT was found[13,14,88]. LMT fistulas terminated into PA in 47% and LAD fistulas ended in the PA in 75%[41,65,89-92]. On the other hand, exit to the RA/CS of Cx fistulas was found in 52% and of RCA fistulas was found in 37%. These differences in termination may be related to developmental embryological and anatomical issues. Few LAD fistulas ended in the LV, RV, RA and LA[1,38,93,94]. The clinical presentations of LAD fistulas were usually chest pain[76], angina pectoris[90,95], dyspnea[41,82,92,96-98], fatigue[99], palpitations[1,74], syncope[100], CHF[77,101-103] or IE[1,38]. Cx fistulas terminated into the PA in (23%)[47,104], but the majority ended in the CS in 40%[43,105-109] and the RA in 15%[73,78,110] of cases. The clinical presentations consisted of dyspnea[111,112], palpitations[69,81], syncope[83], angina pectoris[113,114], chest pain[84], fatigue[66,115], CHF[45] and IE[39,40,43]. The termination of RCA fistulas was variable: RA 26%, RV 25%, PA 16%, CS 11%, left LV 12%, LA 3%, SVC 5%, RVOT 1% and PV 1%[33,41,72,70,110,116]. The clinical presentations were angina pectoris[27,35,79], chest pain[9,31,51,117], dyspnea[36,68], palpitations[33] and syncope[118]. In some cases, an abnormal shadow on a chest X-ray brought the subjects to further medical attention[34,119,120]. A comparison between unilateral, bilateral and multilateral fistulas is presented in Table 2. Bilateral fistulas were present in 18% of the total group. The distribution of the origin is summarized in Table 3. The PA pressure was reported frequently to be normal[121-124], but mild[29], moderate[62,125-127] or severe[28] pulmonary hypertension has been reported in this category of fistulas. Fistulas of multilateral origin (i.e. 3 or more fistulas) had a variety of clinical presentations; as-

Table 2 Comparison between unilateral, bilateral and multilateral fistulas related to site of origin, aneurysmal formation, mode of termination and management

	Unilateral (n = 243) (80%)	Bilateral (n = 55) (18%)	Multilateral (n = 6) (2%)
Termination			
PA[1]	44%	73%	75%
CS/RA	28%	18%	10%
LA	2%	5%	--
LV	6%	4%	15%
RV	13%	4%	--
Aneurysm	13%	16%	33%
Management			
SL	57%	51%	66%
CMM	20%	32%	17%
PTE	23%	17%	17%

[1]Statistical significance was reached between termination into pulmonary artery (PA) (29%) *vs* exit to all other sites (10.6%) (P = 0.000). CS/RA: Coronary sinus/right atrium; LA: Left atrium; LV: Left ventricle; RV: Right ventricle; SL: Surgical ligation; CMM: Conservative medical management; PTE: Percutaneous therapeutic embolization.

Table 3 Distribution of origin of bilateral fistulas in adult patients n (%)

Bilateral fistulas	n = 55
LMT-LAD	3 (5)
LMT-RCA	2 (4)
LAD-RSV	3 (5)
LAD-Cx	1 (2)
LCA-RCA	2 (4)
RCA-LAD	31 (56)
RCA-Cx	8 (15)
RSV-Cx	1 (2)
RCA-D	3 (5)
RCA-im	1 (2)

LMT: Left main trunk; LAD: Left anterior descending coronary artery; RCA: Right coronary artery; RSV: Right sinus of Valsalva; Cx: Circumflex coronary artery; LCA: Left coronary artery; D: Diagonal branch; im: Intermediate branch.

Table 4 Comparison of demographic data, major fistula characteristics and fistula-related complications between coronary-cameral fistulas and coronary-vascular fistulas *n* (%)

	CCFs (*n* = 135) (44%)	CVFs (*n* = 169) (56%)	*P* value
Mean age (range, yr)	46.2 (18-85)	55.6 (18-86)	0.000
Female gender	68 (50.4)	93 (55)	NS
Aneurysm	24 (18.2)	19 (11.2)	NS
MI	None	5 (3)	0.042
IE	11 (8)	None	0.000
PE	4 (2.9)	4 (1.8)	NS
Abnormal chest X-ray	3 (2)	8 (5)	NS
Origin from LMT and LAD	33 (24.1)	94 (55.6)	0.000
Fistulas having multiple origins (bilateral and multilateral)	17 (13)	44 (26)	0.003

CCFs: Coronary-cameral fistulas; CVFs: Coronary-vascular fistulas; MI: Myocardial infarction; IE: Infective endocarditis; PE: Pericardial effusion; LMT: Left main trunk; LAD: Left anterior descending coronary artery.

Table 5 Fistula characteristics and fistula-related major complication in relation to demographic data

	Age (yr), mean (range)	Female gender (%)
Origin of fistulas		
Unilateral		
LMT	50.4 (21-74)	47
LAD	55.6 (18-86)	51
Cx	51.4 (21-82)	52
RCA	44.9 (18-78)	53
Bilateral	57.4 (24-83)	60
Multilateral	58.0 (38-79)	67
Clinical presentation		
CHF	60.6 (27-86)	70
IE	41.8 (22-65)	36
MI	58.0 (44-78)	33

LMT: Left main trunk; LAD: Left anterior descending coronary artery; Cx: Circumflex coronary artery; RCA: Right coronary artery; CHF: Congestive heart failure; IE: Infective endocarditis; MI: Myocardial infarction.

ymptomatic, chest pain, fatigue, palpitations, dyspnea and syncope[5,6,21,63,128,129]. Termination was mainly into the PA (Table 2).

Aneurysm: In 43 patients (14%), aneurysmal formation was detected. Aneurysms were associated with unilateral (74%), bilateral (21%) and multilateral fistulas (5%). Overall, exactly the same figure (14%) was found in a mixed pediatric and adult population of 236 patients between 1993 and 2004 reviewed in 2006[64]. Although there were no differences found in the frequency of aneurysm formation, the composition of the 2 studies was completely different. The current review included no pediatric subjects. Aneurysmal formation is infrequently reported in a pediatric population.

Angiographic fistula characteristics related to the mode of termination: A comparison between CCFs and CVFs is shown in Table 4. In CCFs, unilateral fistulas were more prevalent (87%) than in those subjects with CVFs (74%). The fistulas with multiple origins (bilateral and multilateral) were present in 13% and 26% of CCFs and CVFs, respectively. In unilateral CVFs, an origin from the LCA was predominantly involved in fistula formation in 86% of subjects and the RCA in only 14%. In unilateral CCFs, equal distributions of LCA and RCA were found. Comparing the therapeutic strategy between the two reviews of 2010 and 2006[64], we found a specific increase in SL and PTE procedures; from 38% to 56% for SL and from 5% to 22% for PTE, while CMM remained unchanged 21% (2010) *vs* 24% (2006).

DISCUSSION

Up till now, no data has been available describing a large cohort of adults with congenital CAFs. The purpose of this review was to systematically investigate the current characteristics of this anomaly in adults. Generally, CAFs may have 2 angiographic appearances; a solitary form and coronary artery-ventricular multiple micro-fistula form[130]. In the current review further classification of the solitary CAFs according to their mode of termination was undertaken: CCFs and CVFs. On comparison of the current findings with the review of 2006[64], we found that a continuous heart murmur was heard in significantly more patients (82% *vs* 32%). Furthermore, CHF was reported in more patients (8% *vs* 3%). The percentage of asymptomatic presentation remained unchanged (11%) compared with the review of 2006 (9%)[64]. In this study, fatigue was present in 6% and palpitations in 13%, while these were both reported as 7% in 2006. IE was not reported in 2006 but was diagnosed in 4% of the patients in this review. CCFs were associated with the development of IE ($P = 0.000$). None of the patients with CVFs developed IE. Part of the reason for the occurrence of IE in CCFs is that the extent of turbulent flow may be higher in a dilated cardiac chamber compared with a vascular structure and endothelial damage caused by a continuous fistulous jet may be pointed at the wall of the cardiac chamber. In contrast, MI was associated with CVFs ($P = 0.042$) and it was not seen in any of the patients with CCFs. CVF patients with MI (60.8 years) were 10 years older than the rest of the group (50.7 years). Borderline significance was reached in CCF patients with IE who were 10 years younger (41.8 years) than those who did not develop IE (51.2 years) ($P = 0.068$). More investigations are warranted to identify subjects who require antibiotics for prophylaxis of IE. Among the subjects in both IE and MI subsets, nearly one-third were female in contrast to the CHF subset where the majority (two-thirds) were female. The lowest mean age was found in the IE subset (41.8 years) and the highest in the CHF subset (60.6 years) (Table 5), implying that subjects with IE are diagnosed earlier and female subjects with congenital CAFs are prone to develop CHF at an older age. Patients with unilateral fistulas and an origin from the

RCA, had the lowest mean age (44.9 years) and patients with bilateral and multilateral fistulas were older (57.4 and 58 years, respectively). This may indicate that fistulas from the RCA may become symptomatic earlier and are detected at a relatively young age, while diagnosis may be delayed, for obscure reasons, in fistulas with multiple origins. The behavior of the fistulas in CCFs and CVFs is quite variable, as we found that the frequency of fistulas presenting with multiple origins (bilateral and multilateral) in CVFs (26%) was twice that in CCFs (13%) ($P = 0.003$), and the termination of bilateral or multilateral fistulas into the PA (29%) was significantly higher than into other outflow sites (10.6%) ($P = 0.000$). Not only unilateral CAFs may be suspected and diagnosed by echocardiography[2,46,48,67,128] and their presence confirmed by CAG or MDCT[48,131], but also distinctive echocardiographic findings may suggest the presence of bilateral CAFs[48,132]. In the series of Vitarelli *et al*[2], transthoracic echocardiography was suggestive for the presence of CAFs in 33% of cases and trans-esophageal echocardiography (TOE) confirmed the diagnosis in all patients. In the previously published 2006 review[64], CAG was performed in 83%, while this review found an increase to 97% of subjects. The selective nature of CAG visualizes mainly a single origin of CAFs from a unique coronary artery during its super selective engagement, while MDCT, owing to its non-selective nature is easily able to demonstrate multiple origins of bilateral or multilateral fistulas originating from the coronary arteries or possessing a separate origin directly from the ascending thoracic aorta. Currently, the cornerstone in diagnosis remains echocardiography (68%) and CAG (97%), however MDCT (16%)[48,131], is gaining ground and has proved to be more useful in detecting multilateral fistulas, especially fistulas with multiple origins from the ascending aorta[5,6]. Non-invasive MDCT or TOE should be included alongside CAG in the workup of this category of patient to detect CAFs with suspected or unrecognized multiple origins. The usefulness and advantages of MDCT for the visualization of CAFs are well known. Recognition of CAFs by MDCT has become increasingly popular in adults with congenital CAFs[93].

It was reported in 2006 that the origin of the fistulas was from the LCA in 58% and from the RCA in 42% of patients[64]. In the current review, the overall figures were 69% and 31%, respectively. In 2006, the fistulas were unilateral, bilateral and multilateral in 93%, 6% and 1%, respectively. Currently, the majority, as expected, were unilateral fistulas (80%), followed by bilateral fistulas (18%) and finally multilateral fistulas (2%). Among the unilateral fistulas, the LAD was predominantly the origin (42%) of the fistulas, followed by the RCA (31%), the Cx (20%) and finally the LMT (7%). In this study, it was possible to identify 2 distinct subtypes of clinically relevant fistulas with specific termination sites; the CCFs and the CVFs. In this study, the proportion of fistulas with multiple origins (20%) was significantly increased compared with a few years earlier (7%)[64]. There appears to be distinct differences in terms of mean age, gender and complications

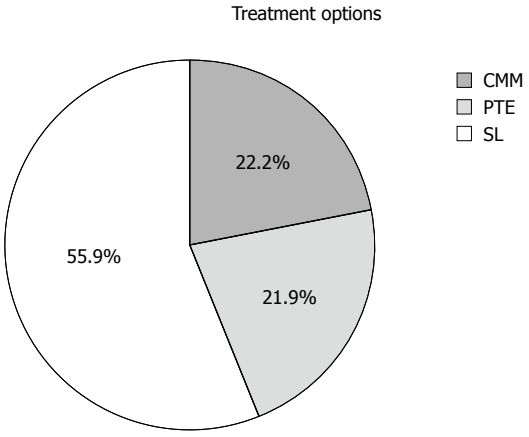

Figure 2 Treatment modalities in adult patients (n = 304) with congenital coronary artery fistulas. CMM: Conservative medical management; PTE: Percutaneous therapeutic embolization; SL: Surgical ligation.

between CCFs and CVFs. The difference in mean age between CCF (46.2 years) and CVF (55.6 years) subjects was statistically significant ($P = 0.000$). The difference in gender was insignificant. No significant difference was found between aneurysmal formation, rupture and PE in CCFs and CVFs. The origin from the LMT and LAD of CCF fistulas was significantly less frequent (24.1%) than of CVFs (55.6%) ($P = 0.000$) (Table 4).

During the last decade, advances in diagnostic and therapeutic techniques and devices as well as the fruitful collaboration between interventional cardiologists and radiologists[31] have encouraged clinicians to apply sophisticated diagnostic methods and advanced treatment modalities for complex CAFs. Despite the increasing reported numbers of bilateral fistulas, PTE was performed in 22% of subjects. The broad availability of modern occluding materials and devices[133], the rapid gain in experience[134], the collaboration between interventional radiologists and cardiologists[31,134], and the increased number of diagnosed patients as witnessed by the increased proportion of bilateral fistulas, have led to increased rates of SL and PTE procedures (Figure 2). In 2006, SL was performed in 38% of patients, currently reported as increased up to 56%, while PTE was undertaken in only 5%, but is now significantly increased up to 22%, while CMM remains unchanged at 24% *vs* 21%. The statistical analysis produced significant figures with the application of the univariate method, but this was completely abolished when the multivariate test was performed with correction for age and gender. Age was the confounder and driving force for these differences. Regarding these latter findings and in view of the lack of available data concerning a large cohort of adult patients with congenital CAFs, a national registry and international cooperation should be launched. The conduction of a coordinated and well orchestrated study to build a database according to a prospective well-defined protocol seems to be necessary in the future.

The main findings of this review are summarized

as follows: (1) 20% of adults with congenital CAFs are elderly; (2) 63% of patients presented with a single symptom; (3) severe complications such as IE and MI are relatively uncommon and occurred more commonly in males (IE 64% and MI 67%), but presentation with CHF occurred more frequently in females (70%) and had a higher (60.6 years) mean age; (4) CCFs may predispose to the development of IE, which was exclusively reported in patients with CCFs either having a unilateral or a bilateral origin; (5) regardless of the origin from the left or right coronary arteries, either in a unilateral or bilateral fashion, MI was infrequently recorded but selectively occurred in patients with CVFs ($P = 0.042$); (6) echocardiography and CAG remain the mainstay to suspect and detect CAFs in symptomatic and asymptomatic adult subjects; MDCT is rapidly gaining ground in the diagnostic armamentarium; (7) currently, LCA is the origin of unilateral fistulas in two-thirds of subjects; subjects with unilateral fistulas originating from the RCA are relatively younger age (44.9 years) and may be diagnosed earlier compared with the LCA (54.4 years) and multilateral fistulas (58 years); moreover, fistulas with multiple origins are more readily reported (20%); and (8) in the last decade, SL (56%) and PTE (22%) have tremendously increased as a treatment option of congenital CAFs in adults.

There are some recognized limitations of this review. One is that many publications of the last decade were not included in this work due to incompleteness and lack of specific data needed for the current review. Therefore there may be a problem of limited sample size. The important question of whether there is a need for IE antibiotic prophylaxis in all subtypes of CAFs, or should it be reserved for CCFs is difficult to answer from the present data. Further investigations are warranted. A further shortcoming is the fact that the numbers in the subgroups are small. The need for a prospective national and international registry is of pivotal importance.

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COMMENTS

Background

Coronary artery fistulas (CAFs) are a rare congenital anomaly of termination of the coronary arterial tree. The incidence of CAFs is low but is currently increasingly detected with the broad application of echocardiography, conventional coronary angiography (CAG), and the use of sophisticated multi-slice detector computed tomography (MDCT).

Research frontiers

These anomalies may be associated with longevity extending into the septuagenarian and octogenarian stage of life. For detection of CAFs, invasive and non-invasive modalities are readily available. The anatomical delineation of the course of the fistula and assessment of functional properties are of pivotal significance in the determination of the therapeutic strategy. In the current review, data is presented of adult patients with congenital CAFs. The correct diagnosis necessitates a multi-diagnostic approach. Initiation of a prospective national/international database to collect all relevant data is of distinctive value to properly evaluate this rare congenital anomaly.

Innovations and breakthroughs

Recent reports have highlighted and emphasized the importance of appropriate delineation of the angiographic and anatomic course of the fistulous pathway in patients with congenital CAFs.

Applications

Despite the wide availability of MDCT, echocardiography and conventional CAG with its limited 2-dimensional character is still a very important diagnostic tool in establishing the diagnoses of CAFs. In some patients, MDCT may be a complementary or supplemental non-invasive diagnostic modality to echocardiography and conventional CAG. With further sophistication and its 3-dimensional properties it may, in the future, even replace conventional CAG in the detection of congenital CAFs.

Terminology

CAFs: CAFs are considered when an abnormal communication exists between one or more coronary arteries and a cardiac chamber or an intrathoracic vascular structure. According to their mode of termination, CAFs may be classified into coronary-cameral or coronary-vascular fistulas.

Peer review

This article is a very comprehensive review about the characteristics of congenital coronary artery fistulas in adults. However, it should be noted that coronary artery fistula is not infrequently observed, and most of them are not published. Therefore, unusual and complicated cases were more frequently reported than it really was. So, the review of published literature may result in the selection bias and this should be pointed out in the study limitation. Otherwise, this paper is well organized and well written about this issue.

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CASE REPORT

Coronary spasm-related acute myocardial infarction in a patient with essential thrombocythemia

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Abstract

We report a case of essential thrombocythemia (ET) in a 30-year-old female who exhibited inferior wall ST-elevation acute myocardial infarction (AMI) without significant obstructive coronary artery disease. Right coronary vasospasm was observed after intra-coronary methylergonovine administration and she received verapamil 120 mg/d thereafter and hydroxyurea 1500 mg/d for thrombocythemia. After discontinuation of the hydroxyurea for 9 mo based on the impression of coronary spasm-related instead of coronary thrombosis-related AMI, her platelet count rose but no chest pain was observed. It is suggested that coronary spasm potentially plays a role in patients with ET, AMI and no significant coronary artery stenosis.

Key words: Coronary spasm; Acute myocardial infarction; Essential thrombocythemia

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INTRODUCTION

It has been reported that essential thrombocythemia (ET) causes coronary thrombosis and acute myocardial infarction (AMI), however, coronary spasm-related AMI in the setting of ET has rarely been reported[1,2]. With regard to ET and AMI, four cases have been reported where no significant obstructive coronary artery disease was demonstrated on coronary angiography[2-5]. By contrast, however, coronary vasospasm has never been demonstrated. Herein, we report the case of a female patient without significant obstructive coronary artery disease where right coronary vasospasm was provoked on coronary angiography after acute inferior wall ST-elevation myocardial infarction.

CASE REPORT

A 30-year-old woman with no history of heart disease was admitted to our hospital having suffered sudden-onset chest pain for the preceding 4 h. Associated diaphoresis had occurred. She denied a history of cigarette smoking, hypertension, diabetes mellitus, or hypercholesterolemia. There was no family history of premature coronary artery disease. Clinical examination of the patient revealed a heart rate of 70 beats per minute, respiratory rate of 17 breaths per minute, blood pressure of 114/62 mmHg, and no fever. Other findings of the physical examination were unremarkable. The 12-lead electrocardiogram (ECG) revealed ST-elevations at the inferior leads and incomplete right bundle branch block (Figure 1A). Heart and lungs were normal on chest X-ray. Complete blood count was 16 700/mm^3 with normal differential count, hematocrit 38.6%, and platelet count of 1 277 000/mm^3. Maximal serum cardiac troponin-I was 6.80 ng/mL and peak creatine kinase was 706 IU/L, with MB isoenzyme of 11.6%. High-sensitivity C-reactive protein was 4.29 mg/L. Total cholesterol was 148 mg/dL. Echocardiography revealed

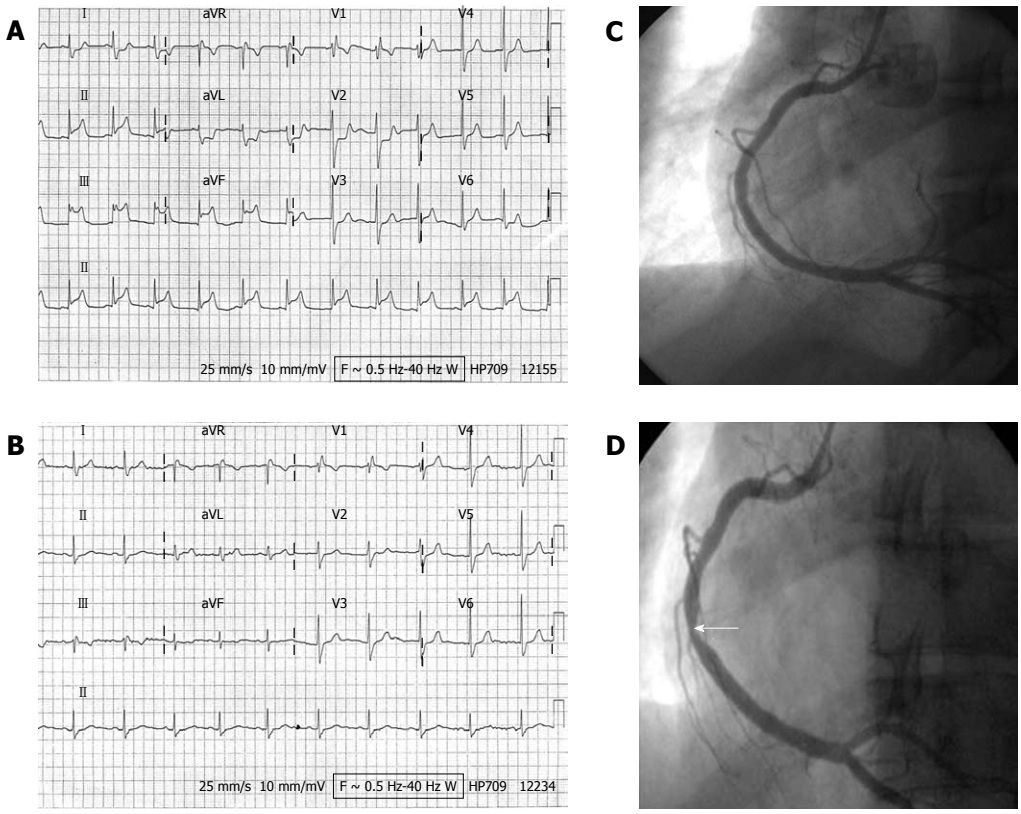

Figure 1 Twelve-lead electrocardiograms and right coronary arteriograms. A: ST elevation in leads Ⅱ, Ⅲ, aVF on baseline electrocardiogram (ECG); B: Complete resolution of ST changes without Q-wave development on ECG on day 2 after admission; C: No evidence of significant coronary artery stenosis on baseline coronary angiogram; D: Coronary vasospasm with diameter reduction of 90% in the distal portion of the right coronary artery (arrow).

no abnormal wall motion and a left ventricular ejection fraction of 73%. The patient was immediately started on sublingual nitroglycerin, aspirin and clopidogrel with bolus doses of 325 and 300 mg then 100 mg and 75 mg, respectively, once daily, and subcutaneous enoxaparin 50 mg every 12 h for 48 h. She did not undergo primary coronary intervention or thrombolytic therapy because she felt no more chest pain after the initial treatments. The follow-up 12-lead ECG (Figure 1B) on day 2 showed no evolutional ST-T changes, which suggested a rapid resolution of coronary artery occlusion in this patient.

Coronary angiography on day 3 revealed no evidence of significant obstructive coronary artery disease (Figure 1C). Based on the possibility of dynamic coronary artery obstruction and coronary vasospasm-related electrocardiographic changes, intra-coronary methylergonovine was administered incrementally (1, 5, 10 and 30 μg) at 3 min intervals. After administration of 10 μg methylergonovine into the right coronary artery, a reduction in diameter of 90% was noted in its distal portion (Figure 1D) with concurrent chest pain. Intra-coronary nitroglycerin 100 μg was then administered, reversing the right coronary vasospasm. After coronary angiography, the patient was started on verapamil 120 mg once daily. A bone marrow study on day 10 revealed megakaryocytic hyperplasia consistent with ET. On the same day, the patient's platelet count was 1 292 000/mm^3. The hematologist suggested that thrombocythemia may have played a role in the development of AMI, and hydroxyurea was prescribed. The patient was discharged on day 12 with verapamil 120 mg once daily and hydroxyurea 500 mg three times daily.

During outpatient clinic follow-up at the cardiology department, she still occasionally experienced chest tightness so the verapamil dosage was increased to 120 mg twice daily 2 wk after discharge. The chest tightness almost disappeared thereafter but recurred twice after she discontinued verapamil of her own accord. The hematologist had prescribed hydroxyurea for 15 mo and the platelet count was decreased to 408 000/mm^3 8 mo after discharge (Figure 2). Since the patient had no risk factors for coronary artery disease and ET-related thrombus and coronary artery-related complications due to the prior AMI were less likely, the necessity of ET treatment was questioned by the hematologist. After discussion with the cardiologist, the hydroxyurea was discontinued and the platelet count rose to 1 154 000/mm^3 9 mo later. The chest pain did not recur despite the presence of thrombocythemia during the 9 mo follow-up after discontinuation of hydroxyurea.

DISCUSSION

ET is a clonal myeloproliferative disorder of unknown origin characterized by abnormal megakaryocyte proliferation that frequently causes thrombus formation in the systemic arteries. It is manifested clinically by overproduction of platelets in the absence of a definable cause. The incidence of ET-related thrombotic events was 13%-17.6% and 8.7%-10% at diagnosis and during follow-up, respec-

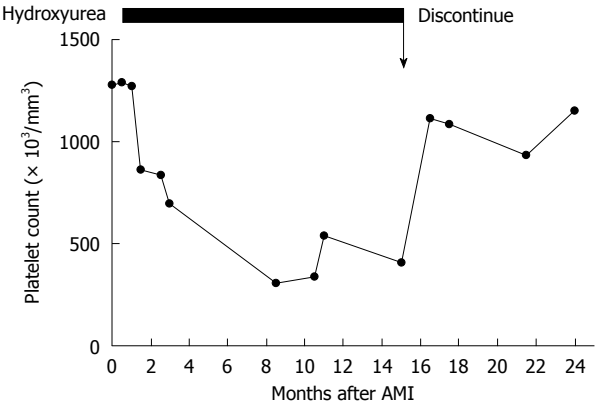

Figure 2 Platelet count in relation to hydroxyurea therapy after acute myocardial infarction. AMI: Acute myocardial infarction.

tively, in Oriental studies[6,7], compared with 15%-26.4% and 11%-31.8% in analogous Western research[8,9]. Although ET may cause systemic vascular thrombosis with subsequent tissue ischemia, involvement of the coronary arteries without stenotic lesions, as determined by coronary angiography, is extremely rare. In reported cases involving ET, AMI and no coronary artery stenosis, most authors[2-5], except Koh *et al*[10], who have suggested that coronary vasospasm plays a role, have proposed that the AMI is related to an increase in platelet count and aggregability. However, the proposed role for coronary vasospasm was speculative without angiographic confirmation. To our knowledge, coronary vasospasm-related AMI in patients without significant coronary artery stenosis and ET has never been documented before the presented case.

We presumed that the patient's AMI was due to coronary vasospasm based on the following evidence: (1) the patient had not received thrombolytic therapy; (2) there was no indication of evolutional ST-T changes on the ECG; (3) there was no significant coronary stenosis from coronary angiography on day 3 after admission; and (4) there was no recurrent acute coronary syndrome resulting from thrombocythemia after withdrawal of hydroxyurea. In previous case reports involving ET, AMI and normal coronary arteries, patients underwent coronary angiography 10 d to 3 mo after AMI[3-5]. Even after thrombolytic therapy, it is uncommon not to have significant coronary artery stenosis with a nearly normal coronary artery as determined by coronary angiography 3 d after AMI. Furthermore, the patient initially received antiplatelet and anticoagulation therapy without thrombolysis. Although the infarct-related artery vasospasm was provoked by intra-coronary methylergonovine administration, the possibility of ET-related AMI with a thrombus or thromboembolic material in infarct-related coronary artery could not be excluded. In contrast, thromboxane A2 platelet release increased the tendency for coronary vasospasm. The cytoreductive agent, hydroxyurea, was therefore prescribed by the hematologist during follow-up. Based on the possibility that the AMI would be related to coronary vasospasm instead of ET in a young female without cardiac risk factors and significant coronary artery stenosis, the hydroxyurea was discontinued 15 mo post AMI. In their report of a 49-year-old patient with ET and AMI, Douste-Blazy *et al*[4], described AMI recurring 2 mo after withdrawal of hydroxyurea. Our presented patient did not experience any recurrent chest discomfort after discontinuation of hydroxyurea for 9 mo, even though her platelet count range was 937 000-1 154 000/mm^3. In addition, there were two episodes of chest pain when she discontinued verapamil of her own accord without concomitant discontinuation of the hydroxyurea. From the clinical response point of view, it appears that the coronary vasospasm-related chest pain was controlled by the verapamil not by the decreased platelet count.

The present case report has some limitations. First, the patient did not undergo coronary angiography immediately because we did not have a primary percutaneous coronary intervention team at the time. Second, we did not obtain the 12-lead ECG immediately after sublingual nitroglycerin administered. The ECG on day 2 is less important in the diagnosis of coronary vasospasm.

In summary, the presented case demonstrates that coronary vasospasm is a possible cause of vascular occlusion in patients with ET and no significant coronary artery stenosis.

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CardioRhythm 2011
Hong Kong, China

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San Diego, CA, United States

March 25
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London, United Kingdom

April 1-2
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Brussels, Belgium

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EuroPRevent 2011
Genova, Switzerland

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ATC 2011 - 2011 American Transplant Congress
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May 15-18
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Amstedan, The Netherlands

May 19-20
Adult Cardiovascular Pathology
London, United Kingdom

May 20-22
XXIX NATIONAL CARDIOLOGY CONGRESS
Córdoba, Argentina

May 20-22
4th Meeting Uremic Toxins and Cardiovascular Disease
Groningen, The Netherlands

May 21-24
Heart Failure Congress 2011
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June 2-5
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EHRA EUROPACE 2011
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INSTRUCTIONS TO AUTHORS

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Acknowledgments

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In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

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No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

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Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

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