Review

Cardiothoracic interventions in Behçet's disease

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ABSTRACT

Objective. *Cardiothoracic interventions for cardiovascular complications of Behçet's disease have not been sufficiently elucidated.*

Methods. *A comprehensive literature search of cardiovascular complications of Behçet's disease was made for year range 2000–2013. The articles on the cardiothoracic procedures for cardiovascular complications of Behçet's disease were screened and analysed.*

Results. *The 221 major cardiothoracic procedures performed in this patient setting included 176 (79.6%) cardiac, 9 (4.1%) thoracic, 31 (14.0%) interventional and 5 (2.3%) hybrid procedures (χ^2=478.03, p<0.0001). Of the major cardiac operations, there were 74 (42%) valvular, 58 (33%) aneurysmal, 23 (13.1%) thrombotic, 10 (5.7%) coronary and 11 (6.3%) miscellaneous procedures. The postoperative morbidity, recurrence and mortality rates were 21.4%, 11.7% and 15.0%, and the reintervention rates were 15.4% for recurrence, and 43.2% for morbidity patients. Dehiscence of the prosthetic valve was the major morbidity (52.3%) and the major cause of death (63.6%). The cardiac surgical patients carried the highest mortality rate comparing with thoracic, interventional and hybrid treatment patients.*

Conclusion. *Cardiovascular operations prevailed thoracic and interventional procedures for the cardiovascular complications of Behçet's disease. Postoperative complications and recurrence rates were high. Aortic valve regurgitation, pulmonary artery aneurysm, and intracardiac and great vessel thrombosis were the most common indications for a cardiothoracic intervention. Dehiscence of the prosthetic valve was the main cause of death of the cardiothoracic interventions. Intense immunosuppressive treatment may reduce the postoperative complications and the need for reinterventions.*

Introduction

Behçet's disease (BD) is a multisystem disease of unknown etiology characterised by recurrent attacks of a symptom triad of oral and genital ulcerations and uveitis. Cardiovascular complications of BD were rare, accounting for only 1–5%, but life-threatening (1). It was often associated with poor prognosis and higher risks of recurrence, morbidity and mortality (2). The cardiovascular complications of BD commonly represent a spectrum of valve disorder, recurrent aneurysm, intracardiac and great vessel thrombosis, and coronary artery disease (3). Many sporadic case reports described this rare involvement, and conservative treatment regimens with immunosuppressive and anti-inflammatory agents have well been described (4). However, few reported comprehensively the surgical and interventional management of these rare complications, and the clinical outcomes subjected to surgical treatment in terms of morbidity, reintervention and mortality rates still remain unknown. In order to highlight the surgical and interventional aspects of the cardiovascular complications, the present study was designed and a careful analysis was conducted on basis of comprehensive literature retrieval.

Materials and methods

A comprehensive literature search of cardiovascular complications of BD was made for year range 2000–2013. The literature search ended on June 30, 2013. The articles concerning cardiothoracic interventions for cardiovascular complications of BD were carefully screened and analysed. Quantitative data were expressed in mean ± standard deviation with range and median values. Comparisons of frequencies were made by Fisher's exact test. A p-value <0.05 was considered statistically significant.

Results

Patient information

Under the retrieval policies, information of a total of 221 patients was obtained from 120 reports (2, 3, 5-122) including 15 (12.5%) original articles (2, 6, 24, 29, 47, 49, 51, 56, 65, 69, 71, 85, 88, 106, 110), 87 (72.5%) case reports (5, 7-9, 11-19, 21, 23, 25-28, 31-41, 44-46, 48, 50, 52-54, 57-60, 62-65, 68, 70, 72-74, 76-81, 83, 84, 86, 87, 89-91, 93, 94, 96-104, 107-109, 113-118, 120-122), 7 (5.8%) case series (3, 10, 20, 67, 92, 95, 112), 8 (6.7%) case images (22, 30, 42, 43, 61, 105, 111, 119), 2 (1.7%) letters (75, 82), and 1 (0.8%) "how-to-do" (55). The patients aged 35.3±11.7 (range, 10–73; median, 35) years (n=184) at the onset of cardiovascular complications. Eleven (6.0%) patients were at the age of ≤18 (mean, 15.2±2.4; range, 10–18; median, 16) years (n=11); while 173 (94.0%) patients were >18 (mean, 36.6±10.9; range, 19–73; median, 35) years (n=173). A significant difference could be noted in the incidence of cardiovascular complications between paediatric and adult patients (χ^2=285.26, p<0.0001). There were 154 (72.3%) males and 59 (27.7%) females (χ^2=84.74, p<0.0001) with a male-to-female ratio of 2.61:1, while gender could not be tracked for 8 patients.

Clinical manifestations

Before current admission, 102 (45.5%) patients had significant manifestations of BD. Duration of BD was recorded as "history" (7, 10), "already presented" (42), "previously diagnosed" (32, 40, 60, 75, 79, 81, 84, 105, 109), "diagnosed with" (20), "with BD when admitted" (62), "over the past several years" (117), "remote" (25), "recently" (72), "with a diagnose of" (55), or "with known BD" (11) in 19 cases, and the calculated result of the disease course of the other 83 patients was 6.5±7.1 (range, 0.17–39; median, 3) years (n=83). Another patient was diagnosed as BD at admission (114). The patients' major symptoms of cardiovascular complications at admission were described in 139 patients. Two (1.4%) patients were asymptomatic (27, 114). Of the remaining 137 (98.6%) patients, there were totally 219 symptoms developed with 1.6±0.9 (range, 1–4; median, 1) symptoms per patient, with one symptom in 89 (65.0%) (3, 8, 10-13, 16-19, 21-24, 26, 32, 35-40, 42, 44, 47-49, 51-53, 57, 59, 60, 62, 66, 67, 78, 81, 84, 85, 87, 91, 92, 94, 95, 97-99, 102, 103, 105, 106, 108, 109, 111, 112, 115-119, 120-122), two symptoms in 27 (19.7%) (3, 14, 25, 41, 43, 46, 47, 49, 54, 61, 64, 70, 74, 77, 80, 82, 83, 85, 88, 89, 93, 96, 104, 107), three symptoms in 12 (8.8%) (7, 15, 19, 31, 33, 50, 68, 76, 79, 90, 100, 101), and four symptoms in 9 (6.6%) (3, 5, 28, 34, 58, 65, 67, 72, 73), respectively. There was a significant difference in the frequency between patients with single and multiple symptoms (χ^2=162.83, p<0.0001). Chest pain, dyspnea and haemoptysis were the three most common symptoms in the patients with a single symptom, and fever, dyspnea and chest pain were the three most common symptoms of the patients with multiple symptoms. More patients manifested haemoptysis and chest pain in the single symptom group, whereas more patients presented with cough, fever/fever of unknown origin, and weight loss in the multiple symptom group (Table I). The durations of cardiovascular symptoms before current admission were 3.7±9.5 months (range, 30 minutes to 5 years; median, 1 month) (n=53). The erythrocyte sedimentation rate was described in 58 patients: 50 results were quantitative (5, 6, 10, 12, 14-16, 18, 21, 31, 35-41, 50, 52, 54, 55, 64, 65, 68, 70, 72, 73, 79-81, 83, 84, 90, 94, 96, 100-102, 104, 107, 108, 110, 112, 117, 120, 122) and 8 were qualitative (23, 24, 26, 57, 77, 119). The calculated result of erythrocyte sedimentation rate was 56.5±33.4 (range, 5–128; median, 54) mm/h (n=50). It was normal/negative in 6 (10.3%) patients (15, 21, 38, 77, 94, 102), and elevated/positive in 52 (89.7%) patients (χ^2=72.97, p<0.0001). The C-reactive protein values were reported in 53 patients with 44 quantita-

Table I. A comparison between patients with a single and multiple symptoms.

Symptom	Single symptom (n=89)	Multiple symptoms (n=130)	p-value (Fisher's exact test)
Chills	0 (0)	2 (1.5)	0.51531
Congestive heart failure	2 (2.2)	5 (3.8)	0.70354
Cough	0 (0)	9 (6.9)	0.01178
Discomfort, chest	0 (0)	2 (1.5)	0.51531
Distension, abdominal	2 (2.2)	2 (1.5)	1.00000
Dizziness	0 (0)	2 (1.5)	0.51531
Dysphagia	0 (0)	1 (0.8)	1.00000
Dyspnea	19 (21.3)	24 (18.5)	0.48836
Fatigue	0 (0)	3 (2.3)	0.27297
Fever/fever of unknown origin	3 (3.4)	26 (20)	0.00038
Haemoptysis	18 (20.2)	6 (4.6)	0.00037
Hoarseness	2 (2.2)	1 (0.8)	0.56780
Mass, neck	2 (2.2)	0 (0)	0.51531
Night sweats	0 (0)	2 (1.5)	0.51531
Numbness arm	0 (0)	1 (0.8)	1.00000
Pain (migratory), joints	1 (1.1)	1 (0.8)	1.00000
Pain, abdominal	0 (0)	2 (1.5)	0.51531
Pain, back	1 (1.1)	0 (0)	1.00000
Pain, chest	27 (30.3)	12 (9.2)	0.00006
Pain, leg	1 (1.1)	2 (1.5)	1.00000
Pain, shoulder arm	1 (1.1)	1 (0.8)	1.00000
Palpitation	2 (2.2)	3 (2.3)	1.00000
Paresthesia, arm	0 (0)	2 (1.5)	0.51531
Presyncope	0 (0)	3 (2.3)	0.27297
Swelling, cervical	1 (1.1)	0 (0)	1.00000
Swelling, facial, arms	1 (1.1)	1 (0.8)	1.00000
Swelling, facial, cervical	1 (1.1)	1 (0.8)	1.00000
Swelling, facial, cervical, arm	1 (1.1)	1 (0.8)	1.00000
Swelling, legs	1 (1.1)	6 (4.6)	0.24518
Syncope	3 (3.4)	0 (0)	0.06577
Weight loss	0 (0)	9 (6.9)	0.01178

tive (5, 6, 9, 10, 16, 18, 21, 31, 35-38, 40-42, 45, 46, 52, 53, 59, 60, 65, 67, 70, 72, 74, 76, 79-81, 83, 84, 86, 87, 91, 94, 100, 102, 107, 108, 112, 120, 122) (one of them was shown a different unit as "12 U" (38), and was excluded from the statistical analysis) and 9 were qualitative (12, 14, 23, 26, 57, 77, 115, 118, 119). The quantitative result was 11.4±20.3 (range, 0.38–118.8; median, 4.8) mg/dl (n=43). It was normal/negative in 8 (15.1%) patients (14, 21, 45, 59, 77, 94, 102, 118) and elevated/positive in 45 (84.9%) patients (χ^2=51.66, p<0.0001).

Categories of cardiovascular complications

Cardiovascular complications requiring a cardiothoracic intervention could be divided into 5 types: valve disorder, aneurysm, thrombus, coronary artery disease and miscellaneous. Four of the 105 (3.8%) patients with a valve disorder were associated with infective endocarditis (8, 24, 50, 68). Aortic valve, pulmonary artery and right heart chamber were the most commonly involved structures of the first three types of complications, respectively (Table II). Comparisons of BD duration between the 5 types of cardiovascular complications revealed it was much longer in the patients with complicated coronary artery disease than in those with valvular, aneurysmal and thrombotic complications (Fig. 1).

Cardiothoracic interventions

The major cardiothoracic procedures performed in this patient setting included 176 (79.6%) cardiac (2, 3, 5-86), 9 (4.1%) thoracic (68, 85, 87-92), 31 (14.0%) interventional (93-117), and 5 (2.3%) hybrid procedures (118-122) (χ^2=478.03, p<0.0001). Of the major cardiac operations, there were 74 (42%) valvular (6, 8, 18, 20, 24, 29, 49-51, 55, 56, 60, 68, 71, 75, 83, 85), 58 (33%) aneurysmal (3, 9, 10, 12, 13, 15-17, 21, 22, 27, 30, 32-34, 42, 46, 48, 51, 59, 61, 62, 64, 66, 72-74, 77, 78, 81, 82, 84, 85), 23 (13.1%) thrombotic (5, 7, 11, 14, 23, 25, 26, 28, 31, 40, 41, 44, 47, 49, 57, 63, 65, 76, 79, 80, 86), 10 (5.7%) coronary (36-39, 43, 45, 69, 70), and 11 (6.3%) miscellane-

Table II. Cardiovascular complications of the 221 patients with Behçet's disease requiring a cardiothoracic intervention.

Cardiovascular complications	n (%)
Valve disorder	**105 (47.5)**
AR, pure	*69 (70.5)*
*AR, secondary to aortic aneurysm**	*13 (12.4)*
AR + mitral valve regurgitation	*8 (7.6)*
Aortic valve stenosis + AR	*1 (1.0)*
Mitral valve regurgitation	*2 (1.3) (1 was due to infective endocarditis, and 1 was associated with RCA aneurysm* and thrombus)*
Tricuspid valve stenosis	*2 (1.3) (both were due to infective endocarditis)*
Aortic valve endocarditis extending to the mitral valve, peri-aortic valve abscess	*1 (1.0)*
Diseased valves not given	*4 (3.8)*
Aneurysm	**69 (31.2)**
Pulmonary artery	*23 (33.3) [7 (30.4) patients with right heart thrombus]*
Aorta	*22 (31.9)*
Ascending aorta	7 (31.8) (all 7 with AR)
Sinus of Valsalva	6 (27.3) (4 with AR, 1 with thrombus)
Aortic arch	7 (31.8) (1 with AR, 1 with LAD 90% stenosis, and 1 with AR and LM thrombus)
Descending aorta	2 (9.1) (both with thrombus)
Coronary artery	*16 (23.2)*
LAD	6 (37.5) (1 with SVC thrombus, and 1 with diagonal branch stenosis,)
RCA	6 (37.5) (1 with RCA thrombus, 1 with RCA stenosis, 1 with mitral valve regurgitation, 2 with left ventricular pseudoaneurysm)
LAD + Cx	1 (6.3) (with descending aorta aneurysm*)
LAD + RCA	1 (6.3)
LAD + marginal branch	1 (6.3)
Left circumflex artery + RCA	1 (6.3)
Aorta branching	*8 (11.6)*
Subclavian artery	6 (75) (1 with thrombus)
Subclavian artery + brachiocephalic artery	1 (12.5)
Common carotid artery	1 (12.5)
Thrombus	**34 (15.4)**
RV + RA	*44 (11.8)*
RV + RA+ coronary sinus	*1 (2.9)*
SVC + innominate vein + subclavian vein	*2 (5.9)*
SVC + innominate vein	*1 (2.9)*
Right ventricular outflow tract	*1 (2.9)*
RV + RA + pulmonary artery	*1 (2.9)*
RV + inferior vena cava	*1 (2.9)*
RV	*8 (23.5)*
RV + pulmonary artery	*1 (2.9)*
RA	*4 (11.8)*
RA + SVC	*1 (2.9)*
SVC	*2 (5.9)*
Inferior vena cava	*5 (14.7)*
Pulmonary artery	*1 (2.9)*
Subclavian vein	*1 (2.9)*
Coronary artery disease	**19 (8.6)**
LAD	*10 (52.6) (2 with sinus of Valsalva aneurysm*)*
LM	*3 (15.8)*
RCA	*2 (10.5) (1 with RA haematoma, and 1 with RCA rupture)*
LAD + first diagonal branch	*1 (5.3)*
LAD + RCA	*1 (5.3)*
LAD + left circumflex artery + RCA	*1 (5.3)*
LAD + first diagonal branch + left circumflex artery + RCA	*1 (5.3)*
Miscellaneous	**11 (5.0)**
Endomyocardial fibrosis	*3 (27.3)*
Left ventricular pseudoaneurysm with thrombus	*2 (18.2)*
Coronary-subclavian artery steal syndrome	*1 (9.1)*
Myocardial inflammatory pseudotumour	*1 (9.1)*
Inferior vena cava fibrous stenosis	*1 (9.1)*
Atrioventricular block	*1 (9.1)*
SVC occlusion with no thrombus	*1 (9.1)*
SVC syndrome with no stenosis	*1 (9.1)*

*17 cases of associated aortic or coronary aneurysms were included for repeat statistics. AR: aortic valve regurgitation; LAD: Left anterior descending coronary artery; LM: left main coronary artery; RA: right atrium; RCA: right coronary artery; RV: right ventricle; SVC: superior vena cava.

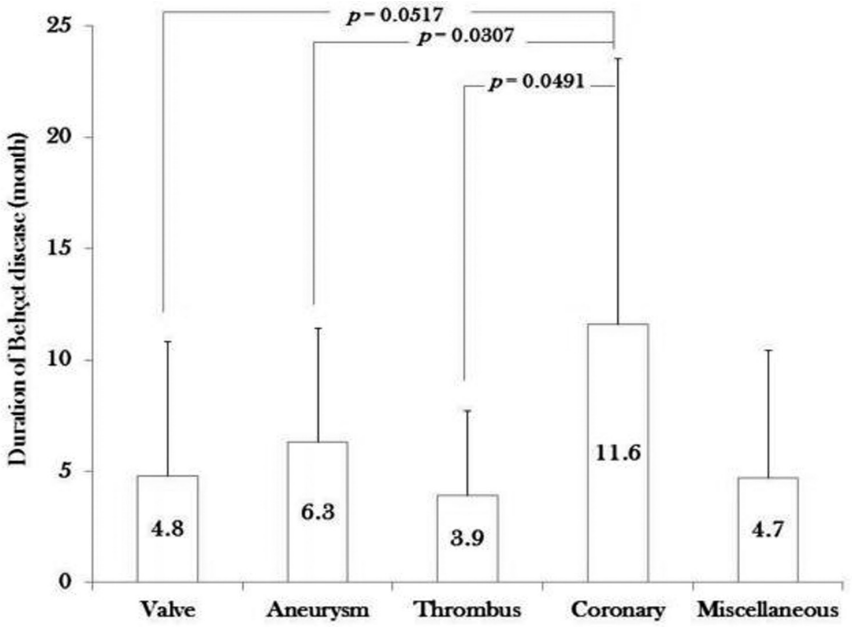

Fig. 1. The duration of Behçet's disease was much longer in the patients with complicated coronary artery disease than in those with valvular, aneurysmal and thrombotic complications.

Table III. Major cardiothoracic interventions.

Major cardiothoracic intervention	n (%)
Cardiovascular operation	**176 (79.6)**
Valve	*74 (42.0)*
AVR	60 (81.1) (2 with aortoplasty, 1 with root reinforcement, and 1 with redo-Ross procedure)
Mitral valve replacement	2 (2.7)
Mitral valve repair	2 (2.7)
Mitral valve replacement + AVR	1 (1.4)
Aortic valve annuloplasty	1 (1.4)
Mitral valve vegetation resection, mitral valve repair, AVR, aortic wall repair	1 (1.4)
Valve cusp replacement with pericardium	1 (1.4)
TVR	1 (1.4)
TV repair	1 (1.4)
Valve surgery (details not given)	4 (5.4)
Aneurysm	*58 (33.0)*
Aorta	40 (69.0)
Bentall operation	25 (62.5) (2 with CABG)
Ross procedure	1 (2.5)
Cabrol operation	1 (2.5)
Aortic repair	13 (32.5)
Aortic arch	5 (38.5)
Sinus of Valsalva	4 (30.8)
Ascending aorta	2 (15.4)
Aortic root	1 (7.7)
Descending aorta	1 (7.7)
Coronary artery (aneurysmectomy)	7 (12.1) (2 with CABG, 1 with aortoplasty + CABG, and 1 with mitral valve repair)
Pulmonary artery	7 (12.1)
PA ligation	2 (28.6)
PAA endoaneurysmorrhaphy	2 (28.6)
PAA excision	3 (42.8)
Aorta branching	4 (6.9)
Axillo-axillary artery bypass	1 (25)

ous procedures (19, 47, 52, 54, 58, 67). Aortic valve replacement, aorta repair and right ventricular thrombus removal were the most common procedures of the first three types of cardiac operations, representing 81.1%, 69.5% and 43.5%, respectively (Table III).

Of the cardiac surgical group, 19 (8.6%) patients had secondary cardiovascular operations including 8 coronary artery bypasses (12, 13, 21, 39, 42, 53, 62, 67), 5 valve operations (30, 49, 68, 76) (one of them had mitral valve and aorta defect repair with aortic valve replacement (68)), 5 aortic repairs (18, 51, 55, 61, 64), and 1 ligation of the innominate vein (44) (Table IV). A patient underwent pulmonary aortoplasty secondary to lobectomy in the thoracic surgical patient (91). In the patients with hybrid procedures, coronary artery bypass was performed in 2 patients (121, 122), patch aortoplasty (118), carotid artery bypass (120), and left ventricular pseudoaneurysm resection + right coronary artery ligation (119) in 1 patient each, respectively. In addition, one patient who had multiple successive operations (mitral valve repair, mitral valve replacement, exclusion of coronary artery aneurysms + catheter placement of occlusion devices, and eventually heart transplantation) was not counted (33).

Prognoses

Patients were at a follow-up of 22.9±24.5 (range, 1–120; median, 13) months (n=115). Prognoses were indicated in 206 patients: 111 (53.9%) patients had a complete recovery, 6 (2.9%) patients showed significant improvement (28, 39, 87, 97, 101, 102), 44 (21.4%) patients were complicated, 24 (11.7%) patients were recurrent, and 31 (15.0%) patients died.

The primary recurrent events occurred at 10.7±20.4 (range, 0.3–60, median, 2) months (n=8). Of them, 13 patients were reported to have recurrent aortic regurgitation from a single report (71). The remaining 11 recurrent events included thrombus formation in 9 (81.8%) patients, and left anterior descending coronary artery occlusion (108), and descending aorta pseudoaneurysm (3) in 1 (11.1%) patient each.

The 9 recurrent thrombi were located in the right ventricle (65, 79), inferior vena cava (47, 110), and both right ventricle and inferior vena cava (31, 34) in 2 (22.2%) patients each, and in the right atrium (41), superior vena cava (116), and left innominate vein (44) in 1 (11.1%) patient each. Two (15.4%) of the latter 11 patients required further interventions including superior vena cava replacement (117), and right atrium-hepatic vein bypass (47) in each; whereas 9 (81.8%) patients did not (χ^2=8.91, p=0.00892).

Forty-four patients developed postoperative cardiovascular complications at 4.4±3.9 (range, 0.1–14; median 3) months (n=24), which could be divided into 6 types: dehiscence of the prosthetic valve, vascular/graft/stent occlusion, thromboembolism, aneurysm, pseudoaneurysm, and others. The reintervention rate of these complications was 43.2% (19/44), which was compatible to the reintervention rate of the recurrent events (χ^2=2.33, p=0.12689). The morbidity, reintervention and mortality rates were prevailed all by dehiscence of the prosthetic valve (Table V).

Lack of necessary immunosuppressive treatment was described in 16 (7.2%) patients, in whom dehiscence of the prosthetic valve developed in 4 (25%) (51), and right ventricular thrombus relapse (79), disseminated venous thrombosis (36), and high fever (117) in 1 (6.3%) patient each. Eight (50%) patients died (51, 102), with 3 of them died after complicated with dehiscence of the prosthetic valve (51), and 4 (25%) was doing well (49, 51, 102). All the remaining patients received regular intense anti-inflammatory treatment after the operation.

In total, 31 (15.0%) patients died. Two patient died of massive haemoptysis intraoperatively (3, 10), and the remaining 29 died postoperatively during follow-up at 5.6±6.2 (range, 0.1–19; median, 3) months (n=11). Their diagnoses were valve disorders (18, 60%), aneurysms (8, 26.7%, including 6 pulmonary artery aneurysms and 1 aortic arch aneurysm), intracardiac thrombus (3, 10%), coronary artery disease (0, 0%), and miscellaneous (2, 6.7%) (χ^2=28.62, p=0.000003). No gender difference was noted in terms of mortality [9.6% (15/156) *vs*. 8.3% (5/60), p=0.77729]. The mortality rates of the cardiac surgical, thoracic surgical, interventional, and hybrid groups were 14.8% (26/176), 33.3% (3/9), 0.3% (1/31) and 0% (0/5), respectively (χ^2=7.86, p=0.04908). The causes of death were described in 11 patients: dehiscence of the prosthetic valve in 7 (63.6%), mas-

(Table III continued)

Major cardiothoracic intervention	n (%)
Common carotid artery-subclavian artery bypass	1 (25)
Subclavian artery aneurysm resection	1 (25)
Subclavian artery-subclavian artery bypass	1 (25)
Thrombus	*23 (13.1)*
Thrombus removal, RA	4 (17.4)
Thrombus removal, RA + superior vena cava	1 (4.3)
Thrombus removal, RV	10 (43.5) (2 with TVR, and 1 with TV repair)
Thrombus removal, RV + RA	5 (21.7) (1 with TVR + pulmonary valvotomy, and 1 with partial removal)
Thrombus removal, RV + RA + coronary sinus	1 (4.3)
Thrombus removal, right ventricular outflow tract	1 (4.3)
Thrombus removal, superior vena cava	1 (4.3) (with ligation of the innominate vein)
Coronary artery disease	*10 (5.7)*
CABG	5 (50)
Off-pump coronary artery bypass	5 (50)
Miscellaneous	*11 (6.3)*
Endomyocardial fibrosis removal	4 (36.4)
Left ventricular pseudoaneurysmectomy	3 (27.3) (1 with CABG)
Subendocardial haematoma removal	1 (9.1)
Myocardial inflammatory pseudotumour removal	1 (9.1)
RA haematoma removal	1 (9.1)
IVC fibrous tissue extirpation	1 (9.1)
IVC graft reconstruction	1 (9.1)
Thoracic operation	**9 (4.1)**
Lobectomy	*5 (55.6) (1 with PA plasty)*
Thoracic duct ligation	*2 (22.2)*
Pneumonectomy	*1 (11.1)*
Video-assisted thoracic surgery (to relieve the tamponade)	*1 (11.1)*
Intervention	**31 (14.0)**
PAA embolisation (with Amplatzer Vascular Plug/Amplatzer duct occluder/coils/n-butyl cyanoacrylate/ details not given)	*11 (1/1/2/2/5) [34.4 (9.1/9.1/18.2/18.2/45.5)]*
Coronary artery stent	*8 (25)*
IVC stent	*2 (6.3)*
Superior vena cava stent	*1 (3.1)*
Descending aorta stent	*1 (3.1)*
Common carotid artery stent	*1 (3.1)*
Subclavian artery stent	*3 (9.4)*
Subclavian vein stent	*1 (3.1)*
IVC suction thrombectomy + balloon angioplasty	*1 (3.1)*
IVC Gunther filter	*1 (3.1)*
Balloon angioplasty for superior vena cava stenosis	*1 (3.1)*
Permanent DDD-R pacemaker implantation	*1 (3.1)*
Hybrid	**5 (2.3)**
Common carotid artery-common carotid artery bypass + common carotid artery stent	*1 (20)*
CABG + coronary artery aneurysm coils	*1 (20)*
CABG + descending aorta stent	*1 (20)*
Coronary angioplasty + patch aortoplasty	*1 (20)*
Coronary angioplasty + left ventricular pseudoaneurysm resection + RCA ligation	*1 (20)*

AVR: aortic valve replacement; CABG: coronary artery bypass grafting; IVC: inferior vena cava; PA: pulmonary artery; PAA: pulmonary artery aneurysm; RA: right atrium; RV: right ventricle; TV: tricuspid valve; TVR: tricuspid valve replacement.

Table IV. Secondary cardiovascular interventions in 19 patients.

Secondary cardiac operation	n (%)
Coronary artery bypass	8 (42.1)
Valve operation	5 (26.3)
Tricuspid valve replacement	2 (40)
Tricuspid valve replacement, pulmonary valvotomy	1 (20)
Tricuspid valve repair	1 (20)
Mitral valve repair	1 (20)
Aneurysmal repair	5 (26.3)
Aortoplasty	3 (60)
Root reinforcement	1 (20)
Redo-Ross procedure	1 (20)
Miscellaneous procedure	1 (5.3)
Ligation of the innominate vein	1 (5.3)

Table V. Postoperative cardiovascular complications.

Postoperative complication	Case, n (%)	Reintervention, n (%)	Mortality, n (%)	Reference
Dehiscence of the prosthetic valve	23 (52.3)	10 (52.6)	7 (70)	49, 51, 60, 56, 75, 81, 85
Occlusion	7 (15.9)	2 (10.5)	0 (0)	
Bypass anastomosis site	1			62
Common carotid artery	1	1		38
Common carotid artery stent	1			120
Coronary stent	1	1		113
Subclavian artery	1			81
Saphenous vein graft	2			37, 69
Thromboembolism	3 (6.8)	0 (0)	0 (0)	
Thrombosis, disseminated venous (SVC, IVC, MPA, popliteal, right jugular, subclavian, and brachiocephalic veins, and dural sinus)	1			36
Thrombus, subclavian artery	1			51
Embolism, pulmonary artery + superficial thrombophlebitis	1			67
Pseudoaneurysm	3 (6.8)	1 (5.3)	1 (10)	
Left coronary button of Bentall procedure	1	1	1	9
Periaorta	1			68
Right coronary artery	1			67
Aneurysm	2 (4.5)	2 (10.5)	0 (0)	
Abdominal aorta (rupture)	1	1		16
Coronary stent site	1	1		115
Others	6 (13.6)	4 (21.1)	2 (20)	
Haemoptysis	1	1		17
Acute myocardial infarction	1			49
Pericardial effusion	1	1		3
Ileus	1	1	1	47
Not given	2	1	1	49, 54
χ^2	51.27	23.48	25.34	--
p-value	0.00000	0.00027	0.00012	--

IVC: inferior vena cava; MPA: main pulmonary artery; SVC: superior vena cava.

sive haemoptysis, saphenous vein graft rupture, hepatic function failure, and multiorgan failure in 1 (9.1%) patient each (χ^2=13.82, p=0.00791). Dehiscence of the prosthetic valve developed in the aortic position in 6 (85.7%) and in the mitral position in 1 (14.3%) patient, respectively (χ^2=7.93, p=0.02914).

Discussion

Cardiovascular involvement of BD is a rare but lethal complication. BD may affect any vessel of the vascular system (139). The most BD-involved artery is the aorta, followed by femoral and pulmonary arteries, and 65% of these involvements are aneurysms and 35% were occlusions. Aneurysm formation was more common than thrombosis in the arteries, but some aneurysms were associated with total or partial thrombus occlusion (123).

The intervals between the onset of BD and the development of cardiovascular complications were fortuitously reported. It was 3.2–7.9 years (a median of 3 years and 11 months) for heart valve involvement (51), 3 years for pulmonary artery aneurysms (124), 7.8 years for arterial aneurysm (125), 8.0±5.0 years for arterial lesions (126), and 2 months to 25 years for intracardiac thrombus to develop after the onset of the disease (127). No such report was found with regard to the development of coronary artery occlusion. In the present study, aortic valve involvement accounted for 91.5% of valvular complications, which developed 4.8 years after BD onset, compatible to 6.3, 3.9 and 4.7 years of BD duration for aneurysm, thrombus and miscellaneous complications; whereas coronary artery disease complications required much longer time to develop after BD onset. The longest BD durations in coronary complicated patients, 39 and 30 years (70, 93), may arise the suspicion of the association between BD onset and coronary complication, however, coronary vasculitis in the presence of obliterative endarteritis of the vasa vasorum and acute destruction of the vessel wall have been demonstrated in BD (128). The relation between inflammatory mediator monocyte chemoattractant protein-1 and BD was discovered (129). Moreover, some gene mutations such as MyD88 deficiency, NEMO, DIRA, IkBα deficiency, and IRAK-4 deficiency, etc., in relation to systemic inflammatory disorders including BD are attracting increasing attention (130).

The pathogenesis of heart valve involvement in BD was proposed to be aortic or mitral annulus dilation, aortitis of the ascending aorta, and aneurysm of the sinus of Valsalva caused by inflammatory reactions. Lee *et al*. (51) reported that 76.5% patients with BD displayed pathergy-like phenomenon around the annulus suture sites as a result of inflammation and fragility of the dehiscent valvular tissues. Intense

immunosuppressive therapy may significantly reduce the surgical complications and the need for re-operations. By comparison, patients who did not receive an immunosuppressive therapy were associated with a high incidence of postoperative complications such as dehiscence of the prosthetic valve and perivalvular leakage.

Intracardiac thrombosis in BD was usually located in the right heart, with right ventricle being the most common (131). Involvement of the major veins including occlusions of the superior and inferior venae cavea were often accompanied by thrombus of the innominate and subclavian veins (132). The thrombotic tendency, defect in fibrinolysis, and coagulation factor V gene G1691A mutation (factor V Leiden) may be responsible for the thrombotic complications in BD patients (133).

Coronary lesions can be either occlusion or aneurysmal degeneration, but coronary aneurysms are more frequent than stenotic lesions. Vasculitis results in obliterative endarteritis of the vasa vasorum and acute destruction of the vessel wall with formation of true or false aneurysms. Arterial stenosis or occlusion is marked by adherent thrombus. Angioplasty and coronary stent implantation in occlusion coronary artery may cause rapid in-stent restenosis in BD (128).

Patients with pulmonary artery aneurysms and superior vena cava occlusion are usually treated with a combination of cyclophosphamide and methylprednisolone. Immunosuppressive therapy alone may lead to complete resolution of pulmonary artery aneurysm and intracardiac thrombous (134, 135), whereas surgery alone may not (136). Anticoagulant or thrombolytic therapy was the preferable treatment of intracardiac thrombus, and usually an open heart surgery was not required. In the presence of pulmonary aneurysms, in particular, bilateral and large aneurysms, anticoagulant and thrombolytic treatments were prohibited for the potential massive haemoptysis. In addition, immunosuppressives and corticosteroids may show prophylactic effects on thrombus relapses (137). When BD patients show poor responses to immunosuppressives and corticosteroids, infliximab can be a good option for the treatment and prevention of thrombus relapses (138). Although surgical repair is the definitive treatment for vascular lesions of BD disease patients, some authors suggested that the surgical indications should be restrained due to the potentially high operative morbidity and mortality rates (139). However, Tuzun *et al*. (140) described their satisfactory results of surgical treatment of non-pulmonary large arterial disease in BD patients, with only a few late complications including new aneurysm, recurrent aneurysm and graft occlusion. In the event of massive haemoptysis, urgent surgical resection of pulmonary artery aneurysm may be warranted (132). In addition, patients with a heart valve involvement in worsening conditions may warrant a valve replacement in spite of the active inflammatory course (141). Modified surgical techniques of aortic valve replacement such as supra-annular position, subannular ring reinforcement, reinforcement of the aortic wall, and intravalvular implantation technique may defer the postoperative valve dehiscent complications (142). Endovascular intervention procedures represented an advanced technique with a significant reduction in morbidity (122).

The prognosis of BD patients undergoing surgical treatment of the cardiovascular complications was scantly reported, in particular on basis of large patient population. The recurrent rates were 40–55% and 74% for BD patients undergoing aortic valve replacement and those undergoing arterial operation (51). The morbidity of dehiscence of the prosthetic valve and mortality were 20% and 40%, respectively for BD patients with aortic valve replacement as reported by Ando *et al*. (143), whereas higher dehiscence morbidity and mortality rates, 44% and 62%, respectively, were illustrated by Lee *et al*. (51). Iscan *et al*. (144) demonstrated the surgical outcome of 20 BD patients with arterial complications, with an operative mortality rate of 5.8% and a 10-year survival rate of 30%. The present study for the first time revealed the clinical prognosis of BD patients receiving a cardiothoracic intervention. The postoperative morbidity, recurrence and mortality rates were 21.4%, 11.7% and 15.0%, and the reintervention rates were 15.4% for recurrence, and 43.2% for morbidity patients. The cardiac surgical patients carried the highest mortality rate comparing with thoracic, interventional and hybrid treatment patients. Another important finding of this article was BD duration (interval from BD onset to the development of cardiovascular complications) was much longer in the patients with complicated coronary artery disorders than in those with valvular, aneurysmal and thrombotic complications.

Literature review based predominantly on case presentations, which accounted for 87.5% of all data sources, may constitute the major drawback of this study. Due to the rarity of the cardiovascular complications of BD, long-term, multicenter collaborated studies with abundant patient information are necessary for more accurate results.

In conclusion, cardiovascular operations prevailed thoracic and interventional procedures for the cardiac complications of BD. Postoperative complications and recurrence rates were high. Aortic valve regurgitation, pulmonary artery aneurysm, and thrombus formation were the most common indications for a cardiothoracic intervention. Dehiscence of the prosthetic valve was the main cause of death of the cardiothoracic interventions. Intense immunosuppressive treatment may reduce the postoperative complications and the need for reinterventions.

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