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Clinical research

Aorto-cavitary fistulous tract formation in infective endocarditis: clinical and echocardiographic features of 76 cases and risk factors for mortality

Ignasi Anguera[1], Jose M. Miro[2*], Isidre Vilacosta[3], Benito Almirante[4], Manuel Anguita[5], Patricia Muñoz[6], Jose Alberto San Roman[7], Aristides de Alarcon[8], Tomas Ripoll[9], Enrique Navas[10], Carlos Gonzalez-Juanatey[11], Christopher H. Cabell[12], Cristina Sarria[13], Ignacio Garcia-Bolao[14], M. Carmen Fariñas[15], Ruben Leta[16], Gabriel Rufi[17], Francisco Miralles[18], Carles Pare[2], Artur Evangelista[4], Vance G. Fowler Jr[12], Carlos A. Mestres[2], Elisa de Lazzari[2], Joan R. Guma[1], and Aorto-cavitary Fistula in Endocarditis Working Group[†]

[1] *Corporacio Sanitaria Parc Tauli-Hospital de Sabadell, Sabadell, Spain*
[2] *H. Clinic, IDIBAPS (Institut d'Investigacions Biomediques August Pi i Sunyer), University of Barcelona, Barcelona, Spain*
[3] *Hospital Clinico San Carlos, Madrid, Spain*
[4] *Hospital Vall d'Hebron, Barcelona, Spain*
[5] *Hospital Reina Sofia, Cordoba, Spain*
[6] *Hospital Gregorio Marañon, Madrid, Spain*
[7] *Hospital Universitario, Valladolid, Spain*
[8] *Hospital Universitario Virgen del Rocio, Sevilla, Spain*
[9] *Hospital Son Llatzer, Palma de Mallorca, Spain*
[10] *Hospital Ramon y Cajal, Madrid, Spain*
[11] *Hospital Xeral, Lugo, Spain*
[12] *Duke University Medical Center, Durham, NC, USA*
[13] *Hospital de la Princesa, Madrid, Spain*
[14] *Clínica Universitaria de Navarra, Pamplona, Spain*
[15] *Hospital Marques de Valdecilla Facultad de Medicina, Santander, Spain*
[16] *Hospital de Sant Pau, Barcelona, Spain*
[17] *Hospital de Bellvitge, Barcelona, Spain*
[18] *Hospital Carlos Haya, Malaga, Spain*

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Surgery

Aims To investigate the clinical features, echocardiographic characteristics, management, and prognostic factors of mortality of aorto-cavitary fistulization (ACF) in infective endocarditis (IE). Extension of infection in aortic valve IE beyond valvular structures may result in peri-annular complications with resulting necrosis and rupture, and subsequent development of ACF. Aorto-cavitary communications create intra-cardiac

* Corresponding author: Infectious Diseases Service, Hospital Clinic - IDIBAPS, University of Barcelona, Helios-Villarroel Building, Desk no. 26, Villarroel, 170, 08036-Barcelona, Spain. Tel: +34 93 227 55 86; fax: +34 93 451 44 38/54 24.
E-mail address: jmmiro@ub.edu or miro97@fundsoriano.es
† See Appendix for full list of participants.

shunts, which may result in further clinical deterioration and haemodynamic instability.

Methods and results In a retrospective multi-centre study over 4681 episodes of IE, a total of 76 patients with ACF [1.6%, confidence interval (CI) 95%: 1.2–2.0%] diagnosed by echocardiography or during surgery were identified. Fistulae were found in 1.8% of cases of native valve IE and in 3.5% of cases of prosthetic valve IE from the general population and in 0.4% of drug abusers. PVE was present in 31 (41%) cases of ACF. Transthoracic and transoesophageal echocardiography detected the fistulous tracts in 53 and 97% of cases, respectively. Peri-annular abscesses were detected in 78% of cases, fistulae originated in similar rates from the three sinuses of Valsalva, and the four cardiac chambers were equally involved in the fistulous tracts. Heart failure (HF) developed in 62% of cases and surgery was performed in 66 (87% CI 95% 77–93%) patients with a mortality of 41% (95% CI 30–53%) in the overall population. Multivariate analysis identified HF (OR 3.4, CI 95% 1.0–11.5), prosthetic IE (OR 4.6, CI 95% 1.4–15.4) and urgent or emergency surgical treatment (OR 4.3, CI 95% 1.3–16.6) as variables significantly associated with an increased risk of death. Major complications during follow-up (death, re-operation, or re-admission for HF) among the five operative survivors with residual fistulae occurred in 20 and 100% of patients at 1 and 2 years, respectively.

Conclusion Aorto-cavitary fistulous tract formation is an uncommon but extremely serious complication of IE. In-hospital mortality was exceptionally high despite aggressive management with surgical intervention in the majority of patients. Prosthetic IE, urgent surgery, and the development of HF identify the subgroup of patients with IE and ACF that have significantly increased risk of in-hospital death.

Introduction

Spread of infection in infective endocarditis (IE) from valvular structures to the surrounding peri-valvular tissue results in peri-annular complications that may place the patient at increased risk of adverse outcomes including heart failure and death.[1–9] This is particularly true in aortic valve IE where abscesses and pseudo aneurysms involving the sinuses of Valsalva may rupture internally with the subsequent development of aorto-cavitary fistulae (ACF). These aorto-cavitary communications create intra-cardiac shunts, which may result in further clinical deterioration and haemodynamic instability.

ACF have been described after surgical trauma during aortic valve replacement, chest trauma, aortic dissection, sinus of Valsalva aneurysm rupture, and only rarely, during IE. Because previous reports have been limited to necropsy findings[2,3] or small case series,[10–12] the clinical features and prognostic factors of ACF in IE are incompletely understood. Thus, the current study sought to determine the incidence, clinical features, and risk factors for in-hospital mortality in a large cohort of patients with ACF. Since prosthetic valve IE is associated with lethality as high as 40%,[13] we also aimed to describe the distinct clinical characteristics and the prognosis of patients with ACF in native and prosthetic valve IE.

Methods

Study population

We conducted a retrospective, multi-centre, descriptive study at 17 tertiary referral hospitals (16 in Spain, one in the USA) between January 1992 and December 2002. Patients were included in the study if they had definite IE and documented ACF by echocardiography, direct surgical inspection, or post-mortem examination. Necropsy studies confirmed the presence of fistulization in all patients that died without surgical therapy. Cases in which ACF was suspected to originate from conditions other than active IE (e.g. congenital, traumatic, or post-surgical) were excluded. Two patients with echocardiographic detection of ACF were excluded from the study group because a fistulous tract could not be confirmed during surgery. All patients with ACF were obtained from prospective databases from each institution. Case records and/or echocardiographic recordings were reviewed to obtain appropriate variables if they were not included in the original prospective databases. Nine cases from this series have been reported previously.[12]

Clinical definitions

Diagnostic criteria of endocarditis

Diagnosis of IE was made according to the modified Duke criteria[14] and cases were grouped in two subpopulations: native valve endocarditis (NVE) and prosthetic valve endocarditis (PVE). Early PVE was defined as developing 12 months or less after operation, and late PVE as occurring after 12 months.

Complications

Heart failure was defined according to the New York Heart Association (NYHA) classification. Ischaemic and haemorrhagic stroke and brain abscesses were grouped as neurological events.

Echocardiographic definitions

Results of two-dimensional transthoracic (TTE) and/or transoesophageal echocardiography (TEE) were evaluated. Echocardiographic data were obtained according to the database protocol followed for each institution and in some patients by chart

review. Aortic regurgitation was assessed by colour Doppler flow imaging using semiquantitative standard criteria.[15] Abscesses were defined as abnormal echo-dense or echo-lucent areas within the valvular annulus or peri-valvular tissue in more than one echocardiographic plane in the setting of valvular infection.[16] Fistulae were defined as abnormal communications between the aorta and the cardiac chambers with turbulent systolic and diastolic flow assessed by continuous or colour Doppler mapping (*Figure 1*).

Antibiotic therapy

All patients received standard antimicrobial therapy appropriate for the organism grown after antimicrobial susceptibility was determined as recommended by Wilson *et al.*[17]

Surgery

The indication for surgery during the active phase of IE was established following general recommendations.[18,19] Drainage of abscesses with closure of intra-cardiac fistulae were performed at the discretion of the treating physicians. Emergency surgery was defined as surgical intervention <24 h from diagnosis of ACF; urgent surgery as intervention <1 week from the diagnosis of fistula and elective surgery as intervention delayed at least 1 week from diagnosis.

Mortality

Mortality was defined as in-hospital death.

Follow-up

Follow-up was obtained according to the database protocol followed for each institution or by chart review. Death, heart failure requiring hospital admission, and repeat surgery were considered as major complications during follow-up.

Statistical analysis

Variables were compared between patients with NVE and PVE. Qualitative variables were described using contingency tables and compared between groups with the χ^2 test or Fisher's exact test, as appropriate. Continuous variables were described by median and interquartile range (IQR), and compared between groups with Student's *t*-test and Wilcoxon rank sum test, as appropriate. The risk of NVE relative to PVE was estimated for the most relevant clinical variables. The logistic regression model was used to evaluate the effect of explanatory variables on mortality. All factors with a simple *P*-value <0.15 were added stepwise to a multiple model. All *P*-values were based on two-sided testing with a 95% confidence interval (CI). The logistic regression model was calculated with Stata statistical software (Release 7.0. College Station, Stata Corporation, TX, USA). Survival analysis techniques were used to compare event rates during the follow-up period with comparisons made with the log-rank test based on the Kaplan–Meier method.

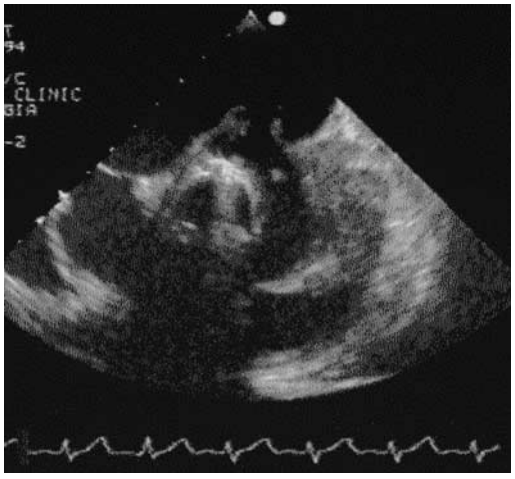

Figure 1 Transoesophageal echocardiographic image of a prosthetic aortic valve endocarditis. A peri-prosthetic abscess cavity is ruptured communicating the left sinus of Valsalva with the left atrium.

Results

Epidemiology

A total of 76 patients [56 men and 20 women, mean age of 54.7 years (range 18–83)] with ACF were identified among 4681 cases of IE in the study institutions (*Table 1*). All abscesses and fistulae were confirmed at surgery or autopsy in all patients undergoing these procedures. Forty-one patients were diagnosed from 1992 to 1997 and 35 from 1998 to 2002. ACF developed in 1.6% (95% CI 1.3–2.0%) of all cases of IE, 2.2% (95% CI 1.7–2.7%) of cases from the general population (non-IV drug users), and 0.4% (95% CI 0.2–0.9%) in IV drug users. Fistula formation occurred only in aortic valve IE and was more frequent in prosthetic aortic than in native aortic valve endocarditis (5.8 vs. 3.6%, $P = 0.04$).

Clinical features

Table 2 summarizes the clinical characteristics of patients. ACF patients included 45 (59%) NVE and 31 (41%) PVE. Among the 31 ACF patients with prosthetic valves, 16 (52%) had early onset and 15 (48%) had late onset PVE. Patients with PVE were older, but gender and underlying significant co-morbidities were not significantly different between native and prosthetic valve patients. Median duration of symptoms to diagnosis of IE was 19 days (<15 days in 35, 16–30 days in 25, and >4 weeks in 16 patients). Median duration of symptoms

Table 1 Frequency of ACF in IE during the study period (1992–2002)

	Cases of IE	ACF *n* (%)
Non-IV drug users	3147	69 (2.2)
Native valve	2105	38 (1.8)
Aortic	1056	38 (3.6)
Mitral	930	0
Other	119	0
Prosthetic valve	872	31 (3.5)
Aortic	536	31 (5.8)
Mitral	326	0
Other	10	0
Pacemaker	170	0
IV drug users	1534	7 (0.4)
Overall	4681	76 (1.6)

Table 2 Clinical characteristics of 76 patients with ACF in IE

	Overall ($n = 76$)	NVE ($n = 45$)	PVE ($n = 31$)	*P*-value
Median age (IQR), years	56 (42–69)	48 (33–67)	66 (50–72)	0.03
Male gender	56 (74)	36 (80)	20 (65)	0.1
Previous valve disease[a]	44 (59)	13 (28)	31 (100)	0.001
Co-morbidity[b]	27 (36)	18 (40)	9 (29)	0.3
Mechanical ventilation	7 (9)	6 (13)	1 (3)	0.2
IV drug abuse	7 (9)	7 (16)	0 (0)	0.04
Median symptoms duration to diagnosis of IE (IQR), days	19 (10–30)	20 (10–30)	15 (9–30)	0.5
Median symptoms duration to diagnosis of fistulous tract (IQR), days	25 (18–47)	25 (18–45)	25 (19–52)	0.9
Moderate or severe heart failure	47 (62)	31 (69)	16 (52)	0.1
Neurologic events	12 (16)	8 (18)	4 (13)	0.5
Renal failure	28 (37)	20 (44)	8 (26)	0.09
Peripheral emboli	15 (20)	8 (18)	7 (23)	0.6
Complete aortic valve block	11 (14)	5 (11)	6 (19)	0.3

Data presented are median (IQR) or number of patients (%). Comparisons were made between native and prosthetic valve group.
[a]In native valve endocarditis: aortic stenosis ($n = 7$), aortic regurgitation ($n = 1$), mitral regurgitation ($n = 1$), bicuspid aortic valve ($n = 4$).
[b]Co-morbidity: liver cirrhosis ($n = 5$), diabetes mellitus ($n = 6$), malignancy ($n = 3$), chronic obstructive pulmonary disease ($n = 2$), renal failure ($n = 4$), HIV infection ($n = 3$), other ($n = 4$).

to echocardiographic detection of fistulization was 25 days and median time interval from diagnosis of IE to diagnosis of fistulization was 5 days (simultaneous diagnosis of IE and ACF occurred in 25 patients, with delays of 1–7 days in 26 patients, 8–21 days in 18 patients, and >21 days in seven patients). All seven IV drug users had native aortic IE; aorto-tricuspid valve involvement was present in three out of seven IV drug users.

Clinical or radiological signs of moderate or severe heart failure were present in 47 patients (62%) and seven patients (9%) required mechanical ventilation before surgery. There was a trend toward an increase in the frequency of heart failure in patients with NVE when compared with PVE (69 vs. 52%, $P = 0.1$).

Microbiological characteristics

Distribution of microorganisms is shown in *Table 3*. Staphylococci were the most common microorganisms causing 35 (46%) episodes of ACF (coagulase-negative staphylococci in 19 patients, *Staphylococcus aureus* in 16 patients). Five strains of *S. aureus* and 10 of *Staphylococcus epidermidis* were methicillin resistant (31 and 59%, respectively). Other commonly identified pathogens included streptococci (33%) and enterococci (5%) and no pathogen was identified in five patients (7%). There were three cases of fungal endocarditis and polymicrobial infection was documented in two cases (one case of *S. aureus* + *Candida albicans* and one case of *Klebsiella pneumoniae* + *Candida turulopsis*). *S. aureus* was more frequent in NVE than in PVE (29 vs. 10%, respectively, $P = 0.05$), whereas coagulase-negative staphylococci were more common in PVE than in NVE (48 vs. 9%, respectively, $P = 0.001$).

Echocardiographic data

Out of 76 cases, echocardiography made the diagnosis of ACF in 73 patients with confirmation at surgery ($n = 70$) or at post-mortem examination ($n = 3$). Three cases of fistulae were not detected by echocardiography and were found during surgery [median time from echocardiogram to surgery of 1 day (range 1–7)]. The necropsy study confirmed the presence of a fistula in the three patients that died without surgery. TTE detected the fistulous tract in 53% of cases and TEE was diagnostic of ACF in 97% of cases; the superiority of TEE over TTE was observed in both native and prosthetic valves (*Table 4*). Echocardiographic results are shown in *Table 5*. All patients had aortic valve involvement and multivalvular infection occurred in one-third of patients (30%). The majority of patients had peri-annular abscesses (78% of patients) with a median maximal diameter of 12 mm. Abscesses larger than 10 mm were detected in 42% of cases and an associated ventricular septal defect was present in 20% of cases. Patients with PVE had larger abscesses (58 vs. 31%, $P = 0.03$).

The site of origin of the fistulous tract was equally distributed between the three sinuses of Valsalva (37, 38, and 25% for right, left, and non-coronary sinuses, respectively). The four cardiac chambers were also equally involved in the fistulous tract (*Table 5*). Multiple fistulous tracts were present in 12% of cases and four patients had additional communications between the left ventricular outflow tract and the right atrium. The most common fistula tracts involved the right coronary sinus to right ventricle, the non-coronary sinus to right ventricle, and the left coronary sinus to left atrium (*Table 6*).

Nearly 50% of patients had moderate or severe aortic regurgitation (64% for NVE and 26% for PVE, $P < 0.001$).

Table 3 Distribution of microorganisms among 76 patients with ACF in IE

	Overall ($n = 76$), *n* (%)	Native valve endocarditis ($n = 45$), *n* (%)	Prosthetic valve endocarditis ($n = 31$), *n* (%)	*P*-value
Staphylococcus spp.	35 (46)	17 (38)	18 (58)	0.1
S. aureus	16 (21)	13 (29)	3 (10)	0.05
Coagulase-negative staphylococci[a]	19 (25)	4 (9)	15 (48)	0.001
Streptococcus spp.	25 (33)	16 (35)	9 (29)	0.6
Viridans group streptococci[b]	15 (20)	10 (22)	5 (16)	0.6
Streptococcus bovis	2 (3)	2 (4)	0 (0)	0.5
Other streptococci[c]	8 (10)	4 (9)	4 (13)	0.7
Enterococcus spp.	4 (5)	2 (4)	2 (6)	0.8
Culture negative	5 (7)	5 (11)	0 (0)	0.07
Other[d]	9 (12)	7 (15)	2 (6)	0.3

Comparison were made between native vs. prosthetic valve group. Seventy-eight microorganisms were isolated in 76 patients (two patients had polymicrobial infection).

[a]*S. epidermidis* ($n = 17$), *S. lugdunensis* ($n = 1$), *S. simulans* ($n = 1$).

[b]*S. viridans* ($n = 15$).

[c]*S. pneumoniae* ($n = 5$), *S. agalactiae* ($n = 3$).

[d]*Prevotella oralis* ($n = 1$), *K. pneumoniae* ($n = 1$), *Brucella* spp. ($n = 1$), *Haemophilus aphrofilus* ($n = 1$), *Neisseria* spp. ($n = 1$), *Aspergillus* spp. ($n = 1$), *Coxiella burnetti* ($n = 1$), *C. albicans* ($n = 1$), *C. turulopsis* ($n = 1$).

Table 4 Detection of ACF by TTE and TEE among patients with NVE and PVE

	TTE *n* (%)	TEE *n* (%)
NVE	26/44 (59)	31/33 (94)
PVE	15/31 (48)	28/28 (100)
Overall cases	40/75 (53)	59/61 (97)

Left ventricular dilatation was present in 44% of patients, with a mean ejection fraction of 61.7% and moderate or severe heart failure presented with equal frequencies in fistulae to all four cardiac chambers (62, 55, 58, and 67% of patients for fistulous tracts to the right atrium, left atrium, right ventricle, and left ventricle, respectively).

Surgical treatment

Sixty-six patients (87%, 95% CI 77–93%) underwent surgical treatment (*Table 7*). The mean time interval from diagnosis of ACF to surgery was 4.5 days. Emergency, urgent, and elective surgery were performed in 16 (24%), 28 (42%), and 22 (34%) patients, respectively. In six patients, surgery was delayed for >30 days. A prolonged time-interval from diagnosis of IE to diagnosis of fistulization did not contribute to increased need for urgent surgery (urgent surgery was needed in 53% of patients with <1 week from diagnosis of IE to detection of ACF and in 68% for those with >1 week, $P = 0.3$). Surgical procedures are listed in *Table 7*. Fistulae were closed using different techniques according to the degree of anatomical disruption (simple closure, pericardial, or Gore-Tex patches). Concomitant valve replacement was required in 92% of patients, using mechanical valves (50%), bioprostheses (24%), or cryopreserved homografts (18%).

Mortality and prognostic factors of mortality

In-hospital mortality among the 76 patients was 41% (95% CI 30–53%). Among the 66 surgical patients there were 28 deaths (42%, 95% CI 30–55%) (*Table 7*). Causes of death in surgically treated patients were multi-organ failure ($n = 8$), septic shock ($n = 7$), cardiogenic shock ($n = 6$), and post-operative haemorrhagic shock ($n = 7$).

Among the overall series of 76 patients, only moderate or severe heart failure was significantly associated with an increased risk of death (OR 3.2, CI 95% 1.2–9.1, $P = 0.02$). Prognostic factors of in-hospital mortality in operated patients are summarized in *Table 8*. Multivariable analysis identified moderate or severe heart failure (OR 3.4, CI 95% 1.0–11.5), PVE (OR 4.6, CI 95% 1.4–15.4) and urgent or emergency surgical therapy (OR 4.3, CI 95% 1.3–16.6) as variables independently associated with an increased risk of in-hospital death. A prolonged interval from diagnosis of IE to diagnosis of a fistulous tract was not statistically associated with increased in-hospital mortality (35% mortality in patients with <1 week from diagnosis of IE to detection of ACF and 52% for those with >1 week, $P = 0.2$), yet the absolute difference of 17% may be clinically important.

Further analyses of patients with heart failure were made. Left ventricular ejection fraction did not differ between patients with mild or severe degrees of heart failure for a given degree of aortic regurgitation. In patients with mild degrees of aortic regurgitation, increasing severity of heart failure was associated with higher in-hospital mortality (*Table 9*).

Table 5 Echocardiographic findings in the 76 patients with ACF in IE

	Overall ($n = 76$)	NVE ($n = 45$)	PVE ($n = 31$)	*P*-value
Patients with vegetations, *n*	63 (83)	43 (96)	20 (65)	0.001
Median maximal vegetation size (IQR), mm	11 (5–15)	11 (5–14)	12 (6–16)	0.7
Vegetations >10 mm	35 (46)	21 (47)	14 (45)	1.0
Patients with abscess	59 (78)	32 (71)	27 (87)	0.1
Median maximal abscess diameter (IQR), mm	12 (7–17)	10 (6–14)	15 (8–20)	0.07
Abscesses >10 mm	32 (42)	14 (31)	18 (58)	0.03
Associated ventricular septal defect	15 (20)	9 (20)	6 (19)	0.9
Mean ejection fraction ± SD	61.7 ± 11	62.5 ± 11	60.5 ± 11	0.4
Mean LVEDD ± SD	54.9 ± 7	55.2 ± 7	54.4 ± 8	0.6
Multivalvular infection[a]	23 (30)	15 (33)	8 (26)	0.6
Fistulized sinus of Valsalva				
Right coronary sinus of Valsalva	28 (37)	20 (44)	8 (26)	0.2
Left coronary sinus of Valsalva	29 (38)	16 (35)	13 (42)	0.6
Non-coronary sinus of Valsalva	19 (25)	9 (20)	10 (32)	0.3
Fistulized cardiac chamber				
Right atrium	13 (17)	8 (18)	5 (16)	1.0
Right ventricle	19 (25)	14 (31)	5 (16)	0.2
Left atrium	20 (26)	10 (22)	10 (32)	0.4
Left ventricle	12 (16)	6 (13)	6 (19)	0.5
Multiple fistulization	9 (12)	5 (11)	4 (13)	1.0
Moderate or severe aortic regurgitation	37 (49)	29 (64)	8 (26)	0.001

Data presented are median (IQR), mean ± standard deviation (SD) or number of patients (%). Comparison was made between native and prosthetic valve group.

LVEDD, left ventricular end-diastolic diameter.

[a]Aorto-tricuspid ($n = 3$), aorto-pulmonary ($n = 1$), aorto-mitral ($n = 19$).

Table 6 Echocardiographic tracts among 76 patients with ACF in IE

	Patients ($n = 76$), *n* (%)
From right coronary sinus of Valsalva	28 (37)
to right atrium	12 (35)
to right ventricle	15 (44)
other or multiple	7 (21)
From non-coronary sinus of Valsalva	19 (25)
to right atrium	5 (24)
to right ventricle	6 (28)
to left ventricle	5 (24)
other or multiple	5 (24)
From left coronary sinus of Valsalva	29 (38)
to left atrium	19 (59)
to left ventricle	7 (22)
other or multiple	6 (19)

Follow-up in operated patients

Thirty-four operative survivors (89%) have been followed. Five patients (14%) had residual fistulae detected after a median follow-up of 27 months (range 1–144). Major complications during follow-up among the five operative survivors with residual fistulae occurred in 20 and 100% of patients at 1 and 2 years, respectively. The remaining 29 patients had no residual fistulae after a median follow-up of 18 months (range 4–120). In operative survivors without residual fistulae, major complications during follow-up occurred in 8 and 8% of patients at 1 and 2 years, respectively. Major complications during follow-up were more frequent in patients with residual fistulae ($P < 0.001$, log-rank). There were no cases of recurrent endocarditis. Patients with post-operative residual fistulae had no specific clinical, echocardiographic, microbiological, or operative characteristics.

Outcome and follow-up in non-operated-upon patients

A total of 10 patients did not undergo surgical treatment. Three patients died before planned surgical intervention because of cardiogenic shock (one patient), uncontrolled infection (one patient), and sudden death in another patient. Conservative treatment was decided in seven patients because of excessive co-morbid surgical risk (previous prosthetic valve surgery in four patients and advanced age, advanced renal disease, and stroke complicating endocarditis in one case each) and a relatively non-aggressive disease. Median age of non-operated patients was 69 years (range 48–83), all seven patients were in NYHA class I or II, aortic regurgitation was absent or mild in six patients, and six patients had aortic abscesses with a median maximal diameter of

Table 7 Surgical procedures and outcome of 76 patients with ACF in IE

	Overall ($n = 76$), *n* (%)	NVE ($n = 45$), *n* (%)	PVE ($n = 31$), *n* (%)	*P*-value
Surgical treatment	66 (87)	39 (87)	27 (87)	0.9
Time to surgery				
<24 h	16 (24)	13 (33)	3 (11)	0.04
2–7 days	28 (42)	14 (36)	14 (52)	0.2
>7 days	22 (34)	12 (31)	10 (37)	0.6
Closure of fistula	66 (100)	39 (100)	27 (100)	1.0
Simple suture	27 (41)	16 (41)	11 (41)	1.0
Pericardial patch	32 (48)	18 (46)	14 (52)	0.8
Gore-Tex patch	7 (11)	5 (13)	2 (7)	0.7
Valve replacement	61 (92)	37 (95)	24 (89)	0.4
Bioprosthesis	16 (24)	11 (28)	5 (19)	0.4
Mechanical prosthesis	33 (50)	19 (49)	14 (52)	
Homograft	12 (18)	7 (18)	5 (19)	1.0
Pacemaker implant	15 (20)	9 (20)	6 (19)	0.9
In-hospital mortality ($n = 76$)	31 (41)	16 (36)	15 (48)	0.3
Surgical mortality ($n = 66$)	28 (42)	13 (33)	15 (55)	0.08
Medical mortality ($n = 10$)	3 (30)	3 (50)	0 (−)	0.3

Comparisons were made between native and prosthetic valve groups.

Table 8 Univariate and multivariable analysis of risk factors influencing in-hospital mortality in operated patients

	Crude mortality		Adjusted mortality	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age >65 years	2.8 (1.0–7.9)	0.05		
Male gender	0.8 (0.2–2.4)	0.6		
Prosthetic endocarditis	2.5 (0.9–6.8)	0.07	4.6 (1.4–15.4)	0.01
Symptoms duration >30 days	0.8 (0.2–2.6)	0.7		
Moderate or severe heart failure	2.2 (0.7–6.4)	0.15	3.4 (1.0–11.5)	0.04
Renal failure	1.8 (0.7–5.1)	0.2		
Neurological symptoms	0.6 (0.1–2.8)	0.5		
Infection due to *S. aureus*	1.2 (0.4–3.6)	0.8		
Coagulase-negative *Staphylococcus* infection	0.6 (0.3–2.4)	0.5		
Vegetation >10 mm	1.2 (0.4–3.6)	0.7		
Presence of peri-annular abscess	1.6 (0.5–5.5)	0.4		
Peri-annular abscess >10 mm	2.3 (0.7–7.3)	0.14		
Moderate or severe aortic regurgitation	0.8 (0.3–2.1)	0.7		
Fistulized sinus of Valsalva				
Right	1	0.9		
Left	1.1			
Non-coronary	1.4			
Fistulized cardiac chamber				
Right atrium	1	0.2		
Right ventricle	0.2			
Left atrium	0.4			
Left ventricle	0.4			
Ejection fraction $<65\%$	1.1 (0.4–3.1)	0.8		
Urgent or emergency surgery	2.7 (0.9–7.8)	0.06	4.3 (1.3–16.6)	0.02

7 mm (range 5–11). No patient experienced haemodynamic in-hospital deterioration.

During the follow-up phase of the seven non-operated patients, two patients were lost to follow-up and the remaining five non-operated patients were followed for a median of 33 months (range 1–96). Major complications during follow-up occurred in 40 and 80% of patients at 1 and 2 years, respectively.

Discussion

This study represents the largest cohort of patients to date with aorto-cavitary fistulous tract formation in IE as a result of extension of infection beyond the aortic annulus. Because this complication is not common,[20,21] generalizable data from prior investigations are limited

Table 9 Comparison of ejection fraction and in-hospital mortality according to severity of aortic regurgitation and grade of heart failure

	Mild or absent heart failure	Moderate or severe heart failure	*P*-value
Aortic regurgitation grade I or II			
Mean ejection fraction ± SD	59.5 ± 12.6	61.5 ± 9.40	0.5
In-hospital mortality, *n* (%)	4/20 (20)	12/19 (63)	0.01
Aortic regurgitation grade III or IV			
Mean ejection fraction ± SD	62.9 ± 12.7	62.8 ± 12.4	0.9
In-hospital mortality, *n* (%)	3/9 (33)	12/28 (43)	0.7

by small numbers of patients. In the current investigation, the relatively large sample size allowed us to make several key observations.

The occurrence of a fistulous tract is more common than previously reported. In this study, the incidence of an identified ACF was 2.2% in non-IV drug abusers and only occurred in aortic valve IE. Importantly, 1/20 patients with prosthetic aortic IE had documented ACF. This has important implications in how patients with IE are evaluated. A high index of suspicion should be present regarding the possibility of ACF because of the important management and prognostic implications.

The complication rate of ACF is high. Over 60% of patients with ACF in this study developed significant heart failure and over 40% died. In agreement with prior studies moderate or severe heart failure was a significant independent risk factor for death.[1,6,22] Interestingly, the severity of aortic regurgitation was not associated with mortality in this study. This observation may reflect the significant haemodynamic consequences and high mortality rates associated with ACF. In addition, the advanced septic status and the progressive local tissue destruction with abscess formation has also been recognized as major determinants of mortality in IE and may exacerbate the haemodynamic compromise produced by the fistulous tract.[1–9] Although the haemodynamic consequences of fistulae producing left-to-right or left-to-left shunts may vary depending on the site of rupture and the size of the shunt, our small sample size limited our ability to evaluate the clinical consequences of fistula tracts involving different cardiac chambers.

TTE was able to detect the fistulous tracts in half of the patients, and with the aid of TEE, overall detection increased to 97%. These findings agree with previous reports and suggest that echocardiography, and TEE in particular, is the preferred imaging technique.[16,21,23,24] The high rate of echocardiographic diagnosis of ACF may be due to high pressure differences between the aorta and the cardiac chambers. As a result of these pressure differences, flow across the fistula is highly turbulent and thus is easily detectable by continuous or colour Doppler mapping even when the fistulous orifice is small. TEE allows the detection of almost all fistulae and allows the optimal characterization of the fistula tract. The precise anatomic information obtained with TEE is especially useful for planning surgical approaches.

The likelihood of complications in ACF may be related to the severity of the haemodynamic abnormality. In the current study, left ventricular ejection fraction did not differ between patients with a mild or severe degree of heart failure for a given degree of aortic regurgitation, suggesting that the increase in severity of heart failure was due to higher degrees of volume overload produced by larger shunts. This finding suggests that large shunts producing severe forms of heart failure may be responsible for increased mortality.

The anatomical sites of origin and rupture for ACF were equally involved. In this study, the site of origin of the fistulous tract was equally distributed between the three sinuses of Valsalva and, similarly, the four cardiac chambers were also equally involved in the fistulous tracts. ACF was associated with peri-annular abscesses in 78% of patients and nearly 50% of patients had abscesses >10 mm in diameter. Up to 22% of cases had no clearly visible abscesses. From a pathophysiological point of view, fistula tract formation requires extension of the infection through the aortic wall, creating an abscess cavity, and, if the annular destruction persists, a fistula may develop. However, in some cases, infection may directly dissect the aortic wall and create a pseudoaneurysm or a fistula without the previous formation of an abscess.[25] Complex lesions with multiple fistulous tracts (present in 9% of cases), ventricular septal defects (in 20%), and communications between the left ventricular outflow tract and the right atrium were also frequent.

The role of pathogen virulence in the risk of development of ACF is similarly unresolved. Some,[3,16] but not all[4,5,7] prior investigations have reported an association between the causative pathogen and risk of peri-annular abscess formation. Although staphylococci were the most common cause of ACF in the present investigation, we were unable to identify any associations between the causative pathogen and clinical characteristics or outcome. However, the observation that *S. aureus* was the single most common cause of ACF among patients with NVE is consistent with prior reports describing the unique virulence of this pathogen.[26,27]

Our investigation was not aimed at delineating the clinical characteristics that might predispose to fistula

formation. Since peri-annular erosion with fistula formation represents a further step in aortic annular erosion and extension of infection beyond the leaflets and aortic ring, it can be hypothesized that the clinical features associated with abscess formation can also be responsible for the development of ACF. Hence, traditional risk factors for the development of paravalvular abscesses (e.g. aortic or prosthetic valve involvement, valvular regurgitation, pericarditis, persistent fever, atrioventricular block, virulent pathogens, or intravenous drug use) might also be responsible for fistula formation.[2,3,6,7,28,29]

The results of our investigation support the concept that fistula formation is a surrogate of severe and extensive local tissue destruction and should be considered a strong indication for surgical therapy. Although early surgical intervention prior to the development of heart failure has been reported to improve patient outcome,[6] no data exist regarding timing of surgery in patients with ACF. We observed no differences in mortality rates according to time intervals from symptom onset to diagnosis of IE and from diagnosis of IE to development of fistulization. However, mortality rates among fistula patients requiring urgent surgical therapy were significantly higher than for fistula patients in whom such intervention was not required. This finding is, however, not surprising. Patients referred to emergency or urgent surgery were in dramatic haemodynamic conditions with severely damaged anatomies. Operative survivors with residual fistulae constitute a special subgroup of patients with a high risk of adverse events during follow-up, and, therefore, should undergo frequent follow-up, both by clinical and echocardiographic evaluation in order to forestall late complications. Nevertheless, despite the high death rate in the ACF population, in some patients fistula tract formation was not uniformly fatal in the absence of surgical therapy. In the current series, conservative medical treatment was utilized in seven patients. Within this select group, major complications during follow-up occurred in 40 and 80% of patients at 1 and 2 years, respectively. Thus, the relative benefits of surgical repair in patients with ACF must be weighed against the risk of complex reconstructive surgical techniques. Small fistulae may have little effect on haemodynamics and, therefore, in selected cases with very high surgical risk and when the extent of intra-cardiac shunt appears to be low, conservative management may be contemplated.

Limitations of the study

This study has some limitations. Although ascertainment bias is possible given the multi-centre nature of the study and differences in diagnostic and therapeutic strategies in the different hospitals, the broad availability of TEE in the diagnosis and delineation of fistulous tracts makes this fact of limited impact. In addition, most cases were identified in recent years, in which surgical techniques had achieved high levels of complete reconstructive procedures. It is possible that the severity of ACF appears higher because cases with low-grade shunts may have been under-diagnosed because the flow in the fistulous tract may have been confounded with regurgitant jets. This study was not designed to fully evaluate the impact of surgical intervention on the outcome of patients with ACF, since the majority of patients underwent surgery as a result of complete evaluation of clinical data. Patients submitted to surgical treatment had very high-risk profiles and were not comparable to medically treated patients. In addition, the aim of this study was not to compare surgical and medical treatment, but to describe the clinical course and the characteristics of the fistula tract in patients with ACF. Since the study is retrospective and there were clinical reasons to advance or to delay surgical therapy in each individual case, a definitive observation cannot be derived. However, it seems likely that early fistula detection identifies a population at risk for additional complications who may benefit from consideration for early surgical intervention. Finally, referral bias is possible, as patients referred to surgical treatment were severely ill and differed from medically treated patients.

Conclusions

ACF is an uncommon complication of aortic IE associated with extensive aortic root destruction and the presence of peri-annular abscesses. TEE is the diagnostic tool of choice for the detection of ACF in both native and prosthetic valves. Despite aggressive surgical treatment, rates of heart failure and mortality are high. Prosthetic IE, urgent surgery, and the development of heart failure were associated with an increased risk of death in patients with endocarditis complicated by fistulous tract formation.

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Appendix

Members of the Aorto-cavitary Fistula in Endocarditis Multi-centre Study: I. Anguera, J.R. Gumá (Hospital de Sabadell); J.M. Miró, X. Claramonte, M. Almela, C. García de la María, F. Marco, Y. Armero, M. Azqueta, M.A. Baraldes, C. Paré, M.E. Díaz, C.A. Mestres, S. Ninot, R. Cartaña, J.L. Pomar, M.J. Jiménez Exposito, A. Moreno, N. de Benito, A. del Río, N. Pérez, J. Ramírez, E. de Lazzari, T. Ribalta, J.M. Gatell,

G. Sanz (Hospital Clínic Universitari, Barcelona); I. Vilacosta, C. Graupner, M. Luaces, C. Corros, R. Ronderos (Hospital Clínico San Carlos, Madrid); B. Almirante, A. Evangelista, P. Tornos (Hospital Vall d'Hebrón, Barcelona); M. Anguita (Hospital Reina Sofía, Córdoba); P. Muñoz, P. Avanzas, M. Moreno (Hospital Gregorio Marañón, Madrid); J.A. San Román, J. López, M. Acuña (Hospital Universitario de Valladolid); A. de Alarcón (Hospital Universitario Virgen del Rocío, Sevilla); T. Ripoll (Hospital Son Llàtzer, Mallorca); E. Navas, P. Martín-Dávila (Hospital Ramon y Cajal, Madrid); C. González-Juanatey (Hospital Xeral, Lugo); C.H. Cabell, V.G. Fowler Jr, G.R. Corey (Duke University Medical Center, Durham, NC, USA); C. Sarriá, J.V. Sanmartín (Hospital de la Princesa, Madrid); I. García-Bolao, A. Macías (Clínica Universitaria de Navarra, Pamplona); M.C. Fariñas, A. Pérez-Vázquez (Hospital Marqués de Valdecilla, Facultad de Medicina, Santander); R. Leta (Hospital de Sant Pau, Barcelona); G. Rufi (Hospital de Bellvitge, Barcelona); F. Miralles, J.M. Reguera (Hospital Carlos Haya, Málaga).

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