Archives of Cardiovascular Disease 115 (2022) 348—358

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CLINICAL RESEARCH

Cardiac valvular surgery and history of anorectic drug intake: A retrospective study of a large population of benfluorex-exposed patients☆

Chirurgie valvulaire cardiaque et antécédents de prise de médicaments anorexigènes : une étude rétrospective d'une large population de patients exposés au benfluorex

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Received 26 November 2021; received in revised form 10 March 2022; accepted 14 March 2022
Available online 14 May 2022

Abbreviations: AR, aortic regurgitation; AS, aortic stenosis; AV, aortic valve; AVD, aortic valve disease; AVR, aortic valve replacement; CAVD, combined aortic valve disease; CMVD, combined mitral valve disease; DI-VHD, drug-induced valvular heart disease; IQR, interquartile range; MR, mitral regurgitation; MS, mitral stenosis; MV, mitral valve; MVR, mitral valve replacement; RHD, rheumatic heart disease; VHD, valvular heart disease.

☆ Tweet: This study published in ACVD describes, by far, the largest population of patients who received an appetite suppressant (benfluorex) and who subsequently underwent cardiac valvular surgery. Valve pathology was available in half of the population. Anorectic drugs should not be overlooked as a cause of valvular heart disease. Twitter address: @pvennezat..

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https://doi.org/10.1016/j.acvd.2022.03.006

KEYWORDS
Benfluorex;
Drug-induced valvular heart disease;
Heart valve surgery

Summary
Background. — Anorectic drugs are overlooked as a cause of valvular heart disease (VHD).
Aim. — To describe the characteristics of a large population of patients with severe VHD who underwent cardiac surgery and had a history of benfluorex intake.
Methods. — Retrospective observational and cross-sectional study of patients from a large French database (Office National d'Indemnisation des Accidents Médicaux). Clinical, echocardiographic, surgical and pathology findings were comprehensively collected from medical files.
Results. — From a chart review of 9584 subjects, 1031 patients with VHD underwent cardiac surgery; 453 surgical patients were excluded because of VHD obviously unrelated to benfluorex exposure, six because of missing data and eight declined to participate. The final study population comprised 564 patients who had surgery between 1987 and 2019. Median age was 58 (interquartile range 50—65) years; 85% were female. Median duration of preoperative benfluorex exposure was 5.8 (3.3—10) years. Most patients had aortic and mitral valve disease. Pure or predominant aortic and/or mitral regurgitation were found in 84% of patients ($n = 471$), and aortic or mitral stenosis (pure or combined with regurgitation) in 12% ($n = 67$) and 15% ($n = 84$), respectively. Overall, 403 aortic, 402 mitral and 64 tricuspid valve surgical procedures were collected. Aortic and mitral valves were found to be thickened, rigid and/or restrictive in most cases; restrictive tricuspid valve disease was seldom documented. Pathology was available in half of the population (276 patients); valvular fibrosis suggestive of drug-induced VHD was found in 222 patients, including 146 with expert examination. Mixed VHD aetiologies were discussed in 107 patients, including 54 with available pathology.
Conclusions. — Drug-induced VHD features are miscellaneous, including well-known restrictive valvular regurgitation, but also stenosis or combined regurgitation and stenosis. Besides a history of drug taking, thorough echocardiography and comprehensive surgical reports, pathology is key in the diagnostic procedure.

MOTS CLÉS
Benfluorex ;
Valvulopathies médicamenteuses ;
Chirurgie valvulaire cardiaque

Résumé
Contexte. — L'origine médicamenteuse des valvulopathies est souvent méconnue.
Objectif. — Décrire les caractéristiques d'une large population de patients opérés de valvulopathies sévères et exposés préalablement au benfluorex.
Méthodes. — Étude rétrospective observationnelle de patients issus d'une base de données de l'Office National d'Indemnisation des Accidents Médicaux. Les critères retenus étaient cliniques, échocardiographiques, chirurgicaux et si possible anatomopathologiques.
Résultats. — À partir d'une base de 9584 dossiers de demandes d'indemnisation, 1031 patients avaient eu une chirurgie valvulaire. Les 453 patients avec une valvulopathie sans lien avec l'exposition au benfluorex étaient exclus de notre étude, 6 pour des données majeures manquantes et 8 refusaient de participer. La population étudiée comprenait 564 patients, opérés entre 1987 et 2019, dont 85 % de femmes. L'âge médian était de 58 ans (écart interquartile 50—65) et la durée médiane d'exposition pré-chirurgicale de 5,8 ans (écart interquartile 3,3—10). Il existait une insuffisance aortique ou mitrale dans 84% des cas ($n = 471$) et une sténose aortique ou mitrale, pure ou associée à une régurgitation (« maladie ») respectivement dans 12% ($n = 67$) et 15% ($n = 84$) des cas. La majorité des patients avaient une double atteinte aortique et mitrale. Au total, 403 procédures aortiques, 402 mitrales et 64 tricuspides ont été rassemblées. Les valves apparaissaient épaissies, rigides et/ou restrictives dans la très grande majorité des cas; l'atteinte tricuspide organique était rare. L'examen anatomopathologique, disponible dans la moitié des cas (276 patients exactement), montrait une fibrose valvulaire suggestive chez 222 patients avec une expertise spécifique dans le domaine des valvulopathies toxiques disponible dans 146 cas. Des causes multiples étaient discutées chez 107 patients dont 54 avec examen histologique.
Conclusions. — L'atteinte valvulaire toxique est polymorphe, comprenant, outre des régurgitations restrictives bien connues, en général aortiques et/ou mitrales, des sténoses pures ou combinées à des fuites. Outre l'anamnèse de la prise du toxique, l'échocardiographie détaillée et la description peropératoire des lésions, l'anatomopathologie est un élément-clé du diagnostic.

Background

The first reports of drug-induced valvular heart disease (DI-VHD) were triggered by the use of ergot alkaloids in the mid 1960s [1]. Fenfluramine and its derivatives were marketed from the 1960s until November 2009. Despite the seminal report by Connolly et al., DI-VHD caused by the prescription of appetite suppressants has long been poorly recognized [2]. Benfluorex itself was an anorexigenic drug, marketed in France for the management of overweight patients with diabetes and dyslipidaemia between 1976 and 2009, whereas dexfenfluramine was marketed between 1985 and 1997. Landmark case-control studies confirmed the higher prevalence of mild valvular regurgitation in patients with a history of fenfluramine or dexfenfluramine [3] or benfluorex exposure (31% vs. 12.9% in controls in a cohort of diabetic subjects) [4], but patients with severe VHD were not enrolled [4]. Increasing evidence that benfluorex also produced DI-VHD features other than mere restrictive fibrotic valve regurgitation [5–10] is still overlooked, and surgical DI-VHD cases, although rare, are being accumulated [5,7,8,10–15] (Table A.1).

We aimed to describe the characteristics of a large population of patients with VHD who underwent cardiac surgery and had a history of benfluorex intake.

Methods

Design, setting and participants

This retrospective observational cross-sectional study of patients stems from a large French database from the ''Office National d'Indemnisation des Accidents Medicaux'' (ONIAM; French National Office for Compensation for Medical Accidents); this governmental agency is collecting medical files of subjects who request compensation for presumed cardiac valvular disease related to benfluorex exposure (Fig. A.1). The following data were extracted by chart review: evidence of benfluorex intake for a minimum duration of 3 consecutive months, based on prescription certificates, pharmacy or hospital records and medical files (benfluorex intake had to precede documented echocardiographic abnormalities or significant VHD worsening); medical history, including cardiovascular risk factors and co-morbid conditions; history of rheumatic fever, thoracic radiation therapy, systemic disease or other drugs known to induce restrictive VHD; echocardiographic abnormalities suggestive of DI-VHD (Fig. A.2); and surgery reports including macroscopic description and valve pathology reports, when available (Fig. A.3).

Patients

Between January 2012 and June 2020, 9584 files were examined, including a large majority of minor valve diseases, but also 1031 patients who underwent cardiac valvular surgery. Among the patients who had a VHD surgical procedure, 453 were excluded from the present analysis after careful file review, because VHD was obviously deemed unrelated to benfluorex exposure: moderate or severe VHD preceding benfluorex intake; history of rheumatic heart disease (RHD) or degenerative aortic stenosis (AS); or VHD caused by other conditions (Fig. 1). In addition, six patients were excluded because of missing major data. Patients who underwent transcatheter aortic valve replacement (TAVR) were included. Among the remaining 572 patients, informed consent was obtained from 564, who were kept for the present analysis. Patients who were exposed to other drugs known to produce VHD (fenfluramine/phentermine, dexfenfluramine, rye ergot alkaloids, ergot derivatives [including pergolide and cabergoline]) were also included if VHD was not documented before or worsened following benfluorex exposure.

Patients were classified into four groups, as follows: group A, patients with expert pathology analysis showing isolated DI-VHD lesions (type 1) on at least one valve; group B, patients with pathology analysis showing isolated valvular fibrosis (type 2) on at least one valve, without signs suggestive of VHD aetiologies other than DI-VHD; group C, patients without pathology analysis and without additional VHD cause other than DI-VHD; and group D, patients with VHD causes additional to DI-VHD, with or without available pathology analysis.

The Board of Directors of ONIAM and Benfluorex Victims Associations approved the study. The study was registered at the Commission Nationale de l'Informatique et des Libertés (CNIL) with the number 2218523 and the reference methodology MR-04 for non-interventional studies.

Full details of the methods are provided in Appendix A.

Statistical analysis

All analyses were performed using BiostaTGV and SPSS software. Normality of continuous variables was tested using the Kolmogorov-Smirnov test. Continuous variables are expressed as median (interquartile range [IQR]), and were compared using the Mann-Whitney *U* test. Categorical variables are expressed as counts and percentages, and were compared using Fisher's exact test or the χ^2 test, as appropriate. Statistical significance was set at a two-sided *P* value < 0.05 for all analyses. A Bonferroni-corrected post hoc pairwise comparison was made between subgroups.

Results

The main characteristics of the 564 patients are depicted in Table 1. Female patients constituted the majority of the population (85%) and the median age was 58 years (IQR 50–65 years; range 28–81 years). Cardiovascular risk factors were common, including diabetes, dyslipidaemia, being overweight and obesity. Median duration of preoperative benfluorex exposure was 5.8 years (IQR 3.3–10 years; range 0.3–30 years). The median time between benfluorex initiation and DI-VHD diagnosis was 4.4 years (IQR 1.9–8.3 years; range 0–35 years), and between benfluorex initiation and surgery was 8.6 years (IQR 4.7–14.4 years; range 0.4–40 years). Associated history of dexfenfluramine intake was found in 88 patients, and of other appetite suppressants, antimigraine ergot alkaloids or cabergoline in seven patients. The geographical and temporal distributions of patients are shown in Fig. A.1.

The circumstances of VHD diagnosis were highly variable, including incidental finding of murmur, shortness of

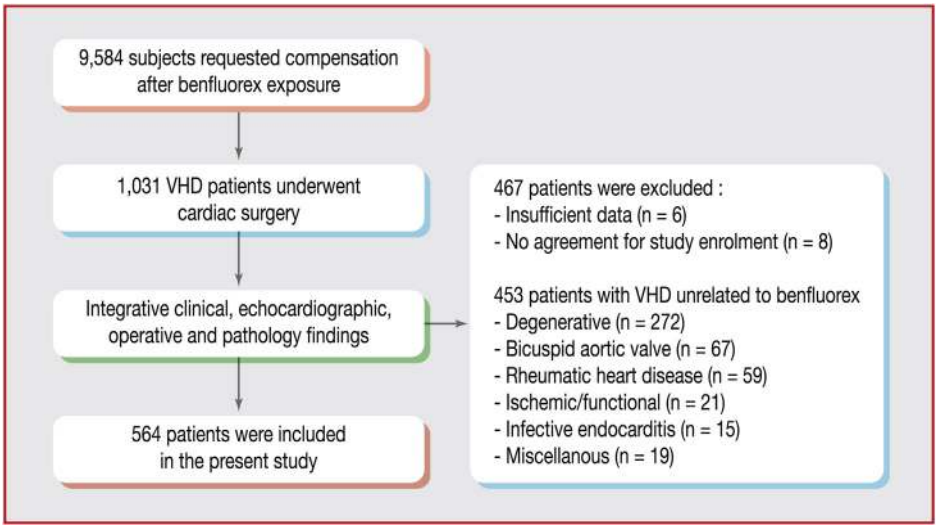

Figure 1. Flow chart of the study population. VHD: valvular heart disease.

breath or pulmonary oedema. Preoperative New York Heart Association functional class was III—IV in the majority of patients, with congestive heart failure in half of patients. Paroxysmal or permanent atrial fibrillation was found in 20%, and coronary artery disease was documented in 20%. Left ventriculography and/or aortography ($n = 279$) showed a mean ejection fraction of $62 \pm 11\%$, moderate-to-severe or severe mitral regurgitation (MR) in 177 cases and moderate-to-severe or severe aortic regurgitation (AR) in 166 cases. Right cardiac catheterization was performed in 207 patients, and showed postcapillary pulmonary hypertension in 63%. Peripheral artery disease was found in 10%, chronic obstructive or restrictive pulmonary disease in 24% and chronic kidney disease in 5%.

RHD was first suspected in 42%, but a history of rheumatic fever was documented in 3.5%. History of chest radiation therapy was found in 4% ($n = 22$). Minor valve regurgitation or valve sclerosis was reported before benfluorex exposure in 7% (Table 1).

Doppler echocardiography examination

Aortic valve disease

In the 403 patients who underwent aortic valve (AV) surgery, in the vast majority the aortic valve disease (AVD) was pure or predominantly restrictive moderate-to-severe or severe AR ($n = 336$), and less often AS ($n = 39$) or combined aortic valve disease (CAVD) with AR and AS ($n = 28$) (Fig. 2). Whereas typical features of restrictive DI-VHD were found in most patients with AR, valve calcifications were seldom found in AR, but often in AS and CAVD. Aortic valve prolapse was diagnosed in 12 patients (Table A.2).

Mitral valve disease

In the 402 patients who underwent mitral surgery, in the vast majority the mitral valve disease (MVD) was pure or predominantly moderate-to-severe or severe MR ($n = 318$), and less often mitral stenosis (MS) ($n = 44$) or combined mitral valve disease (CMVD) ($n = 40$). Restrictive leaflet motion associated with features of DI-VHD was found in most patients, and commissural fusions were found in 12%. Leaflet prolapse was found in four patients, and chordal rupture in two patients (Table A.3).

Overall regurgitant lesions were predominant, with 84% of patients ($n = 471$) having AR and/or MR requiring surgery.

Tricuspid valve disease

Tricuspid regurgitation was reported in 77% and was moderate-to-severe or severe in 10%. In the 64 operated patients, annular dilation was reported in 28%, and restrictive and thickened leaflets in 23% and 6%, respectively.

Multivalve disease

Most patients (80%) had both AVD and MVD, but only 43% required concomitant MV and AV surgery (Table A.4).

Cardiac dimensions and function

Left ventricular enlargement was greater in patients with AV or MV regurgitation than in those with valve stenosis (left ventricular diastolic diameter 57 ± 7 vs 49 ± 7 mm; $P < 0.0001$); 10% a had left ventricular ejection fraction < 50%. Left atrial dilation was often documented in MR (85%) and in MS (95%). Systolic pulmonary arterial pressure > 40 mmHg was found in 284 patients (50%), and more often in those with MVD (101/159, 63%) or AVD + MVD (149/243, 61%) than in those with isolated AVD (34/160, 21%; $P < 0.0001$). Right cardiac chambers were dilated in 90 patients (Table A.5).

In 46 patients, the VHD (16 AR + MR, 12 AR, one CAVD, 13 MR, three MS and one CMVD) emerged on a repeat echocardiogram, whereas a first normal echocardiogram was available before (0—3 years) or at benfluorex initiation.

Surgery

After excluding redo surgery, the 403 AV and 402 MV surgical procedures were collected from 65 surgical centres (215 surgeons). A total of 392 AV replacements (AVRs) and 333 MV replacements (MVRs) were performed, with the use

Table 1 Baseline characteristics ($n = 564$).

Demographics	
Age (years)	58 (50—65)
Female sex	479 (85)
Female age (years)	57 (50—65)
Male age (years)	60 (53—66)
Body mass index (kg/m^2)	29 (26—33)
Body mass index > 30 kg/m^2	246 (44)
Benfluorex exposure	
Benfluorex intake duration (months)	69 (39—119)
Benfluorex daily dose (mg)	450 (300—450)
Time from starting benfluorex to surgery (months)	103 (56—173)
Time from ending benfluorex to surgery (months)	3 (0—43)
Associated toxic medications	95 (17)
Dexfenfluramine	88 (16)
Other appetite suppressants	10 (1.8)
Ergotamine, cabergoline	6 (1.1)
Pre-existing valve disease	40 (7)
Emerging valve disease	46 (8.1)
Co-morbidities and associated conditions	
History of rheumatic fever	20 (3.5)
Thoracic radiotherapy	22 (3.9)
Breast cancer	16
Hodgkin's disease	4
Others	2
Systemic/inflammatory disease	12 (2.1)
Hypertension	345 (61)
Diabetes mellitus	259 (46)
Hyperlipidaemia	365 (65)
Past or active smoker	312 (55)
Peripheral artery disease	58 (10)
Chronic obstructive/restrictive pulmonary disease	138 (24)
Chronic kidney disease	29 (5)
Cardiac status	
NYHA III—IV	410 (73)
NYHA I—II	154 (27)
Left heart failure	256 (45)
Global heart failure	73 (13)
Atrial fibrillation	114 (20)
Coronary angiography	557 (99)
Left main trunk disease	2 (0.4)
Three-vessel disease	14 (2)
Two-vessel disease	38 (7)
One-vessel disease	58 (10)
No significant coronary stenosis	445 (79)
Right heart catheterization	207 (37)
Postcapillary pulmonary hypertension[a]	131 (23)

Continuous variables are expressed as median (IQR); dichotomous variables as number (%). NYHA: New York Heart Association.

[a] Mean pulmonary arterial pressure > 25 mmHg; pulmonary capillary wedge pressure > 15 mmHg.

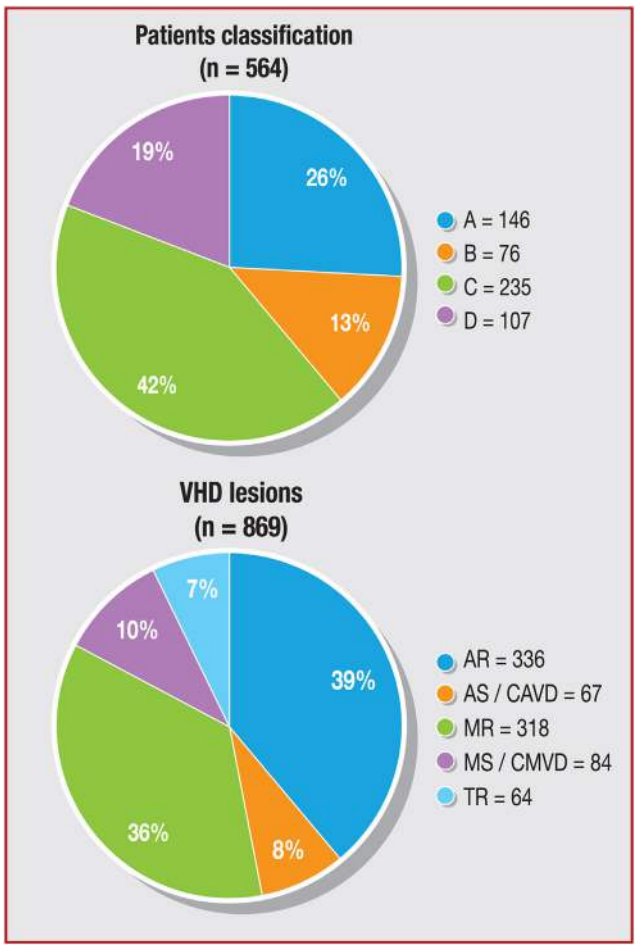

Figure 2. Top: patient classification (number and %). Group A: patients with expert pathology analysis showing isolated drug-induced valvular heart disease (DI-VHD) lesions (type 1) on at least one valve; group B: patients with pathology analysis showing isolated valvular fibrosis (type 2) on at least one valve, without signs suggestive of valvular heart disease (VHD) aetiologies other than DI-VHD; group C: patients without pathology analysis and without additional VHD cause other than DI-VHD; and group D: patients with VHD causes additional to DI-VHD, with or without available pathology analysis. Bottom: VHD lesions (valve heart lesions) (number and %). AR: aortic regurgitation; AS/CAVD: aortic stenosis or combined aortic valve disease; MR: mitral regurgitation; MS/CMVD: mitral stenosis or combined mitral valve disease; TR: tricuspid regurgitation.

of mechanical prostheses in 68%. Concomitant MV and AV surgery was performed in 243 patients, including 198 who had both MVR and AVR. Isolated MV repair was performed in 27 patients, whereas AVR was associated with MV repair in 37 patients. Repair for AR was performed in 11 patients, including four with concomitant MV repair. Tricuspid valve surgery was performed in 11%, including restrictive annuloplasty in 58 patients and bioprosthesis in six patients. An isolated tricuspid annuloplasty ring was implanted in one case, and an isolated tricuspid bioprosthesis in another (Table A.6). Coronary artery bypass grafting was associated in 11% of cases. Of note, operative mortality was 2.1% (12/564).

Peroperative findings

Both the AV and MV were commonly found thickened, rigid, retracted and/or restrictive, in 78% and 91% of patients, respectively; they were also considered ''rheumatic-like'' in 11% and 12%, and normal or near normal in nine patients and one patient, respectively (Table 2). Valve description was missing in 11% of reports for the AV and 5% for the MV. Cusp or leaflet calcifications were frequent on the AV (25%), especially in case of stenosis, but were less frequent (14%) on the MV. Commissural fusion was found in 18 patients (4%) on the AV and 68 (17%) on the MV.

AV prolapse was described in 37 patients (11%) with AR, affecting the non-coronary cusp in 80%. A subaortic membrane was found in one case, published previously [15]. Two patients had bicuspid AV, and one had a postendocarditis aortic cusp perforation.

On the MV, thickened subvalvular apparatus was delineated in 50%. When reported, MV lesions were found on the posterior leaflet in 39% of cases, on the anterior leaflet in 9% and balanced on both leaflets in 52%. Mitral valve prolapse was found in six patients, affecting the anterior leaflet in two and the posterior leaflet in four; chordal rupture was present in three patients; and restrictive lesions of the opposite leaflet were consistent.

On the tricuspid valve, a brief description existed in 59% of the 64 surgical procedures (replacement or repair). Annulus dilation was reported in 33 patients, and restriction, retraction or thickening of leaflets in 11 patients.

Pathology analysis

Pathology of valves and/or subvalvular apparatus was available in half of the population. Gross pathology findings are detailed in the Appendix B. In two thirds of cases, a repeat analysis of the histology slides was performed by an expert in the field of DI-VHD (Fig. 3).

Histologic findings

Valve analysis was available in 194 patients with AVD and 176 with MVD, showing unequivocal DI-VHD features (type 1), with endocardial fibrosis, preserved valve architecture, no inflammatory or rheumatic changes in 98 cases of AVD (51%) and 101 of MVD (57%), valvular fibrosis (type 2) in 66 cases of AVD (34%) and 58 of MVD (33%), and type 3 (mixed aetiologies) in 30 cases of AVD (15%) and 17 of MVD (9%). In type 1, mild-to-moderate aortic calcifications were found in a minority of cases ($n = 35$), and on the MV, subvalvular fibrotic lesions were deemed important in 76 cases, with chordal fusion in 55.

Type 3 lesions were associated with DI-VHD features on the AV and MV, with degenerative lesions in 20 and four patients, features of RHD in two and five patients, potential radiation injury in seven and four patients and non-specific inflammation in one and one patient, respectively, and ischaemic or functional mitral abnormalities in three patients.

On the tricuspid valve, pathology analysis was only available in one patient with isolated tricuspid regurgitation, and showed type 1 DI-VHD.

Patient classification

The 564 patients were classified according to integrative clinical, echocardiographic, operative and pathology findings (Table 3 and Fig. 2). Most patients ($n = 457$; 81%) were classified as having isolated DI-VHD related to benfluorex alone or associated with other valvulotoxic agent exposure, including 146 (26%) with histologic type 1 DI-VHD features (group A), 76 (13.5%) with type 2 valvular fibrosis (group B) and 235 (41.6%) without available pathology analysis (group C). The number of patients with isolated DI-VHD and no past history of other appetite suppressant drugs other than benfluorex intake, radiation therapy or rheumatic fever was 369 of the 457 (81%) patients, and 117 (80%) within group A. Exposure to other valvulotoxic agents was associated with benfluorex in 82 of the 457 (18%) patients, and 23 in group A (16%). In addition, four patients with a clinical history of rheumatic fever were classified in group A as having type 1 DI-VHD pathology features and the absence of pre-existing VHD before benfluorex exposure. In the 107 remaining patients (19%, group D), VHD was considered related to mixed aetiologies; additional causes were mainly degenerative ($n = 33$), rheumatic ($n = 21$), postradiotherapy ($n = 20$) and — more rarely — functional or ischaemic, inflammatory systemic, congenital, infectious (bacterial endocarditis) or pre-existing of unknown origin (Table A.7). Among patients with isolated DI-VHD, there were no differences in baseline characteristics and types of valve diseases between those with pathology analysis and those without. In contrast, patients with additional VHD causes more had often hypertension, AS or CAVD (Table 3).

VHD causes in addition to benfluorex exposure and follow-up data are detailed in Appendix C and Appendix D, respectively.

Discussion

The present study describes, by far, the largest population of patients who received an appetite suppressant and subsequently underwent cardiac valvular surgery. Our report shows that: (1) pathology analysis is key to the understanding of VHD aetiology and pathophysiology; (2) DI-VHD features are miscellaneous, including well-known restrictive valvular regurgitation, but also stenosis or combined regurgitation and stenosis, commissural fusions, cusp prolapse and valvular calcifications; and (3) overlap of multiple potential VHD causes may often be considered.

In all cases, diagnosis was based on history, echocardiography and surgical findings. When available (around half of our surgical patients), valve pathology analysis demonstrated drug-induced VHD, including type 2 and type 1 features, after repeat detailed expert examination in 80% of cases. The pathology procedure found mixed VHD aetiologies in the remaining 20%.

Drugs such as fenfluramine derivatives may produce VHD through activation of the 5-hydroxytryptamine (5-HT2B) receptor by norfenfluramine [16]. Serotonin activation produces endocardial fibrosis of the leaflets, with chordae tendineae fusion at the subvalvular apparatus level [17]. In 1997, Connolly et al. reported on nine patients who underwent valve surgery and 15 with moderate or severe valve

Table 2 Intraoperative findings in aortic and mitral valve surgery.

	Operated valve disease					
	AR	CAVD	AS	MR	CMVD	MS
	(*n* = 336; 60%)	(*n* = 28; 5%)	(*n* = 39; 7%)	(*n* = 318; 56%)	(*n* = 40; 7%)	(*n* = 44; 8%)
Restriction	177 (53)	19 (68)	25 (64)	258 (81)	34 (85)	42 (95)
Thickening	206 (61)	22 (79)	35 (90)	275 (86)	38 (95)	40 (91)
Restriction or thickening	255 (76)	25 (89)	35 (90)	286 (90)	39 (98)	44 (100)
Valve calcification	38 (11)	19 (68)	29 (74)	28 (9)	10 (25)	18 (41)
Commissural fusion	15 (4)	2 (7)	1 (3)	35 (11)	17 (43)	16 (36)
Leaflet/cusp prolapse	37 (11)	0	0	6 (2)	0	0
Subvalvular lesion	NA	NA	NA	153 (48)	25 (63)	27 (61)
Mitral annular calcification	NA	NA	NA	10 (3)	4 (10)	6 (14)
Mitral annular dilatation	NA	NA	NA	54 (17)	0	0
Normal or near normal	9 (3)	0	0	1 (0.3)	0	0
Not described	37 (11)	3 (10)	3 (8)	21 (7)	1 (3)	0

Data are expressed as number (%). AR: aortic regurgitation; AS: aortic stenosis; CAVD: combined aortic valve disease; CMVD: combined mitral valve disease; MR: mitral regurgitation; MS: mitral stenosis; NA: not applicable.

regurgitation following fenfluramine/phentermine treatment [2]. Later, Dahl et al. reported on 38 operated patients among 5743 with fenfluramine use [18]. Nevertheless, the DI-VHD aetiology seems to have been underestimated in surgical patients. The first report of severe VHD following benfluorex exposure was published in 2003 by Rafel Ribera et al., although this anorectic drug had been marketed since 1976 [8]. This Spanish case is particularly insightful because of the development of DI-VHD in the four cardiac valves in a 50-year-old patient who received benfluorex for less than 1 year, and subsequently had combined AVR and MVR, with tricuspid ring repair; pathology demonstrated typical DI-VHD. Two large national French linked databases—health insurance system and hospitalization—found, in the 2 years following benfluorex exposure, an adjusted 3.1-fold increased risk of hospitalization for any cardiac valvular insufficiency, and a 3.9-fold increased risk of valve replacement [19].

The MV and AV are predominantly affected, and the tricuspid valve much less often. Typical DI-VHD findings include variable degrees of leaflet and subvalvular apparatus thickening and retraction. Pathological examination of the valve is a major key to DI-VHD diagnosis, by showing non-inflammatory dense endocardial fibrosis that predominates on ventricular side of aortic cusps or on the atrial side of mitral leaflets (Fig. 3 and Fig. A.3). Furthermore, the valve architecture is preserved without inflammation or neovascularization [1,2,20,21]. This pattern contrasts with the postinflammatory scarring fibrosis found in RHD, showing valve layer disruption and thick-walled neoangiogenesis (Fig. 3) [21].

In agreement with previous reports [11—15], our findings confirm that the spectrum of DI-VHD features is wider than previously thought, including possible extensive valve apparatus calcifications, AV and/or MV commissural fusions and valve stenosis. These latter atypical DI-VHD features have seldom been reported (Table A.1). Valve fibrosis induced by benfluorex may also distort the geometry of the AV, and thereby result in AV cusp prolapse [12]. This particular feature was described in 11% (*n* = 37) of patients with AR. It is worth mentioning that carcinoid heart disease, which shares pathophysiological similarities with DI-VHD (serotonin pathway), may produce tricuspid and/or pulmonic stenosis, and also AS or MS, mostly in patients with atrial shunt, which may require valvuloplasty or valve surgery [22]. Right heart valve stenoses have not been yet documented in patients who have taken benfluorex.

The issue of other or associated potential causes of VHD is crucial in the diagnostic procedure of VHD in benfluorex-exposed patients. Our report found that valvular injury as a result of benfluorex exposure may overlap with other causes of VHD, such as aging, cardiovascular risk factors, bicuspid AV, history of rheumatic fever, radiation therapy, rheumatoid arthritis, endocarditis or the intake of other anorectic agents. In agreement, Volmar and Hutchins, who reviewed 35 AVs and 43 MVs from 64 patients with a history of fenfluramine/phentermine intake, found on two AVs and seven MVs (11%), DI-VHD features associated with floppy MV, RHD, degenerative calcific mitral annulus or infectious endocarditis [21]. In the study by Dahl et al., four of 38 valves showed mixed drug-induced and degenerative or postinflammatory lesions [18]. In the REGULATE study, mild valvular abnormalities did pre-exist benfluorex exposure in around 50% of randomized patients [23]. Conversely, these latter conditions may add further to pre-existing pure benfluorex-induced VHD. Of note, our study shows that pre-existing disease, such as rheumatoid arthritis or rheumatic fever, may not be involved in VHD, as the pathology showed pure DI-VHD without any feature of postinflammatory disease. Similar to pulmonary arterial hypertension associated with benfluorex [24], DI-VHD may progressively worsen late after the cessation of benfluorex therapy. Volmar and Hutchins observed considerable individual variation in the time course of anorectic agent use and the severity of DI-VHD, suggesting that drug-induced lesions may evolve despite drug withdrawal [21]. Aging and degenerative-induced lesions are likely to produce progressive severe

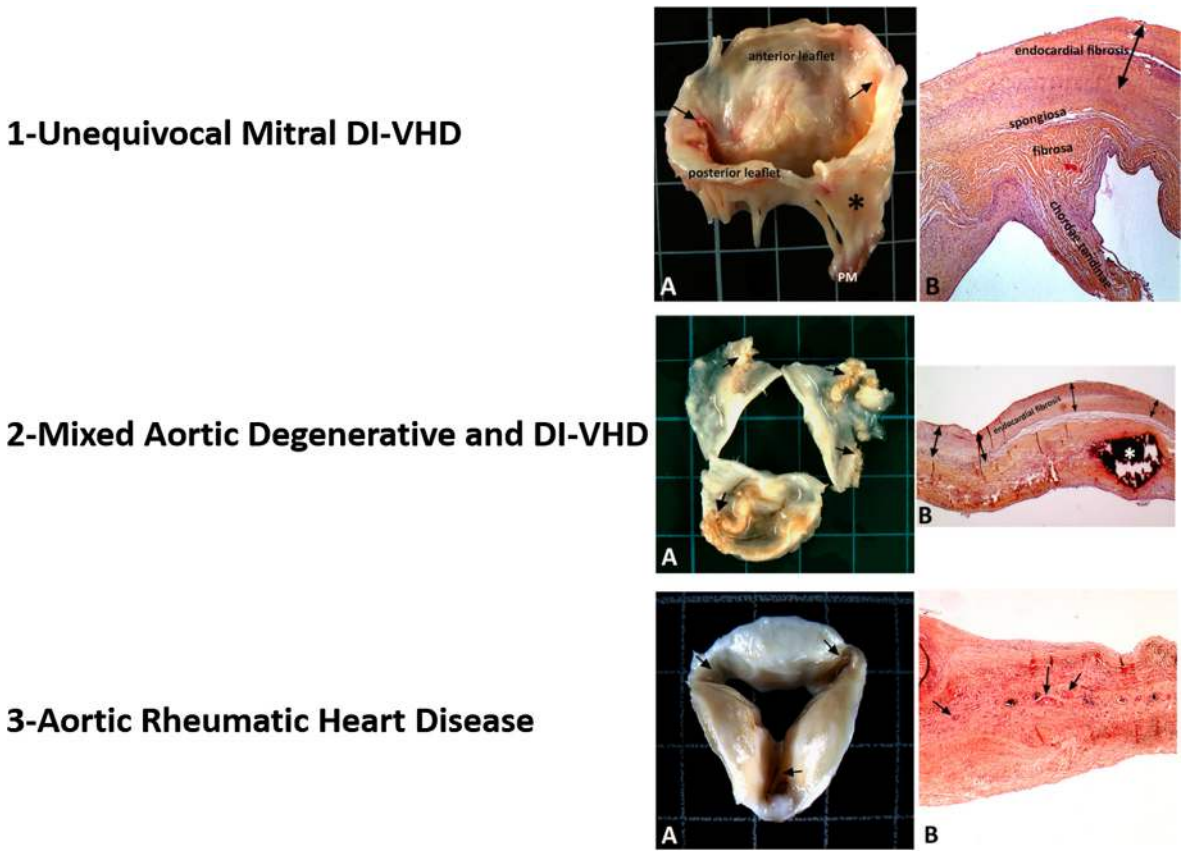

Figure 3. Valve pathology. 1A—B. Isolated drug-induced mitral valve disease. 1A. Gross pathology view of the complete mitral valve apparatus showing severe fibrous thickening of both leaflets and commissural fusion (arrows). The chordae tendinae are thickened and shrunken. Note fusion of some chordae tendinae (asterisk). This pattern cannot be specifically differentiated by gross pathology from rheumatic mitral valve disease (centimetre scale). 1B. Low magnification view of anterior leaflet histological section showing the preserved structure of the leaflet with clear fibrosa and spongiosa layers. The leaflet is severely thickened by endocardial fibrosis (arrow). Haematoxylin and eosin [H&E] stain; original magnification ×5. 2A—B. Mixed degenerative and drug-induced aortic valve disease. 2A. Gross pathology view of the complete aortic valve showing diffuse fibrous thickening of the cusps associated with multifocal calcifications (arrows) (centimetre scale). 2B. Low magnification view of aortic cusp histological section showing the preserved structure of the cusp with clear fibrosa and spongiosa layers. The leaflet is markedly thickened by endocardial fibrosis (arrows). Note focal calcification in the fibrosa (asterisk). H&E stain; original magnification ×5. 3A—B. Aortic rheumatic heart disease. 3A. Gross pathology of rheumatic aortic valve: the cusps are thickened by fibrosis; and there are commissural fusions (arrows). This pattern cannot be specifically differentiated by gross pathology from DI-VHD (centimetre scale). 3B. At histology, the architecture of the cusp is disrupted by scarring fibrosis blurring the spongiosa and the fibrosa layers. Note that the scarring fibrosis tissue exhibits many vessels including typical thick-walled vessels (arrows). H&E stain; original magnification ×10.

VHD in addition to DI-VHD. Several benfluorex-exposed patients exhibited isolated DI-VHD type 1 features on the MV, along with degenerative lesions on the AV, suggesting that the AV is particularly sensitive to degenerative changes. Similar to RHD, with superimposed degenerative lesions with aging, these patients were diagnosed with DI-VHD for both valves. Secondary calcifications related to aging and cardiovascular risk factors may supervene upon drug-induced valve fibrosis, and thereby produce valve stenosis. Subsequent caseous necrosis of the mitral annulus has been reported recently [25]. However, the respective role of potential drug-induced or degenerative VHD lesions cannot be ascertained from the present or other data [26]. Interestingly, in the population-based Hypertension Genetic Epidemiology Network study, treatment with fenfluramine or dexfenfluramine was associated with aortic regurgitation and, importantly, with aortic fibrocalcification [27]. Conversely, drug-induced valve fibrosis may develop on previously calcified valves. The presence of calcifications should not therefore preclude the diagnosis of DI-VHD.

At first glance, RHD may produce similar echocardiographic abnormalities, but definitely distinctive pathology lesions [20]. History of rheumatic fever is far from being constant. Le Ven et al. estimated a 0.2—2.7% probability of RHD-related VHD in a patient born between 1940 and 1960 in France presenting with VHD and a history of benfluorex intake [28]. In our study population, clinical history of rheumatic fever was suggested in 42%, but was clearly identified in only 3.5% of our patients, but in 12.6% of the 467 excluded operated patients. Interestingly, type 1 DI-VHD pathology features were evidenced in four patients with a clinical history of rheumatic fever.

Radiation-related VHD occurs late, and mostly in patients with a history of Hodgkin's disease [29,30]. Calcifications are very frequent, and typically involve the mitral-aortic curtain and the aortic root. Endocardial fibrosis can be induced

Table 3 Classification of patients according to clinical history and pathology findings (see Methods section).

	Overall	A	B	C	D	*P*
	(*n* = 564)	(*n* = 146)	(*n* = 76)	(*n* = 235)	(*n* = 107)	
Demography						
Age (years)	58 (50—65)	60 (52—67)	56 (48—64)	55 (49—62)	62 (56—68)	0.13
Female sex	479 (85)	129 (88)	65 (86)	199 (85)	86 (80)	0.38
Body mass index (kg/m^2)	29 (26—33)	28 (25—34)	30 (27—33)	29 (25—33)	30 (26—34)	0.92
Benfluorex exposure						
Benfluorex intake duration (months)	69 (39—119)	67 (32—120)	74 (38—115)	66 (36—117)	69 (41—116)	0.92
Benfluorex daily dose (mg)	450 (300—450)	450 (300—450)	450 (300—450)	450 (450—450)	450 (300—450)	1
Associated intake of other toxic drugs	95 (17)	23 (16)	18 (24)	42 (18)	12 (11)	0.15
Associated intake of dexfenfluramine	88 (16)	22 (15)	17 (22)	37 (16)	12 (11)	0.24
Pre-existing valve disease	40 (7)	4 (2.7)	4 (5.3)	4 (1.7)	28 (26)	< 0.0001[a]
Emerging valve disease	46 (8.1)	10 (6.8)	7 (9.2)	23 (9.8)	6 (5.6)	0.55
Clinical characteristics						
History of rheumatic fever	20 (3.5)	4 (2.7)	0	0	16 (15)	< 0.0001[a]
History of thoracic radiotherapy	22 (3.9)	2 (1.4)	0	0	20 (19)	< 0.0001[a]
Systemic/inflammatory disease	12 (2.1)	4 (2.7)	1 (1.3)	0	7 (6.5)	0.001[b]
Hypertension	345 (61)	85 (58)	44 (59)	137 (58)	79 (74)	0.03[b]
Diabetes mellitus	259 (46)	61 (42)	41 (55)	99 (42)	58 (54)	0.06
Hyperlipidaemia	365 (65)	92 (63)	54 (71)	147 (63)	72 (67)	0.5
Past or active smoker	312 (55)	86 (59)	49 (64)	129 (55)	48 (45)	0.04
Peripheral artery disease	58 (10)	17 (12)	7 (9.2)	17 (7.2)	17 (16)	0.09
Chronic obstructive/restrictive pulmonary disease	138 (24)	33 (23)	20 (26)	55 (23)	30 (28)	0.72
Chronic kidney disease	29 (5)	9 (6.1)	4 (5.3)	11 (4.7)	5 (4.7)	0.92
Coronary artery disease	112 (20)	26 (18)	12 (16)	43 (18)	31 (29)	0.07
Types of operated valve disease[e]						
AR	336 (60)	87 (60)	57 (75)	141 (60)	51 (48)	0.003[c]
AS or CAVD	67 (12)	14 (10)	5 (7)	18 (7.6)	30 (28)	0.0001[a]
MR	318 (56)	76 (52)	49 (64)	135 (57)	58 (54)	0.32
MS or CMVD	84 (15)	31 (21)	11 (14)	30 (13)	12 (11)	0.09
TR	64 (11.3)	27 (18.5)	5 (6.6)	22 (9.4)	10 (9.3)	0.01[d]

Data are expressed as median (interquartile range) or number (%). AR: aortic regurgitation; AS: aortic stenosis; CAVD: combined aortic valve disease; CMVD: combined mitral valve disease; MR: mitral regurgitation; MS: mitral stenosis; TR: tricuspid regurgitation.

[a] Denotes a significant Bonferroni-corrected post hoc pairwise difference between groups D and A, D and B, D and C.

[b] Denotes a significant Bonferroni-corrected post hoc pairwise difference between groups D and C.

[c] Denotes a significant Bonferroni-corrected post hoc pairwise difference between groups D and B.

[d] Denotes a significant Bonferroni-corrected post hoc pairwise difference between groups A and C.

[e] Group D had a higher proportion of AS or CAVD and a smaller proportion of AR.

by drugs and/or radiation, precluding specific diagnosis. A possible ''multihit'' phenomenon, combining several cardiac toxic effects, was evoked by Desaï et al. [29]. In patients with a history of radiotherapy for breast cancer, the incidence and prevalence of VHD are poorly documented in prospective cohorts with systematic echocardiography examination.

In a study by Hooning et al., 4% VHD was reported with a median follow-up of 18 years, and a higher risk of VHD (hazard ratio 3.17) in patients who received radiation therapy for breast cancer before 1979 [31].

Study limitations

Limitations are inherent to retrospective data collection and uncontrolled real-life studies. From the initial database, about 6% of benfluorex-exposed patients had severe VHD with evidence of benfluorex-mediated toxicity, and underwent cardiac surgery. However, this study population may not serve as an epidemiological basis, as around 2.6—5 million people [32] were exposed to benfluorex between 1976 and 2009, whereas fewer than 10,000 medical files (''the tip of the iceberg'') were examined, and the vast majority were sent by applicants who were still alive, on a self-declaration basis, resulting in selection bias. Therefore, it is not possible to deduce from this non-consecutive study population, the number of patients with moderate or severe DI-VHD who did or did not undergo cardiac surgery at a national level during the same period. Pathology was available in only 50% of patients; this low rate nevertheless reflects routine practice in cardiac operating theatres at a national level. Rheumatic fever is a classic differential diagnosis of DI-VHD, and was indeed very often suggested in benfluorex-exposed patients. Because of the miscellaneous presentations of rheumatic fever, also by geographical origin and ethnicity, one cannot exclude a higher prevalence of RHD than reported. Conversely, rheumatic VHD was repeatedly suggested in 94 (42%) medical records of the 222 patients with VHD with type 1 and type 2 pathology findings. Withdrawal of benfluorex occurred in November 2009, so randomized controlled trial testing of benfluorex toxicity is definitely unethical. In the future, longitudinal multicentre studies are likely to produce indisputable evidence of DI-VHD when a new potential valvulotoxic agent is marketed.

Conclusions

In conclusion, benfluorex — as well as other serotoninergic appetite suppressant agents — may produce severe regurgitant and/or stenotic VHD requiring valve surgery. Pathology in expert hands is key for demonstrating DI-VHD, and should be requested systematically in patients with VHD with a history of valvulotoxic drug intake. Benfluorex toxicity may superimpose on other conditions; conversely, other causes of VHD may supervene on drug-induced valve fibrosis.

Sources of funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Acknowledgements

The authors are indebted to Dr Vincent Auffret (CHU Rennes) for statistical assistance. The members of the Benfluorex Committee for the ONIAM are: André Cariou, MD; Daniel Czitrom, MD; Jean-Marc Dubois, MD; Iradj Gandjbakhch, MD; Emmanuel Gras, MD; Jean-Pierre Gueffet, MD; Alain Leguerrier, MD; Jean-Philippe Lesbre, MD; Sylvestre Maréchaux, MD; and Jacques Paulet, MD.

Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.acvd.2022.03.006.

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