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Drug-induced aortic valve stenosis: An under recognized entity

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ABSTRACT

Background: We have been intrigued by the observation that aortic stenosis (AS) may be associated with characteristic features of mitral drug-induced valvular heart disease (DI-VHD) in patients exposed to valvulopathic drugs, thus suggesting that beyond restrictive heart valve regurgitation, valvulopathic drugs may be involved in the pathogenesis of AS.
Methods: Herein are reported echocardiographic features, and pathological findings encountered in a series of patients suffering from both AS (mean gradient >15 mm Hg) and mitral DI-VHD after valvulopathic drugs exposure. History of rheumatic fever, chest radiation therapy, systemic disease or bicuspid aortic valve disease were exclusion criteria.
Results: Twenty-five (19 females, mean age 62 years) patients having both AS and typical features of mitral DI-VHD were identified. Mean transaortic pressure gradient was 32 +/− 13 mm Hg. Aortic regurgitation was ≥ mild in 24 (96%) but trivial in one. Known history of aortic valve regurgitation following drug initiation prior the development of AS was previously diagnosed in 17 patients (68%). Six patients underwent aortic valve replacement and 3 both aortic and mitral valve replacement. In the 9 patients with pathology analysis,

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aortic valvular endocardium was markedly thickened by dense non-inflammatory fibrosis, a characteristic feature of DI-VHD.

Conclusion: The association between AS and typical mitral DI-VHD after valvulopathic drug exposure may not be fortuitous. Aortic regurgitation was usually associated to AS and preceded AS in most cases but may be lacking. Pathology demonstrated the potential role of valvulopathic drugs in the development of AS.

1. Introduction

Several studies have consistently demonstrated that fenfluramine derivatives as well as ergot alkaloids and pergolide exposure are associated with the development of restrictive heart-valve regurgitation [1–5]. Activation of the cardiac valves 5-HT_{2B} receptor by norfenfluramine (active metabolite of benfluorex, dexfenfluramine and fenfluramine) ergotamine, methylergonovine (active metabolite of methysergide) and pergolide is thought to be the main mechanism of development of drug-induced valvular heart disease (DI-VHD) [6]. McDonald and coworkers demonstrated that valvulopathic drugs produce distinctive features from valve lesions associated with other pathologies including rheumatism and degenerative lesions [7]. Endocardial fibrosis of the leaflets is associated with chordal thickening, retraction and fusion at the level of the mitral valve apparatus; the valve architecture is well preserved without inflammation or neovascularization [7]. There is however increasing evidence that benfluorex also produces other DI-VHD features than mere restrictive fibrotic valve regurgitation. We have long been intrigued by the clinical observation that aortic valve stenosis (AS) may be associated with characteristic features of mitral DI-VHD, thus suggesting that beyond restrictive heart valve regurgitation, fenfluramine derivatives may be involved in the pathogenesis of AS. Hence we report here echocardiographic features and pathological findings when available of a multicenter series of 25 patients exposed to valvulopathic drugs with typical echocardiographic features of mitral DI-VHD associated with AS.

2. Methods

Cardiology departments of public and private medical centers were contacted by e-mail and invited to participate to this retrospective multicenter observational study. All patients had a history of intake of drugs known to produce VHD (rye ergot alkaloids, fenfluramine/phentermine, dexfenfluramine, benfluorex, ergot derivatives including pergolide and cabergoline). Drug exposure had to precede symptoms, cardiac murmur, or diagnosis of echocardiographic abnormalities. Patients were included if they had a typical aspect of mitral DI-VHD including leaflet thickening, retraction towards the ventricular apex during systole (leaflet tenting), reduced valve mobility, and/or thickening and shortening of the chordae tendineae and a mean transaortic pressure gradient >15 mm Hg. Exclusion criteria were rheumatic VHD or history of rheumatic fever, radiation-induced VHD, bicuspid aortic valve and systemic disease known to induce restrictive VHD.

Data including demographic characteristics, cardiovascular risk factors, and surgical and pathology reports were obtained by chart review. Daily doses of benfluorex and total treatment duration were obtained. The duration of dexfenfluramine was less accurate as this valvulopathic drug was withdrawn from the international market in 1997. The duration of ergotamine exposure was more than twenty years.

Echocardiograms were performed on commercially available ultrasound machines. Mean transaortic pressure gradient was obtained using continuous-wave Doppler. Presence of aortic valve calcifications on echocardiography was also reported. Aortic and mitral valve

Table 1
Characteristics of the patient population.

Case	Gender (M/F)	Age (years)	BMI	CV risk factors	Benfluorex exposure duration (years)	DXF	ME	MPG (mm Hg)	Isolated AR History	AR (grade)	AV $Ca2^+$	MR (grade)	AVR	Pathology
1	M	73	32	HTN,CT	6	−	−	27	+	2	0	2		
2	F	55	24	CT,DM,SM	6	−	−	17	+	2	0	3	+	+
3	F	45	21	SM	7	−	−	19	+	2	0	0		
4[a]	F	59	32	HTN,CT	−	1	−	45	+	3	0	3		
5	F	79	27	HTN,CT,DM	9	1	−	19		1	0	1		
6	F	48	30	CT,SM	8	−	−	30	+	3	0	0	+	+
7	F	59	34	HTN,CT,DM,SM	10	1	−	25		2	0	2		
8	F	57	30	HTN, CT	13	−	−	20	+	2	0	1		
9	F	73	26	−	−	−	1	29		1	0	0		
10	F	69	29	HTN	11	−	−	26	+	3	0	1	+	+
11	F	63	30	HTN,CT	8	−	−	23		3	0	2		
12	F	49	33	HTN,SM	0.75	−	−	23		3	0	1		
13	F	80	30	HTN,CT	9	−	−	21	+	2	0	2		
14	M	60	33	CT	6	−	−	32		3	1	0	+	+
15	F	72	24	HTN,CT,DM	8	−	−	62	+	2	1	1	+	+
16	F	58	40	HTN,CT,DM	12	−	−	36	+	Trivial	1	0	+	+
17	M	56	22	HTN,CT,DM,SM	15	1	−	65	+	2	1	3	+	+
18	F	68	34	HTN,CT,DM	26	1	−	53	+	1	1	3	+	+
19	F	67	28	HTN,CT,DM	8	−	−	23	+	2	1	3	+	
20	M	82	25	HTN,CT,SM	10	−	−	31	+	1	1	1		
21	F	70	30	CT	12	−	−	23	+	2	1	3	+	+
22	F	57	37	SM	2	−	−	44	+	3	1	1	+	
23	M	55	37	HTN,CT,DM	0.5	−	−	30		2	1	1	+	
24	F	39	27	HTN,SM	0.5	−	−	41		3	1	1		
25	M	65	30	HTN,CT,DM	6	−	−	42	+	3	1	1		

M: male, F: female, BMI: body mass index, MPG: mean pressure gradient ; AR: aortic valve regurgitation, MV: mitral valve ; MR: mitral regurgitation; AVR: aortic valve replacement; DXF: dexfenfluramine; $AVCa2^+$: aortic valve calcifications. HTN: hypertension, CT: high cholesterol, CV: cardiovascular; DM: diabetes mellitus, ME: methysergide; SM: smoker.

[a] This patient had mechanical mitral valve replacement 22 years earlier due to drug-induced mitral valve disease.