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CASE SERIES
Cardiac Imaging

Caseous necrosis of the mitral annulus: a new feature of drug-induced valvular heart disease? Case series

Tiphaine Leblon [1], Clemence Riolet[1], PierreVladimir Ennezat [2], Sylvestre Marechaux[1]*

[1]Lille Catholic hospitals, Heart Valve Center, Cardiology Department, ETHICS EA 7446, Lille Catholic University, France; and [2]Henri Monder University Hospital, Cardiology department, Paris, France

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Background Drug-induced valvular heart disease (DI-VHD) is a well-defined condition associated with specific pathology features. However, clinical presentations may broadly vary and thereby make DI-VHD diagnosis more challenging.

Case summary We report two patients with a history of benfluorex administration, who developed extensive mitral calcific lesions which evolved towards caseous necrosis.

Discussion Prospective follow-up over several years of these two patients who initially had typical DI-VHD findings provided monitoring evidence of extensive calcifications and subsequent caseous necrosis. These reports suggest a link between calcific heart injury and benfluorex exposure. The diagnosis of DI-VHD may be overlooked at this late stage.

Keywords Caseous necrosis • Benfluorex • Mitral annulus • Case report

ESC Curriculum 2.2 Echocardiography • 4.2 Aortic stenosis • 4.4 Mitral stenosis

Learning points

- Drug-induced valvular heart disease (DI-VHD) may evolve into extensive calcific valvular lesions.
- Possibility of caseous mitral annular calcification in DI-VHD should be explored.
- Importance of a long-term longitudinal follow-up in patients with initially mild DI-VHD.

Introduction

Benfluorex has been marketed since 1976 in Europe, Asia, and South America for the management of overweight diabetic patients and dyslipidaemia. Benfluorex, also widely prescribed off-licence as a slimming-aid, has been involved in the development of fibrotic valvular diseases with restrictive motion (Carpentier type III) owing to its fenfluramine-like properties,[1] resulting in its withdrawal from the market in 2009.[2–4]

* Corresponding author. Tel: +33 3 20 22 59 24, Fax: +33 3 20 22 38 59, Email: Marechaux.Sylvestre@ghicl.net
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Caseous calcification of the mitral annulus is rarely described; it is thought to result from mitral annular calcification (MAC). This latter condition is more common in the elderly, especially in women.[5] Annulus calcifications rarely occur in young patients but may be found in those with advanced renal failure or others with calcium metabolism disorders. Another source of premature onset of annular calcifications might be exposure to benfluorex.[6] Rare cases involving benfluorex in the development of valvular calcifications have been previously reported.

We here report two patients with known typical drug-induced valvular heart disease (DI-VHD), who progressively developed large valvular calcifications and subsequent caseous necrosis.

Timeline

Case report 1	
More than 20 years prior to presentation	Six months period of exposure to Benfluorex
Over the last 10 years prior to presentation	Several episodes of cryptogenic ischaemic stroke
Presentation	Progressive mitral annular calcification with evidence of caseous necrosis at presentation.
Case 2	
More than 20 years prior to presentation	Exposure to Benfluorex for a few months
Over the last 10 years prior to presentation	Restrictive mitral and aortic regurgitation, with a typical aspect of drug-induced valvular heart disease Progression to valvular (aortic and mitral) stenosis with extensive calcifications
Presentation	First episode of heart failure in the context of severe aortic stenosis Diagnosis of caseous necrosis of the mitral annulus

Case presentation

Case 1

A 68-year-old woman with a history of hypertension and dyslipidaemia was admitted in 2011 for the first episode of cryptogenic right-sided hemiplegia. She had no past medical history. Cardiovascular examination was unremarkable. The diagnostic procedure included prolonged Holter monitoring and Doppler ultrasonography of the supra-aortic trunks; both were non-contributive. Bubble study was negative but a typical aspect of DI-VHD was found on transthoracic echocardiography (TTE). The mitral leaflets appeared thickened with reduced valve mobility and shortening of the chordae tendineae, and there was also mild mitral posterior annulus calcification and central mild aortic regurgitation (*Videos 1–3*, Supplementary material online, *Video S1*). Benfluorex exposure as a slimming aid for a 6-month period more than 20 years ago was found.

Similar neurological presentations developed in 2016, 2017, and 2020, with normal cardiovascular examinations, Holter recordings, and aortic trunk Doppler findings. Bubble studies remained negative but successive TTEs documented progressive MAC (*Figure 1A* and *B*, 2017 and 2020 TTE findings, Supplementary material online, *Videos 2–4*). At the time of the last neurological episode, there was evidence of caseous necrosis of the annular calcification (Supplementary material online, *Videos S3* and *S4*; *Figure 1B* and *C*). Given the stereotyped clinical presentation at each episode and the repeatedly normal brain magnetic resonance imaging results, the ultimate neurological diagnosis was epileptic seizures. Neither anticoagulation therapy nor cardiac surgery was indicated for the calcific mass. No intervention was performed. The clinical follow-up has been uneventful as of June 2021.

Case 2

A 77-year-old woman underwent a systematic cardiovascular evaluation for type-2 diabetes. She had a history of systemic hypertension and dyslipidaemia, and her body mass index was 33 kg/m^2. She was currently taking metformin, amlodipine, and irbesartan/

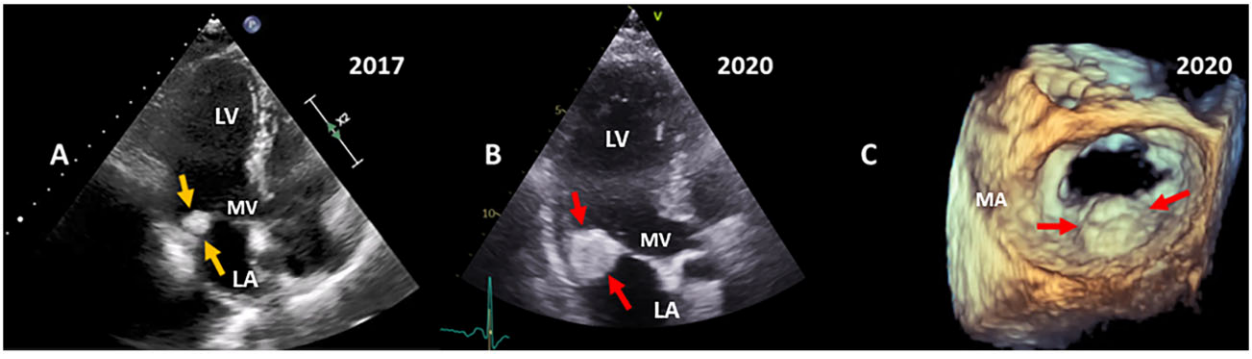


Figure 1 Transthoracic apical three-chamber view showing progression of an ovoid shaped, hyperdense mass at the posterior mitral annulus (*A* and *B*, 2017 and 2020 findings respectively, yellow and red arrows), suggestive of caseous mitral annular calcification. 3D-transesophageal echocardiography with atrial view of the mitral annulus (*C*). LA, left atrium; LV, left ventricle; MA, mitral annulus; MV, mitral valve.

hydrochlorothiazide. She had no cardiovascular symptoms and the physical examination was normal. Holter monitoring and Doppler ultrasonography of the supra-aortic trunks were normal. Transthoracic echocardiography revealed isolated restriction of mitral and aortic valve motion (Supplementary material online, *Videos S5* and *S6*). A history of benfluorex exposure for diabetes in the context of overweight for a long period of 10 years was reported.

Extensive calcifications of both mitral and aortic valves developed secondarily. Severe aortic stenosis associated with caseous necrosis of the mitral annulus and moderate mitral stenosis was found during the first episode of left-sided heart failure in 2019 (*Figure 2*). No pulmonary hypertension was suspected at Doppler ultrasonography. A vibratile element was also observed in the caseous necrosis (*Figure 3*, Supplementary material available online, *Videos S7–S9*), raising the possibility of added endocarditis that was ruled out by the clinical presentation, multiple negative blood cultures, and the lack of any clinical or biological deterioration despite the absence of antibiotic therapy. A transcatheter aortic valve replacement procedure was successfully performed in early 2020 (Edwards Sapien 3 23 mm). One-year follow-up was uneventful. The last echocardiographic examination performed in October 2021 demonstrated the normal function of the prosthetic aortic valve (aortic valve area 1.4 cm^2, Doppler velocity index 0.34 and mean gradient 15 mmHg); mitral stenosis remained moderate (mean transmitral gradient 5 mmHg).

Discussion

A 10.6% prevalence of MAC has been previously reported in echocardiographic studies.[7,8] Among patients with the calcific annular process, 0.6% caseous necrosis was documented representing 0.06% of the study population.[7,8] The 2.7% prevalence of caseous necrosis in the case of MAC on post-mortem examination suggests underdiagnosis using cardiac imaging.[5]

The appetite suppressant benfluorex activates the serotonin 5-HT2B receptor pathway that may lead to cellular proliferation and cardiac valvular fibrosis.[1,9,10] In France, epidemiology studies found that the period of use of benfluorex from 1976 to 2009 is approximately responsible for 3100 hospitalizations and 1300 deaths due to valvular insufficiency.[11] A prospective multi-centre case–control study demonstrated that the use of benfluorex was associated with a three-fold increase in the frequency of left heart valve regurgitation in diabetic patients.[12] Even though the molecule has been banned more than one decade ago from the European market following clinical

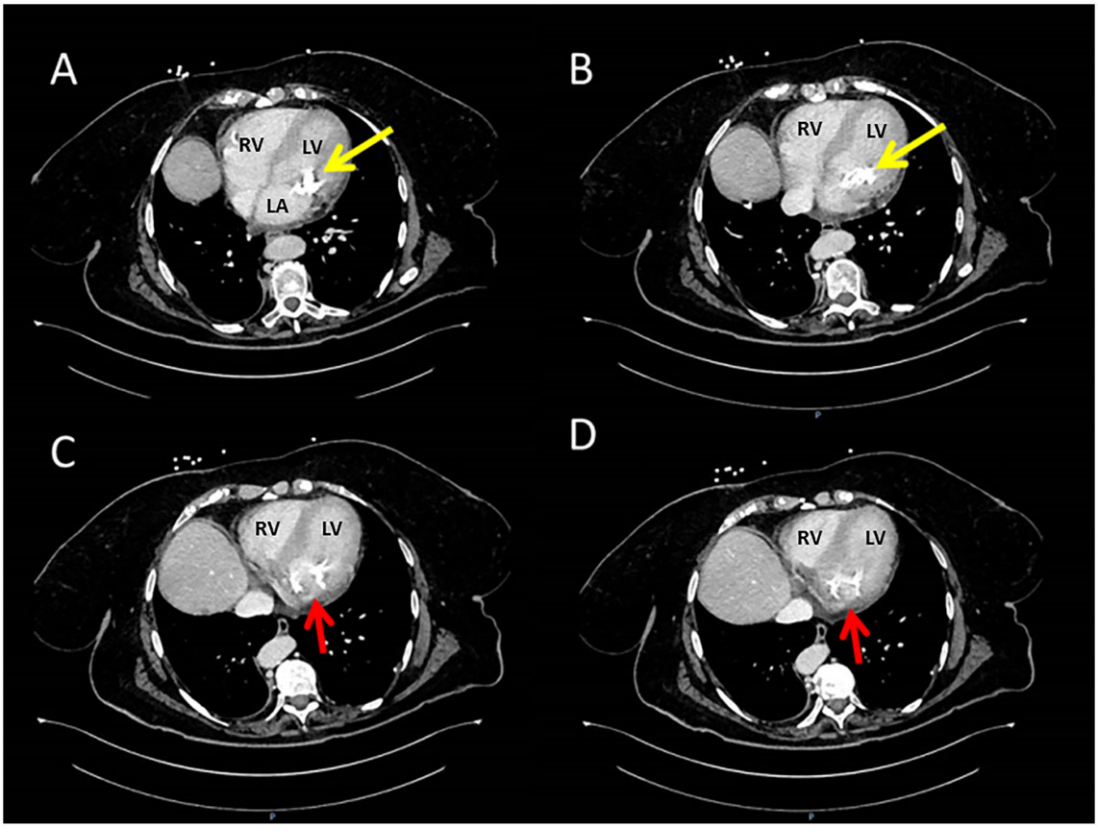


Figure 2 Cardiac computed tomography showing an ovoid shaped, hyperdense mass of the posterior mitral annulus (*A* and *B*, yellow arrows), suggestive of caseous mitral annular calcification, and a central area of lower density attenuation (*C* and *D*, red arrows), consistent with progressive caseous necrosis. LA: left atrium; LV, left ventricle; RV, right ventricle.

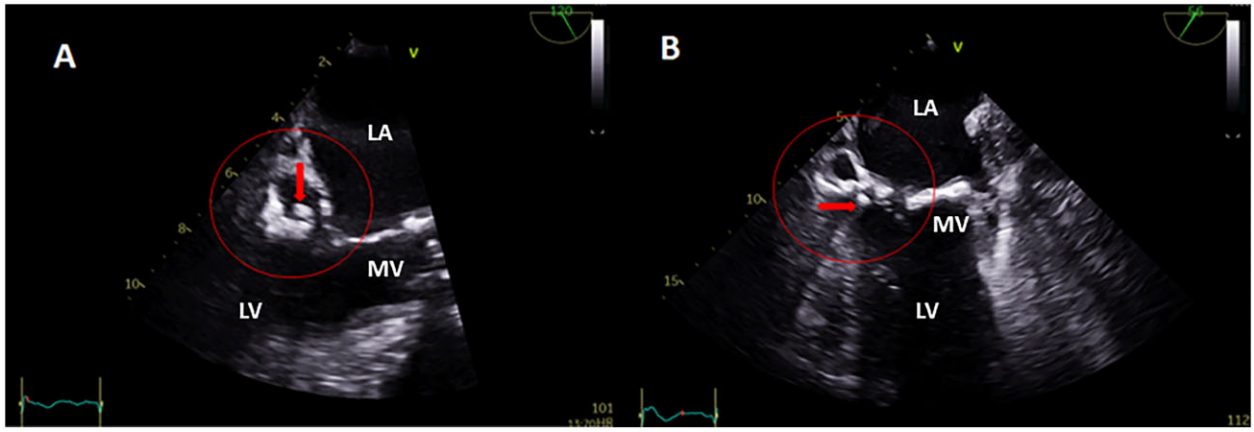
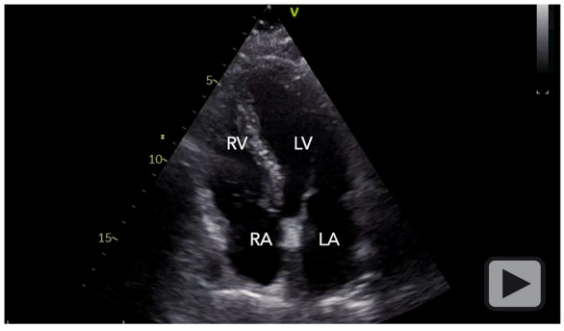
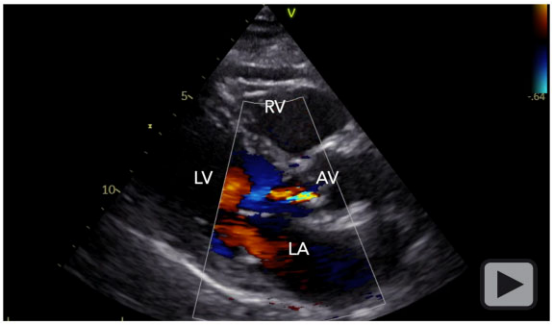


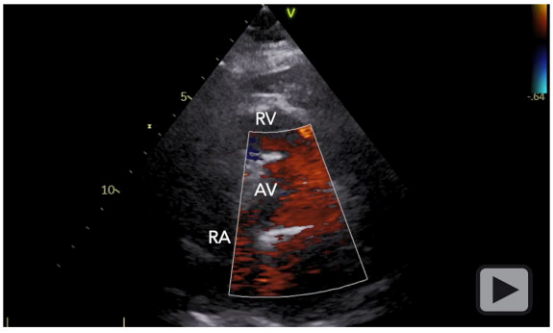
Figure 3 Transoesophageal echocardiography (*A* and *B*, 120-long axis and bicommissural views respectively) of Patient 2, showing caseous necrosis (red circle), with a vibratile element inside (red arrows), raising the possibility of added endocarditis that was ultimately ruled out. LA, left atrium; LV, left ventricle; MV, mitral valve.



Video 1 Transthoracic echocardiography, patient 1, apical 4 chamber view, showing restricting motion of the mitral valve. LA, left atrium; RA, right atrium; LV, left ventricle; RV, right ventricle.



Video 3 Transthoracic echocardiography with color flow Doppler, parasternal long-axis view, showing mild aortic regurgitation and mild mitral posterior annulus calcification.



Video 2 Transthoracic echocardiography with color flow Doppler, parasternal short axis view, showing central mild aortic regurgitation.

observations of severe restrictive VHD following benfluorex exposure,[2–4] the number of exposed patients remains considerable.

Routine diagnosis of DI-VHD is based on morphological echocardiographic abnormalities. For the mitral valve, characteristic features of DI-VHD are leaflet thickening, retraction towards the ventricular apex during systole resulting in leaflet tenting, reduced valve mobility, and/or thickening and shortening of the chordae tendineae.[13] For the aortic valve, characteristic features include the systolic subtle dome-like appearance of the leaflets, valvular thickening, reduced mobility, and/or incomplete diastolic coaptation resulting in a small central triangular valve hiatus during diastole in the short-axis view and thereby central aortic regurgitation.[13] These echocardiographic characteristics, although not pathognomic, are highly specific for drug toxicity, as only one among 376 diabetic patients not exposed to benfluorex from Tribouilloy's study had echocardiographic features of DI-VHD (0.26%).[14] Pathology analysis provides specific features including non-

inflammatory sub-endocardial fibrosis without valve architecture distortion. While calcifications have been seldom reported in DI-VHD,[6] no prospective link between caseous necrosis and benfluorex intake has been established so far.

We report here for the first time longitudinal alterations in valvular morphology and function in patients who initially had typical echocardiographic features of DI-VHD and secondarily had progressive valvular calcifications, MAC, and caseous necrosis. Hence, these two cases illustrate that underlying DI-VHD cannot be ruled out in patients who were previously exposed to valvulotoxic drugs and present with extensive valvular calcifications, MAC, and caseous necrosis. Similar to benfluorex-associated pulmonary arterial hypertension,[15] DI-VHD may progressively worsen late after the cessation of benfluorex therapy. Drug-induced endocardial fibrosis may trigger the calcific process. Conversely, secondary calcifications related to aging and vascular risk factors including diabetes, dyslipidaemia, and chronic kidney dysfunction may supervene upon drug-induced valve fibrosis and thereby produce valve stenosis. Of note, Tribouilloy *et al.*[12] showed that diabetic patients previously exposed to benfluorex had a 4.2-fold increased risk of valvular regurgitation compared with diabetic patients not receiving benfluorex despite a similar cardiovascular risk factors background. Large case/control studies are needed to estimate the prevalence of this condition and to ascertain the causality between valvulotoxic drugs exposure and MAC/caseous necrosis.

Conclusion

Prospective follow-up over several years of these two patients who initially had typical DI-VHD provided monitoring evidence of extensive calcifications and subsequent caseous necrosis. These reports suggest a link between calcific heart injury and benfluorex exposure. Hence, the diagnosis of DI-VHD may be overlooked at this late stage.

Lead author biography

Tiphaine Leblon was born on 23 April 1992. She works as fellow in cardiovascular imaging at the Cardiology department, 'GCS- Groupement des Hôpitaux de l'Institut Catholique' in Lille, France. Her line of research is focused on valvular heart disease and drug-induced valvulopathy.

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Supplementary material

Supplementary material is available at *European Heart Journal—Case Reports* online.

Slide sets: A fully edited slide set detailing these cases and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report, including images and associated text, has been obtained from the patient in line with COPE guidance.

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References

1. Boutet K, Frachon I, Jobic Y, Gut-Gobert C, Leroyer C, Carlhant-Kowalski D et al. Fenfluramine-like cardiovascular side-effects of benfluorex. *Eur Respir J* 2009; **33**:684–688.
2. Frachon I, Etienne Y, Jobic Y, Le Gal G, Humbert M, Leroyer C. Benfluorex and unexplained valvular heart disease: a case-control study. *PLoS One* 2010;**5**: e10128.
3. Tribouilloy C, Rusinaru D, Henon P, Tribouilloy L, Leleu F, Andréjak M et al. Restrictive organic mitral regurgitation associated with benfluorex therapy. *Eur J Echocardiogr* 2010;**11**:614–621.
4. Weill A, Païta M, Tuppin P, Fagot JP, Neumann A, Simon D et al. Benfluorex and valvular heart disease: a cohort study of a million people with diabetes mellitus. *Pharmacoepidemiol Drug Saf* 2010;**19**:1256–1262.
5. Pomerance A. Pathological and clinical study of calcification of the mitral valve ring. *J Clin Pathol* 1970;**23**:354–361.
6. Plurien F, Bruneval P, Jobic Y, Iung B, Ennezat PV. Calcifications in benfluorex-induced valve heart disease: a misknown association. *Cardiology* 2015;**130**: 87–90.
7. Deluca G, Correale M, Ieva R, Del Salvatore B, Gramenzi S, Di Biase M. The incidence and clinical course of caseous calcification of the mitral annulus: a prospective echocardiographic study. *J Am Soc Echocardiogr* 2008; **21**:828–833.
8. Harpaz D, Auerbach I, Vered Z, Motro M, Tobar A, Rosenblatt S. Caseous calcification of the mitral annulus: a neglected, unrecognized diagnosis. *J Am Soc Echocardiogr* 2001;**14**:825–831.
9. Roth B. Drugs and valvular heart disease. *N Engl J Med* 2007;**356**:6– 9.
10. Rothman R, Baumann M, Savage J, Rauser L, McBride A, Hufeisen S et al. Evidence for possible involvement of 5-HT(2B) receptors in the cardiac valvulopathy associated with fenfluramine and other serotonergic medications. *Circulation* 2000;**102**:2836– 2841.
11. Fournier A, Zureik M. Estimate of deaths due to valvular insufficiency attributable to the use of benfluorex in France. *Pharmacoepidemiol Drug Saf* 2012;**21**: 343–351.
12. Tribouilloy C, Rusinaru D, Maréchaux S, Jeu A, Ederhy S, Donal E et al. Increased risk of left heart valve regurgitation associated with benfluorex use in patients with diabetes mellitus. A multicenter study. *Circulation* 2012;**126**: 2852–2858.
13. Tribouilloy C, Rusinaru D, Andrejak M. How can benfluorex-related heart valve disease be identified by echocardiography? *Arch Cardiovasc Dis* 2011;**104**: 489–492.
14. Tribouilloy C, Marechaux S, Jobic Y, Jeu A, Ederhy S, Donal E et al. Frequency of drug-induced valvular heart disease in patients previously exposed to benfluorex: a multicentre prospective study. *Eur Heart J* 2013;**34**:3580–3587.
15. Savale L, Chaumais MC, Cottin V, Bergot E, Frachon I, Prevot G et al. Pulmonary hypertension associated with benfluorex exposure. *Eur Respir J* 2012;**40**: 1164–1172.