Progression of Left Valve Disease during Use of Dopaminergic Drugs

Lívia Santana Barbosa, Ana Clara Tude Rodrigues, Shirlei Novillo Pereira, Hugo Leonardo Medeiros Vieira, Kamila Fernanda Staszko, José Lázaro Andrade

Instituto de Radiologia do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP - Brazil

Abstract

Cabergoline and bromocriptine are dopaminergic drugs deriving from ergot and used for treating hyperprolactinemic idiopathic disorders or pituitary adenomas, whose mechanism of action results from the reduction of prolactin secretion. Some reports in the literature show that cabergoline can cause valvular heart disease after long-term administration. We report the case of a patient diagnosed with macroprolactinoma who did interleaved use of cabergoline and bromocriptine and developed valvular abnormalities that did not exist before.

Case Report

Male patient, 61 years old, followed up in an Endocrinology Service at a tertiary hospital since the age of 22 due to macroprolactinoma diagnosed after sudden loss of the right eyesight, confirmed by magnetic resonance imaging (MRI) of the head/pituitary gland and laboratory tests. The patient was initially treated clinically and subsequently undergone transfrontal hypophysectomy. Two years after surgery, he developed headache and left superior temporal quadrantanopia and was diagnosed tumor recurrence, requiring further surgery, followed by radiotherapy. On the occasion, the patient presented pan-hypopituitarism and was treated with specific medications (testosterone, prednisone, hydrochlorothiazide and levothyroxine). At 26, there was a progressive increase in prolactin levels. Bromocriptine (2.5 mg/day) was introduced and subsequently discontinued due to the normalization of hormonal levels. The patient abandoned the follow-up for 13 years and returned with symptoms of hypogonadism, when bromocriptine was reintroduced and follow-up was started with annual transthoracic echocardiograms. The initial echocardiogram showed valves with normal morphology and dynamics without dysfunction (Figure 1A, Figure 1B). After 2 months, the patient had intolerance to bromocriptine (nausea, dry mouth and headache), which was replaced with cabergoline (0.5 mg/day 4 times a week). At that time, further echocardiogram scan was unchanged compared to the original one. Upon return after 2 years, the patient was asymptomatic, but the physical examination described mitral systolic murmur. Echocardiogram revealed mitral valve with slight thickening and slightly decreased mobility of the posterior cusp without significant stenosis, with mild eccentric regurgitation. The aortic valve was slightly thickened and with mild regurgitation (Videos 1 and 2, Figure 2A, Figure 2B, Figure 2C and Figure 2D). One year from the last return, still in use of medication, echocardiogram showed thickened mitral valve, with decreased mobility of the cusps and the degree of regurgitation had risen to moderate, with jet directed to the atrial septum and aortic valve slightly thickened, with mild regurgitation. Cabergoline was then discontinued and bromocriptine was reintroduced; however, sequential echocardiograms still showed progression of mitral valve disease, with marked thickening and appearance of valvular fibrosis extending to the subvalvular apparatus, leading to reduced opening of the cusps. Regurgitation remained moderate, but maximum and medium left atrial-left ventricular diastolic gradients had increased, estimated at 15 mmHg and 6 mmHg, respectively, and the valve area estimated at 1.8 cm^2 by pressure half time (PHT) . Aortic regurgitation remained unchanged (Figure 3A, Figure 3B, Figure 3C and Figure 3D). Despite the evolution of valvular heart disease, the patient remained in use of bromocriptine; the medication was discontinued only after the age of 61 (2016), when a new echocardiogram scan was performed, showing mitral valve with mild thickening and valvular and subvalvular fibrosis with reduced opening of the cusps and maximum and medium gradients estimated at 23 mmHg and 9 mmHg, respectively, and valve area estimated at 1.6 cm^2 by PHT and planimetry (Figure 4A, Figure 4B, Figure 4C and Figure 4D). Worsening of regurgitation was graded as moderate to severe. The aortic valve still presented slight regurgitation with maximum aortic systolic gradient estimated at 15 mmHg (Videos 3 and 4). Serial echocardiographic description is detailed in Table 1. The patient was maintained with no dopamine antagonists. Only with hormonal control because of the appropriate levels of prolactin; MRI of the pituitary gland showed residual tumor with stable size and volume; the patient is currently under follow-up of valvular lesions in the Cardiology Service of the same tertiary hospital.

Discussion

Dopamine agonists, especially bromocriptine and cabergoline, through their specific agonist action at dopaminergic D2 receptors, inhibit the secretion of prolactin.[1] These drugs have a high affinity for 5-HT 2B serotonin receptors that are present in the heart valves; these receptors mediate mitogenesis leading to the proliferation of fibroblasts.[2] Most studies reported

Keywords

Prolactinoma/diagnosis; Prolactinoma/surgery; Bromocriptine/effects adverse; Heart Valve Diseases/physiopathology; Echocardiography; Magnetic Resonance Spectroscopy.

Mailing Address: Dra. Lívia Santana Barbosa •
Serviço de Ecocardiografia – Instituto de Radiologia (InRad)
Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo
Rua Dr. Ovídio Pires de Campos, 75. Postal Code 05403-010, Cerqueira César, São Paulo, SP – Brazil
E-mail: liviasb12@hotmail.com
Manuscript received February 15, 2017; revised February 20, 2017; accepted February 20, 2017.

DOI: 10.5935/2318-8219.20170017

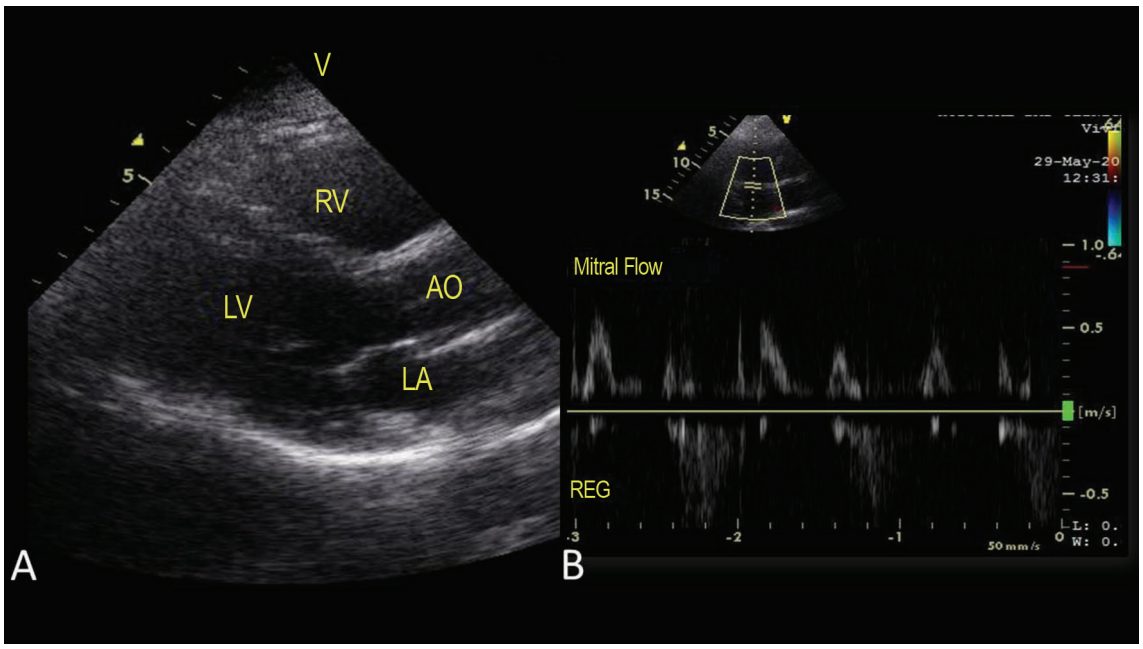
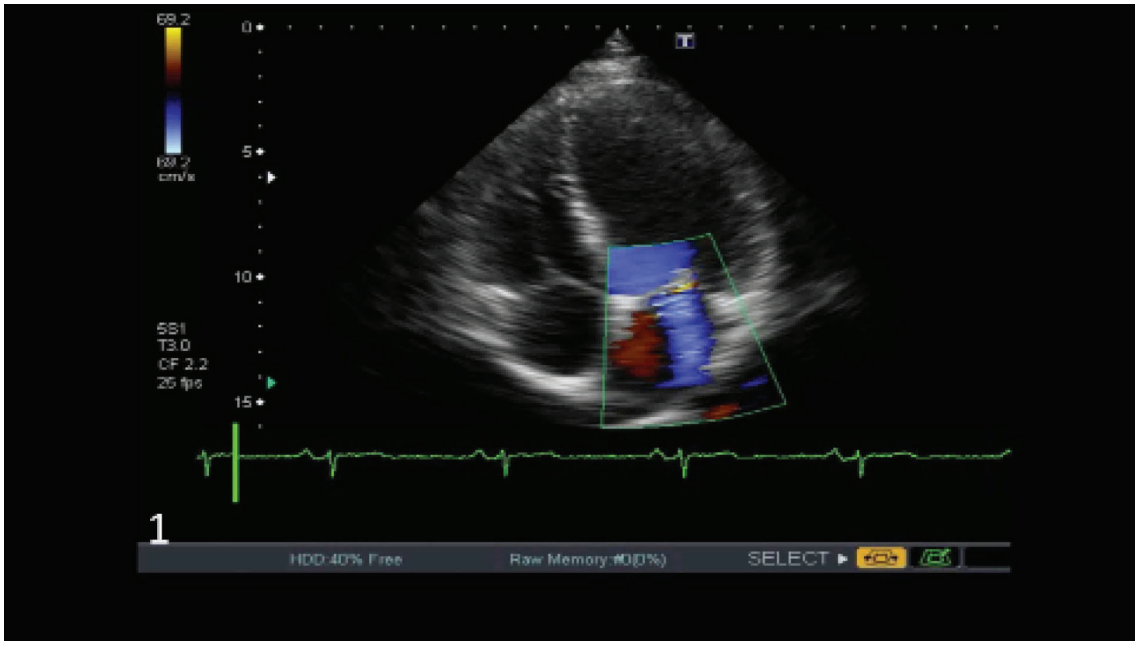
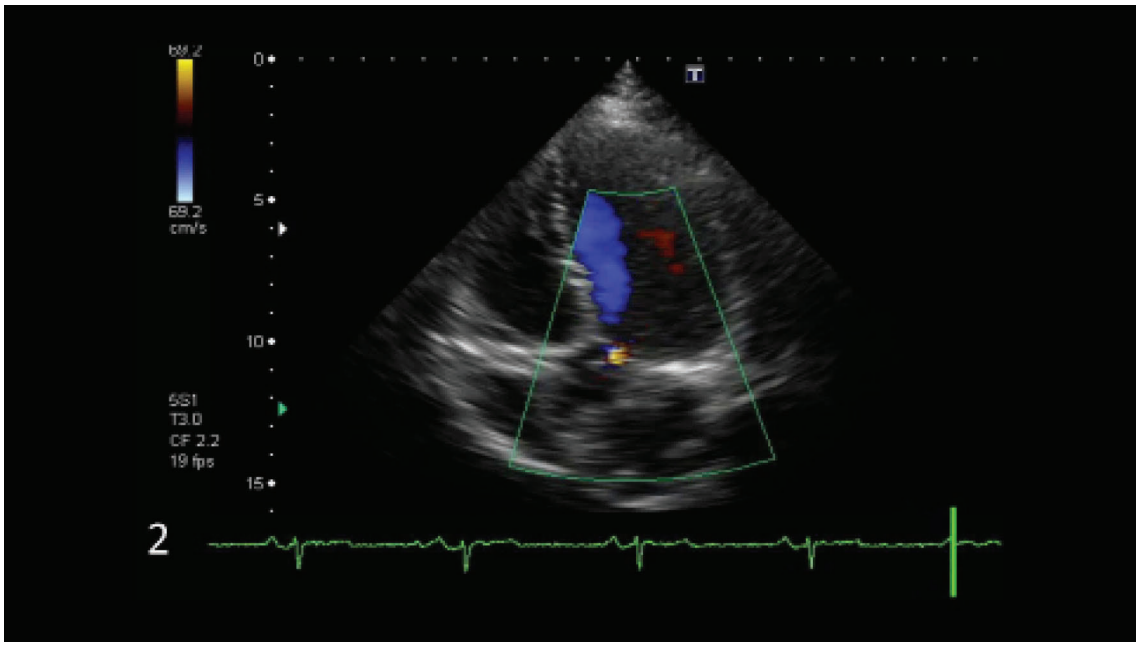


Figure 1 - *Initial Echocardiography before the use of dopaminergic medication. A - Longitudinal parasternal view showing normal mitral and aortic valves; B - Pulsed transmitral Doppler showing normal flow. LA: left atrial; AO: aorta; RV: right ventricle; LV: left ventricle.*



Video 1 – *Echocardiogram after 2 years of dopaminergic medication: Apical 4-chamber view showing mitral valve with mild thickening, mild decrease in mobility and opening of the posterior cusp and mild eccentric regurgitation. Watch the videos here: http://departamentos.cardiol.br/dic/publicacoes/revistadic/2017/v30_2/video_v30_2_178_ingles.asp*



Video 2 – *Echocardiogram after 2 years of dopaminergic medication: Apical 5-chamber view showing aortic valve with mild regurgitation. Watch the videos here: http://departamentos.cardiol.br/dic/publicacoes/revistadic/2017/v30_2/video_v30_2_178_ingles.asp*

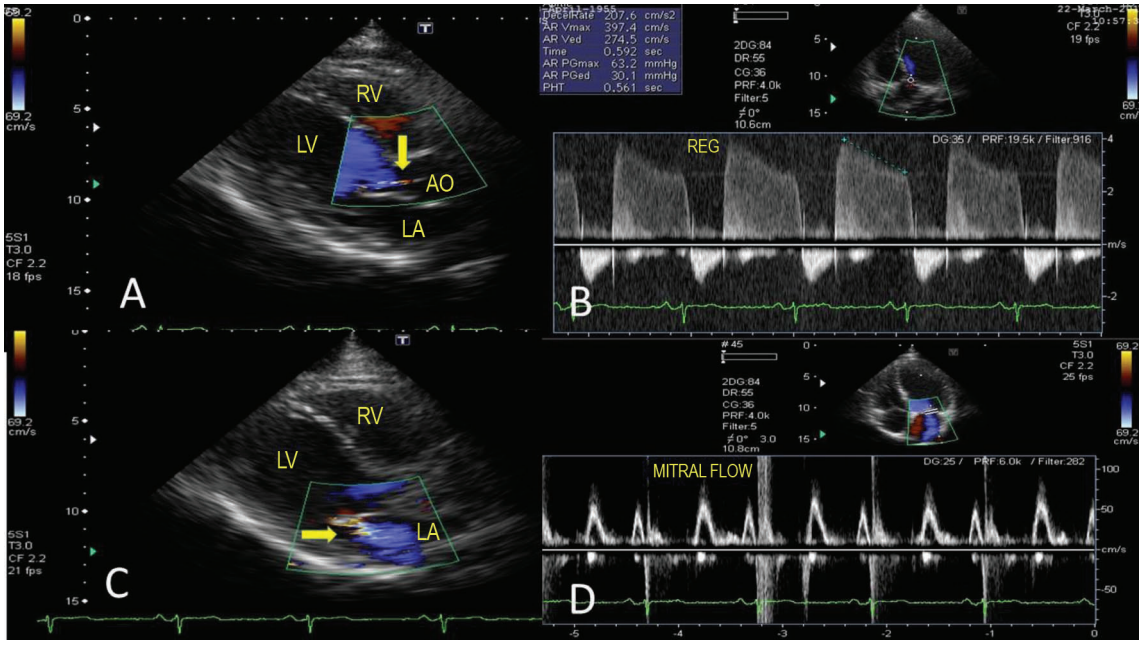


Figure 2 - *Echocardiogram after 2 years of dopaminergic medication. A and B - Longitudinal parasternal view and apical view showing mild aortic regurgitation on color flow mapping (yellow arrow) and continuous Doppler; C and D - color flow mapping and pulsed Doppler showing minimal mitral regurgitation (yellow arrow). RA: right atrium; LA: left atrium; AO: aorta; RV: right ventricle; LV: left ventricle.*

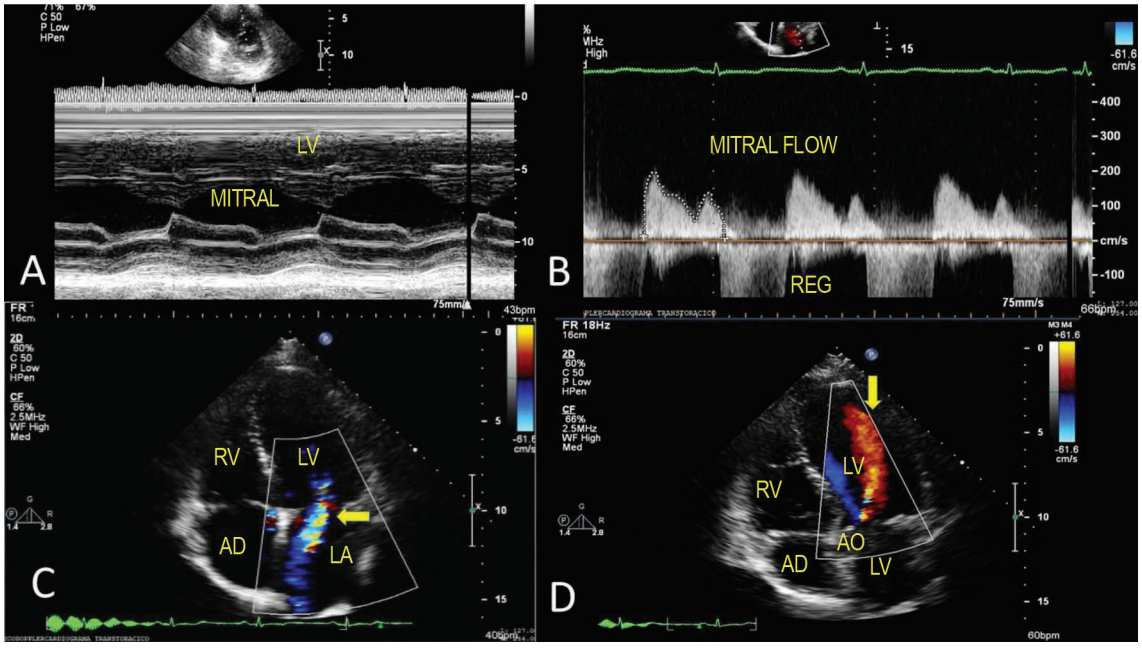
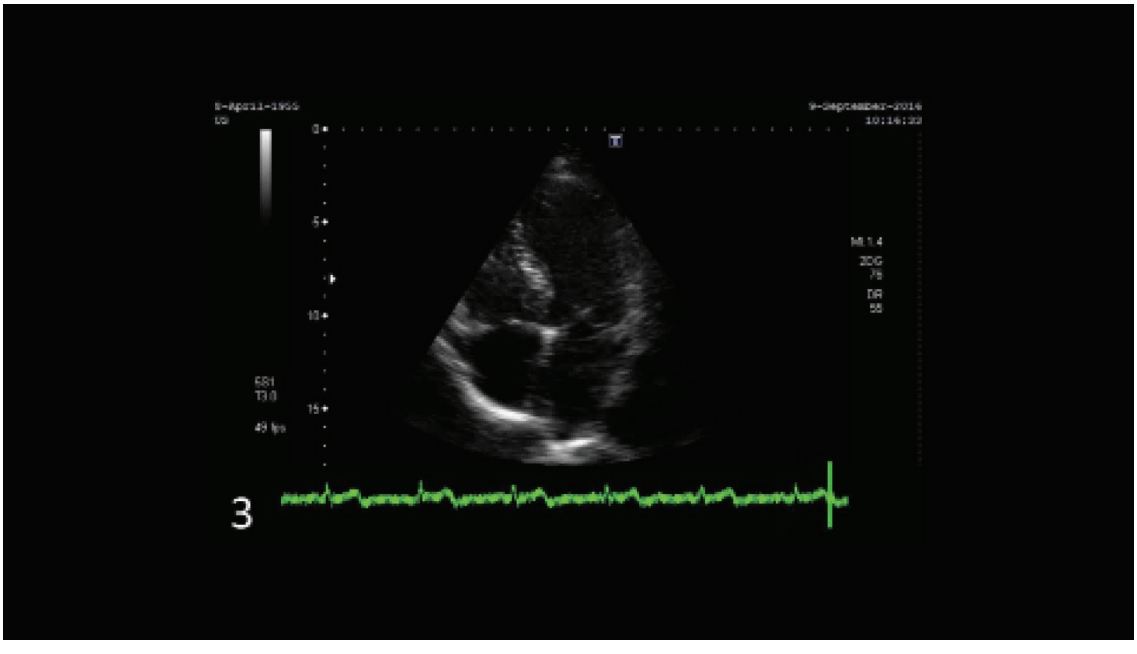


Figure 3 - *Echocardiogram after 4 years of dopaminergic medication. A - Short axis parasternal view, M mode, showing mitral valve with marked thickening; B - Transmitral continuous Doppler showing diastolic gradient LA-LV 15 mmHg and 6 mmHg (medium and peak, respectively) and mitral regurgitation; C and D - Apical view with color flow mapping showing moderate mitral regurgitation and mild aortic regurgitation (yellow arrows). RA: right atrium; LA: left atrium; AO: aorta; RV: right ventricle; LV: left ventricle; REG: mitral regurgitation.*



Video 3 – *Echocardiogram after 7 years of dopaminergic medication: Apical 4-chamber view showing the mitral valve with marked thickening and appearance of valvular fibrosis extending to the subvalvular apparatus, leading to reduced opening of the cusps.*
Watch the videos here: http://departamentos.cardiol.br/dic/publicacoes/revistadic/2017/v30_2/video_v30_2_178_ingles.asp

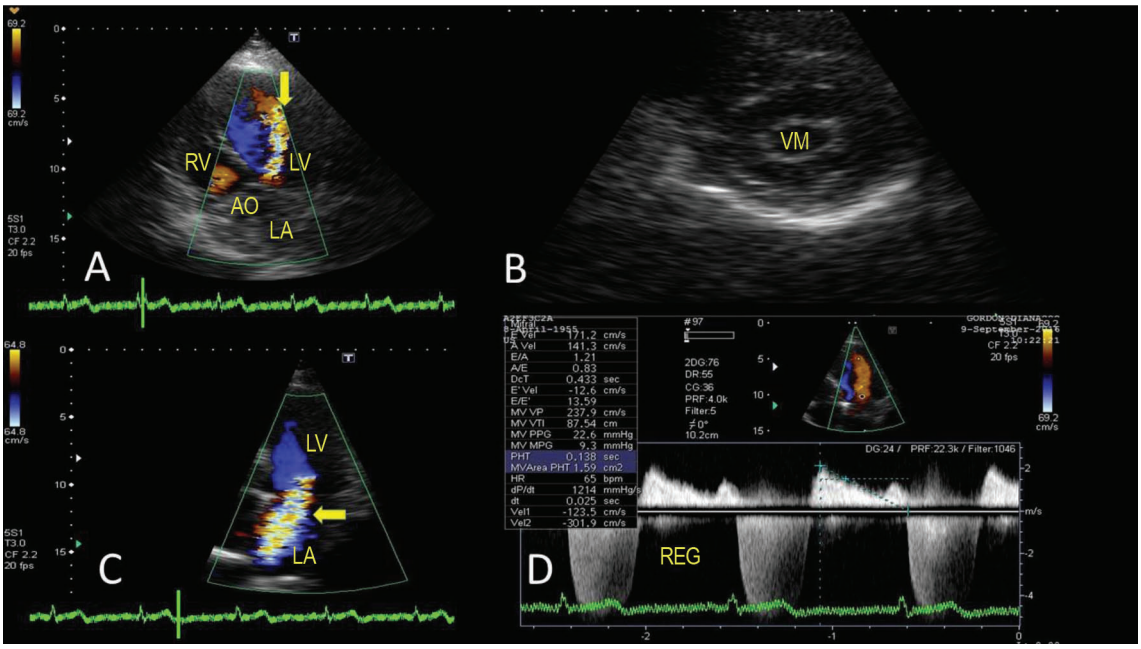
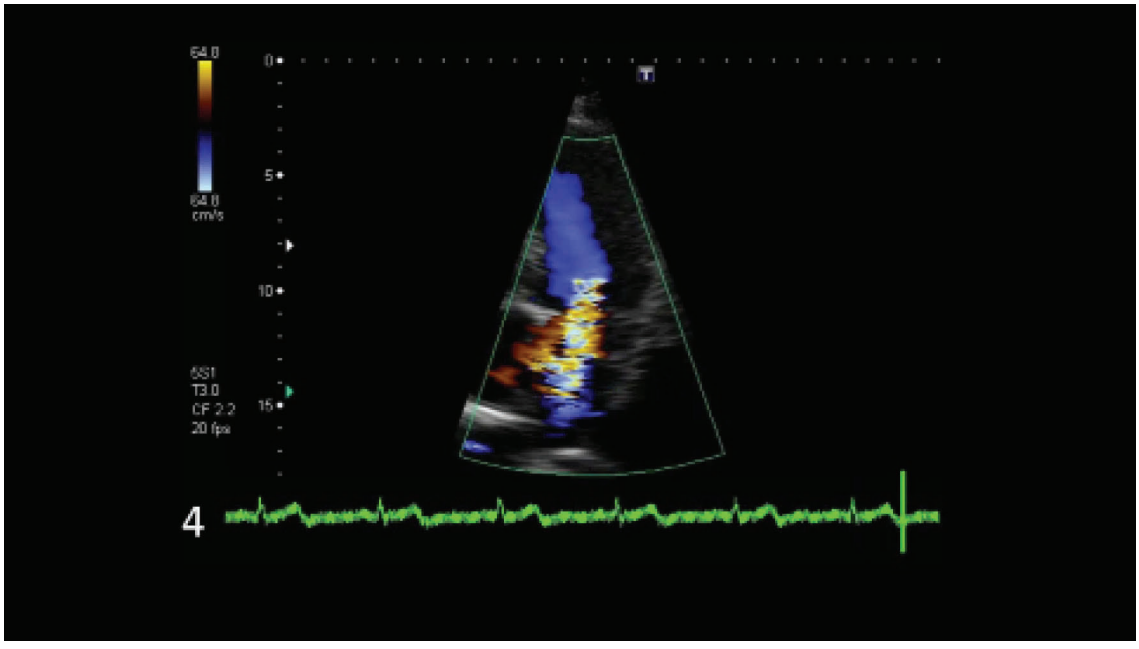


Figure 4 - *Echocardiogram after 7 years of the start of dopaminergic medication. A - 4-chamber apical view showing slight to moderate aortic regurgitation (yellow arrow); B - Parasternal short axis view at the level of the mitral valve showing valve thickening; C - Apical view showing moderate to severe mitral regurgitation (yellow arrow); D - Transmitral continuous Doppler showing medium diastolic gradient LA-LV 9 mmHg, compatible with moderate stenosis.*
RA: right atrium; LA: left atrium; AO: aorta; RV: right ventricle; LV: left ventricle; REG: mitral regurgitation.



Video 4 – *Echocardiogram after 7 years of dopaminergic medication: Apical 4-chamber view showing moderate to severe eccentric mitral regurgitation. Watch the videos here: http://departamentos.cardiol.br/dic/publicacoes/revistadic/2017/v30_2/video_v30_2_178_ingles.asp*

no linear relationship between the severity of valvular lesions and cumulative dose; a possible explanation could be that, at low doses, valvular fibrosis can develop only in the presence of additional pro-fibrotic factors (genetic predisposition, underlying unknown degenerative valvular disease and hypertension).[3] These drugs, especially cabergoline, cause thickening, retraction and stiffness in the valves, which results in coaptation failure and clinically significant regurgitation, requiring surgical replacement in some patients.[4] Different histopathologic analyses demonstrate increased fibroblasts and deposition of cell myxoid matrix on the surface of the valves.[5]

In our patient, we chose to do clinical follow-up mainly due to the scarce symptoms. Most patients remain asymptomatic after using dopamine agonists and the risk of valve disease is underestimated, therefore it is important to conduct echocardiographic controls.[6] The valve progression with rapid development of severe mitral regurgitation and cardiogenic shock, however, is rare.[6]

Cabergoline has been associated with increased risk of valve impairment, particularly in patients receiving daily doses exceeding 3 mg/day.[1] The risk of lesion only increases if the use of medication is equal to or greater than 6 months.[7] In our case, the patient had normal echocardiography scans at the beginning of treatment. Over the years, there was onset of valvular thickening, with progressive worsening of the lesions in the mitral and aortic valves (regurgitation and decreased opening). The dose (0.5 mg/day) was lower than that reported in the literature as a cause of valvular impairment. The use of medications, however, was for too long (over 20 years). The continuous form was for almost two years, which could justify the abnormalities found.

In our patient, the lesions only affected the aortic and mitral valves. Some studies have reported greater impairment of the left valves after the use of cabergoline. However, there is no consensus in the literature.[8] Reports of cases of impairment of the right valves, with thickening and retraction of the tricuspid valve leading to right heart failure have been more related to the use of bromocriptine. The alternate use of bromocriptine with cabergoline may have been related to the absence of abnormalities in the tricuspid and pulmonary valves.[8]

The treatment of valvular lesions is similar to that used for lesions from other causes and can, therefore, evolve to valve replacement surgery in cases of serious abnormalities with severe valvular fibrosis.[5]

Bromocriptine, on the other hand, does not seem to be a safer alternative for individuals who are receiving treatment with cabergoline, or who have pre-existing valvular abnormalities suggesting myocardial fibrosis or interstitial lung fibrosis.[2] Fibrotic abnormalities may occur in the valves, resulting in incomplete coaptation and moderate to severe regurgitation. The exact pathway leading to valvular heart disease is unknown, although the agonism of 5-HT (2B) receptors in the heart is also implicated as a mediator in the process.[3]

Echocardiography during follow-up was essential to the demonstration of valvular impairment, showing the progression of the lesions associated with the alternate use of bromocriptine and cabergoline.

Conclusion

The prolonged use of cabergoline associated with bromocriptine seems to be related to a substantial risk of impairment of cardiac valves, especially on the left side of the heart, thus justifying the serial echocardiographic follow-up.

Authors' contributions

Research creation and design: Barbosa LS, Rodrigues ACT; Data acquisition: Barbosa LS, Pereira SN; Data analysis and interpretation: Barbosa LS, Rodrigues ACT, Pereira SN, Vieira HLM, Staszko KF, Andrade JL; Manuscript drafting: Barbosa LS, Rodrigues ACT, Pereira SN, Staszko KF, Andrade JL; Critical revision of the manuscript as for important intellectual content: Barbosa LS, Rodrigues ACT, Pereira SN, Vieira HLM, Staszko KF, Andrade JL.

Potential Conflicts of Interest

There are no relevant conflicts of interest.

Sources of Funding

This study had no external funding sources.

Academic Association

This study is not associated with any graduate program.

Table 1 – Evolutionary echocardiographic parameters for the years 2009 - 2016 while using dopaminergic drugs

YEAR	DRUGS	PROLACTIN (ng/ml)	AOR (degree)	MR (degree)	TR (degree)	GsVAo (mmHg)	GdVM (mmHg)	MVA (cm^2)
2009	cabergoline	80.3 to 1.5	0	0	0	-	-	-
2010	cabergoline	2.5	0	0	0	-	-	-
2011	cabergoline	2 to 10	I	I	I	-	-	-
2012	cabergoline	4 to 15.2	I	II	I	-	4	-
2013	bromocriptine	4 to 15.2	I	II	I	-	4	-
2014	bromocriptine	3.4 to 18.6	I	II	I	7	6	1.8
2015	bromocriptine	3.4 to 18.6	I	II/III	I	7	5.5	1.6
2016	bromocriptine	87.3	I	II/III	I	15	9	1.6

MVA: mitral valve area; GdVM: mean mitral diastolic gradient; GsVAO: aortic valve systolic gradient; AOR: Aortic regurgitation; MR: Mitral regurgitation; TR: Tricuspid regurgitation; 0: no regurgitation; I: mild; II: moderate; III: severe.

References

1. Shruti K, Anurag RL, Rishikesh P, Milind P, Prafulla K, Tushar B, et al. Long-term cardiac (valvulopathy) safety of cabergoline in prolactinoma. Indian J Endocrinol Metab. 2017;21(1):154-9.
2. Antonini A, Poewe W. Fibrotic heart-valve reactions to dopamine-agonist treatment in Parkinson's disease. Lancet Neurol. 2007;6(9):826-9.
3. Elenkova A, Shabani R, Kalinov K, Zacharieva S. Increased prevalence of subclinical cardiac valve fibrosis in patients with prolactinomas on long-term bromocriptine and cabergoline treatment. Eur J Endocrinol. 2012;167(1):17-25.
4. Pinero A, Marcos-Alberca P, Fortes J. Cabergoline-related severe restrictive mitral regurgitation.N Engl J Med.2005;353(18):1976-7.
5. Hanada T, Shimizu K, Murakami R, Ota T, Okada S, Inoue S, et al. Mitral valve replacement for cabergoline-related severe mitral regurgitation.Kyobu Geka.2007;60(11):1018-21.
6. Luedde M, Helmke B, Katus HA, N Frey. Severe mitral valve regurgitation with fatal cardiogenic shock in a patient on long-term cabergoline treatment. International. Int J Cardiol. 2009;133(3):97-8.
7. Schade R, Andersohn F, Suissa S, Haverkamp W, Garbe E. Dopamine agonists and the risk of cardiac-valve regurgitation. N Engl J Med. 2007; 356(4):29-38.
8. Boguszewski CL, dos Santos CM, Sakamoto KS, Marini LC, de Souza AM, Azevedo M. A comparison of cabergoline and bromocriptine on the risk of valvular heart disease in patients with prolactinomas. Pituitary. 2012;15(1): 44-9.