# Cardiac Surgery for Ergotamine-Induced Multivalvular Heart Disease

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## Abstract

Ergotamine is used to abort or prevent vascular headache. Valvular heart disease as an adverse effect of long-term ergotamine therapy has been rarely reported in the English literature, with only a few cases published. It is hypothesized that ergot-derived agents stimulate serotonergic receptors (5-$HT_{2B}$), causing proliferation of myofibroblasts, with subsequent thickening of valve leaflets and chords. This case presentation aims at increasing clinicians' awareness of this potential complication.

**Keywords**
- ergotamine
- cardiac valve
- cardiac surgery

## Introduction

Ergotamine is an alkaloid produced by the fungus *Claviceps purpura*. Despite its multiple side effects ergotamine has been used in clinical practice for the acute treatment of migraine for more than 50 years, favored by its effectiveness, low cost, and easy availability. Because of its α-adrenergic agonistic action ergotamine causes vasoconstriction. The chronic abuse of ergotamine has often been associated with peripheral ischemia of lower limbs and bowel, as well as myocardial infarction and stroke.[1,2] On the contrary, valvular heart disease as a side effect of long-term ergotamine therapy has been rarely reported. The mechanism of action is suspected to activate serotonin-mediated abnormal fibrogenesis.[3–5]

## Case Report

A 54-year-old woman presented with progressive dyspnea on exertion and ankle edema. She had no history of heart disease or rheumatic fever. The patient suffered from migraine headaches, for which she received 2 to 4 mg ergotamine tartrate and caffeine (Cafergot; Amdipharm Ltd, Dublin, Ireland) for many years almost daily.

On admission, the patient had a clinical evidence of congestive heart failure. The blood pressure was 105/70 mm Hg, the jugular veins were distended, and 2–3/6 systolic and diastolic murmurs were heard above the aortic and mitral valve. Significantly enlarged cardiac silhouette and marked vascular congestion were noted on chest X-ray.

Transthoracic echocardiography (►**Fig. 1**) showed severe mitral regurgitation, with leaflet thickening and restriction. Aortic and tricuspid valves were moderately regurgitant. There was no evidence of calcification. Left ventricular function was not impaired and diameters were within the upper normal limit. Cardiac catheterization showed normal coronary arteries.

The patient was operated on urgently, because of the rapid progression of cardiac dysfunction and hemodynamic compromise. Full cardiopulmonary bypass was established through a median sternotomy, with cannulation of the ascending aorta, as well as bicaval cannulation for venous drainage. The patient was cooled down to 27°C, the aorta was cross-clamped, and cold (4°C) crystalloid cardioplegia (Custodiol; Dr. Franz Köhler GmbH, Bensheim, Germany) was administered. This technique obtained a bloodless operative field. Mitral and aortic (►**Fig. 2**) valves were replaced with mechanical prosthesis. Tricuspid valve was repaired with an annuloplasty ring. The patient tolerated the procedure well and was weaned of cardiopulmonary bypass easily, with minimal inotropic support. She was discharged 7 days after the surgery.

Given the initial clinical suspicion and the patient's history, resected valve leaflets were examined microscopically. Histopathological findings (►**Fig. 3**) demonstrated subendothelial

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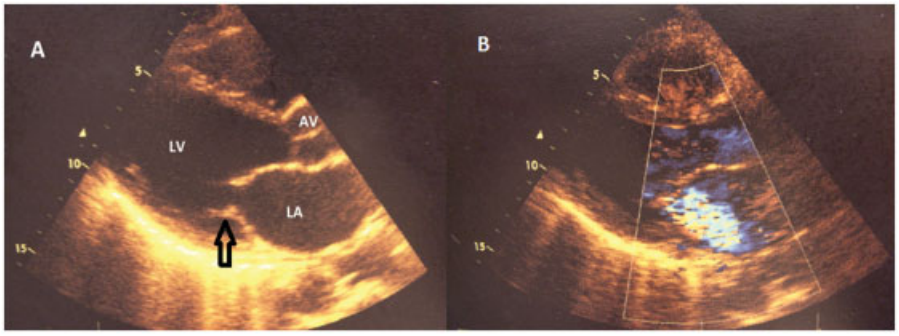


**Fig. 1** Echocardiography, parasternal long axis view. (A) Thickened mitral leaflets and chordae (black arrow) (LA, left atrium; LV, left ventricle; AV, aortic valve). (B) Color flow imaging demonstrating mitral regurgitation.

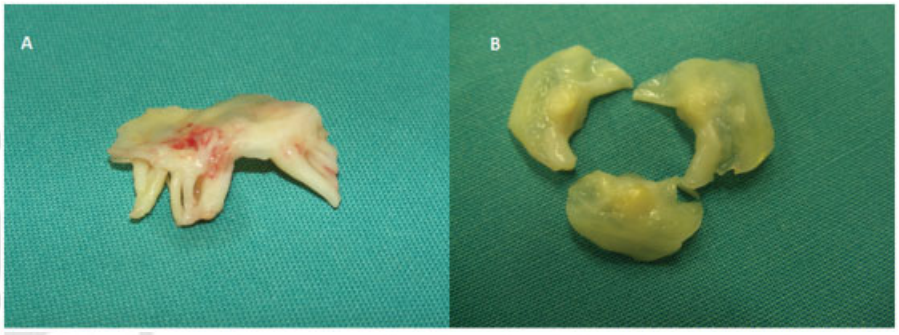


**Fig. 2** White, glistering appearance and marked irregular thickening of excised mitral anterior leaflet and chordate (A) and aortic valve (B).

proliferation of myofibroblastic-like cells, positive for smooth muscle actin, as proven in immunohistochemistry. No appreciable calcification or acute inflammation was present. These findings were associated to the chronic ergotamine abuse, which was considered as the causative agent.

## Discussion

Ergot-derived agents interfere with serotonin metabolism and activate 5-$HT_{2B}$ receptors, which are found in heart valves and other structures such as the pleura, peritoneum, and pericardium.[3,4] The result of this serotonin-agonist effect is the direct stimulation of myofibroblasts growth and subsequent noninflammatory degeneration of the affected structures.

A similar pathophysiological mechanism seems to be activated in carcinoid syndrome, in patients suffering from Parkinson disease treated with ergot-derived dopamine agonists (pergolide [Permax; Valeant Pharmaceuticals International, Costa Mesa, California, United States] and cabergoline [Dostinex; Pfizer, New York, United States]), and in patients treated with the appetite suppressants fenfluramine and phentermine. All these drugs alter serotonin metabolism and have a high affinity for the 5-$HT_{2B}$ receptor.[3–8] Additionally, Rothman et al report that serotonergic medications that do not activate 5-$HT_{2B}$ receptors are unlikely to produce valvular heart disease.[3]

Our 54-year-old patient self-medicated with high doses of Cafergot, almost every day, for more than 15 years. There was no history suggesting rheumatic fever, scarlet fever, or known

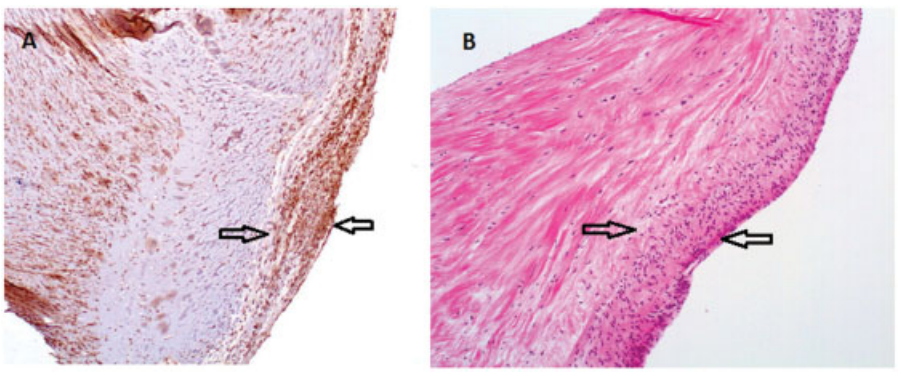


**Fig. 3** (A) Histological section stained with hematoxylin and eosin, magnification ×100. (B) Immunohistochemistry for smooth muscle actin. Arrows show increased thickness of subendothelial layer of myofibroblastic-like cells.

heart murmurs. Furthermore, the patient received no other medication regularly.

Microscopic examination of the resected valve leaflets depicted excessive subendothelial myofibroblastic proliferation, which stained positively for smooth muscle actin in immunohistochemistry, and proved the initial clinical suspicion. Morphologic similarity has been observed between fenfluramine-associated and carcinoid-induced heart lesions.[2,6] Nevertheless, it remains unclear how far treatment duration and dosage affect these lesions and if regression of valvular lesions is possible after withdrawal of the therapy.[8]

This rare case suggests that regular follow-up including assessment of the cardiac function is necessary during long-term treatment with ergot-derived agents. Until more is known about the true prevalence of this, yet undetermined, side effect, clinicians should be aware of its impact.

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