Beneficial Effect of Cibenzoline on Left Ventricular Pressure Gradient With Sigmoid Septum

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An 83-year-old woman with hypertension was admitted to hospital with episodes of dyspnea on effort after having breakfast. Physical examination revealed a systolic murmur at the left sternal border in the third to fourth intercostal space. Cross-sectional echocardiography showed a sigmoid-shaped interventricular septum markedly protruding into the left ventricle, concentric left ventricular hypertrophy, systolic anterior motion of the mitral valve, and a resultant left ventricular outflow tract obstruction with a pressure gradient of 121.8 mmHg. She began daily treatment with 60 mg metoprolol. However, the chest symptoms were not relieved and the left ventricular outflow tract obstruction was still visible on echocardiography. She was then given 200 mg daily of cibenzoline, in addition to 40 mg metoprolol, and the left ventricular pressure gradient significantly decreased and she was free of symptoms without any complications. This case shows that cibenzoline may be useful in the treatment of left ventricular outflow tract obstruction caused by sigmoid septum. (*Circ J 2004; 68: 968–971)

Key Words: Cibenzoline; Left ventricular outflow tract obstruction; Pressure gradient; Sigmoid septum

A sigmoid-shaped ventricular septum is one of the causes of left ventricular outflow tract (LVOT) obstruction in older patients and because it is rarely related to clinical symptoms,1,2 medical therapy for the reduction of the left ventricular pressure gradient (LVPG) associated with sigmoid septum has not been established. It was recently reported that the class Ia antiarrhythmic drug, cibenzoline, attenuates the LVPG in patients with hypertrophic obstructive cardiomyopathy (HOCM),3 and we describe a patient with LVPG caused by a sigmoid-shaped septum who improved after administration of cibenzoline.

Case Report

A 83-year-old-female was admitted to hospital with episodes of dyspnea on effort after having breakfast. She had had hypertension for 20 years prior to admission. Her blood pressure was 154/74 mmHg, and her pulse rate was 100 beats/min and regular. Her physical examination was unremarkable, except for a grade 4/6 systolic murmur at the left sternal border in the third to fourth intercostal space. Routine blood tests were normal except for brain natriuretic peptide (BNP) of 455 pg/ml. An electrocardiography recorded 18 years prior to admission had been normal, whereas that recorded in the current admission showed normal sinus rhythm at a rate of 75 beats/min and left ventricular hypertrophy with ST-segment depression and inverted T waves characteristic of the strain pattern (Fig 1). Chest X-ray showed cardiomegaly with a cardiothoracic ratio of 56%. Two-dimensional transthoracic echocardiography revealed a sigmoid-shaped base of the interventricular septum markedly protruding into the left ventricle and calcification of both posterior mitral leaflet and aortic valve (Fig 2A,B), whereas that performed 18 years prior to admission had been normal (Fig 3). The remainder of the septum and the left ventricular free wall were concentrically hypertrophied, but no enlargement of the left ventricular cavity was observed. The angle between the mid line axis of the ascending aorta and that of the interventricular septum was 97.5° (normal range, 145±7°). M-mode echocardiography demonstrated a systolic anterior motion of the mitral valve (SAM) with fractional shortening (FS) of 39% (Fig 4A). Color Doppler echocardiography showed turbulent systolic flow through the LVOT with a pressure gradient of 121.8 mmHg, mild aortic stenosis, and moderate mitral regurgitation (Figs 2C,4B). Cardiac catheterization was performed and angiography indicated an intermediate stenosis in the mid portion of the right coronary artery. The left ventricular end-diastolic pressure was 18 mmHg and the peak-to-peak LVPG at the LVOT was 146 mmHg. These findings confirmed the diagnosis of LVOT obstruction caused by the sigmoid septum, concentric left ventricular hypertrophy and SAM.

To reduce the LVOT obstruction, 60 mg/day of metoprolol was administered, but despite that treatment the LVPG remained at approximately 100 mmHg. Hence, 200 mg/day of cibenzoline, a class Ia antiarrhythmic agent, was administered in addition to 40 mg/day of metoprolol. After the addition of cibenzoline, the SAM disappeared and the FS registered as 35% (Fig 4D). Continuous Doppler flow velocity at the LVOT decreased to 1.56 m/s and thus the LVPG decreased to 9.8 mmHg (Fig 4E). The E velocity slightly increased and the A velocity decreased in pulsed wave Doppler examination at the transmural level (Fig 4C,F). The patient has not had chest symptoms and has been convalescent on an outpatient basis.
Sigmoid Septum and Cibenzoline

Discussion

Sigmoid-shaped septum is a morphological change characteristic of a diminished angle between basal interventricular septum and ascending aorta. This cardiac malformation has been considered to be the result of aging, and of no pathophysiologic and clinical significance;\textsuperscript{1,2} however, several reports have demonstrated that sigmoid septum sometimes causes a significant narrowing of the LVOT, particularly when complicated by left ventricular hypertrophy or when exposed to exercise load, anesthesia, or surgery.\textsuperscript{4-6} Another report has shown that turbulent flow
through the LVOT with a sigmoid septum is one of the factors causing senile degenerative aortic valvular calcification. In some patients with sigmoid septum, as well as in those with HOCM, dehydration, eating, antihypertensive drugs with vasodilating action, or positive inotropic agents may enhance the LVPG.

In the present patient, the differential diagnosis of the LVOT obstruction included HOCM, concentric left ventricular hypertrophy, and sigmoid septum. In fact, we cannot completely exclude the diagnosis of HOCM in which the myocardial hypertrophy is localized to the base of the interventricular septum. However, in the present case, the ECG and echocardiography examinations 18 years prior to admission were normal. Therefore, it appears reasonable to suppose that the sigmoid septum and concentric left ventricular hypertrophy without ventricular dilation, which are the result of aging and hypertension, contributed to the LVOT obstruction in the present case.

LVOT obstruction with a significant LVPG may be related to clinical symptoms, such as dyspnea on effort, chest pain, and syncope, in patients with a sigmoid septum as well as those with HOCM. However, medical therapy to relieve the LVOT obstruction associated with LVPG in patients with sigmoid septum has not been established. In HOCM, although both β-blockers and calcium antagonists have been widely used, they are often insufficient to reduce the LVPG. The class Ia antiarrhythmic drug, disopyramide, will decrease the LVPG and improve the left ventricular diastolic function in most patients with HOCM but it is frequently not tolerated because of several adverse effects related to its anticholinergic property, such as thirst, dysuria, and tachycardia. On the other hand cibenzoline, which is also a class Ia antiarrhythmic agent, but with less anticholinergic effects than disopyramide, can have beneficial effects on the LVPG and diastolic function in HOCM, including cases of midventricular obstruction. Cibenzoline is a strong Na+ channel-blocking agent, which provokes a decrease in intracellular Ca2+ concentration in patients with HOCM.

Fig 3. Two-dimensional echocardiography from 18 years before the present admission. Sigmoid septum and left ventricular hypertrophy are not evident (A), nor is systolic anterior motion of the mitral valve (B).

Fig 4. Changes in M-mode echocardiography at the level of the mitral valve and Doppler flow velocity profiles before and after the administration of cibenzoline and metoprolol. Systolic anterior motion of the mitral valve disappeared after the treatment (A, D). Continuous wave Doppler recording with a sample volume positioned at the left ventricular outflow tract shows a decrease in the velocity from 5.52 (B) to 1.56 (E) m/s after the treatment. Pulsed wave Doppler recording with a sample volume positioned between the leaflet tips of the mitral valve showed a slight increase in the E velocity from 1.01 (C) to 1.09 (F) cm/s and a decrease in the A velocity from 1.28 (C) to 0.65 (F) cm/s after the treatment.
cardiac myocytes and it also has a Ca\(^{2+}\) channel blocking action. A previous report has indicated that hypercontraction and narrowing of the left ventricle play an important role in the enhancement of LVPG with sigmoid septum. Beta-blockers cannot improve left ventricular diastolic function, but they can suppress left ventricular contractility in hypertrophic cardiomyopathy. Taking the echocardiographic changes in %FS and E/A into consideration, we speculate that cibenzoline contributed to the attenuation of the LVPG and relief from symptoms in the present patient with sigmoid septum and left ventricular hypertrophy through not only its negative inotropic effect but also an improvement of left ventricular diastolic function. We cannot rule out the possibility that the combined therapy of cibenzoline and \(\beta\)-blocker exerted a more beneficial effect than cibenzoline alone. To our knowledge, this is the first report of a sigmoid septum-induced LVOT obstruction that could be relieved by cibenzoline. Further cases are necessary to fully evaluate the effects of cibenzoline on LVPG with sigmoid septum.

The present case demonstrates that sigmoid septum can cause functional abnormality of the heart that is clinically significant. Moreover, it suggests that cibenzoline may be useful in the treatment of LVOT obstruction caused by sigmoid septum.

References