Usefulness of Cibenzoline Stress Echocardiography to Determine Severity of Aortic Stenosis in a Patient with Combined Left Ventricular Outflow Tract Obstruction and Aortic Stenosis

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Abstract: Left ventricular outflow tract obstruction (LVOTO) is sometimes accompanied by aortic stenosis (AS). Reliable estimation of the true severity of AS is often difficult because it cannot be discriminated from dual stenosis. A 75-year-old woman was referred to our hospital due to traumatic hemopneumothorax with exertional dyspnea. Echocardiography revealed AS and LVOTO by chance. A continuous Doppler echocardiography revealed a late-systolic peaking dagger-shaped profile with a 6.0 m/s of peak jet velocity across the LVOT and aortic valve, but it was difficult to discriminate between the coexisting peak flows. For an accurate evaluation of AS, we performed landiolol (short acting beta-blocker) and cibenzoline (Na⁺ channel-blocking agent) stress echocardiography with simultaneous recordings of both left ventricular and aortic pressure by catheter examination. Cibenzoline successfully eliminated the LVOTO, but landiolol did not. Cibenzoline stress echocardiography enabled us to evaluate the AS severity as less than moderate, resulting in proper decision-making. The findings in this case clearly showed that cibenzoline stress echocardiography has a potential utility for determining AS severity in a patient with coexistent dynamic LVOTO.

Keywords: aortic stenosis, left ventricular outflow tract obstruction, cibenzoline, stress echocardiography.

Introduction

The number of patients with calcific aortic stenosis (AS) has been increasing dramatically in developed countries owing to the increase in life expectancy [1, 2]. A further increase in patients with AS is estimated year by year. Once symptoms or deterioration of left ventricular (LV) contractility develop in patients with progressed AS, the prognosis will be poor [1, 2]. Guidelines strongly recommend that these patients undergo aortic valve replacement [3, 4]. Hence, accurate diagnosis and determination of severity are essential for appropriate treatment at the proper timing. Echocardiography is basically used to assess the diagnosis and severity of AS because of its superiority to other imaging modalities in availability and cost-effectiveness, and its non-invasive nature [3–5]. Particularly, Doppler echocardiographic assessment is indispensable for the assessment of hemodynamics and the diagnosis of valvular diseases [5, 6], although it has several
shortcomings, including susceptibility to image quality, limited acoustic window, and angle dependency [5, 6]. Cardiologists and sonographers in clinical settings sometimes face a challenging situation in evaluating AS severity due to these shortcomings. Patients with left ventricular outflow tract obstruction (LVOTO) is one of the typical situations making assessment difficult because it can be challenging to distinguish between the flows across the aortic valve and LVOTO, and mitral regurgitation (MR) [7–9]. The flows go in similar directions, and the highest flow points can be located close to each other.

This report presents a case of coexistent LVOTO and AS whose severity was difficult to evaluate. Cibenzoline (Na+ channel-blocking agent) stress echocardiography with simultaneous catheter pressure measurements enabled a reliable estimation of the severity of AS in this patient, resulting in proper decision-making.

**Case report**

A 75-year-old woman was admitted to our hospital due to traumatic hemopneumothorax with exertional dyspnea. No structural heart disease had been pointed out before admission. She had received treatment for hypertension with bisoprolol 5 mg daily for three months before admission. Her blood pressure was 139/74 mmHg, the pulse 75 / min, afebrile, and the oxygen saturation 98% without oxygen supply. In the present physical examination, a loud systolic ejection murmur (grade 4/6) was heard at the left sternal border between the third and fourth costae with radiation to the neck. No other findings needing to be addressed were observed.

The results of the laboratory test are shown in Table 1. B-type natriuretic peptide was markedly increased to 401 pg/ml, while qualitative troponin was negative. The results of electrocardiography were interpreted as normal, except for evidence of probable LV hypertrophy. Chest radiography showed slight cardiomegaly. Coronary angiography revealed intermediate stenosis in the middle of the left anterior descending artery. Two-dimensional transthoracic echocardiography (TTE) showed LVOTO caused by upper septal hypertrophy with sigmoid septum, systolic anterior motion of the mitral valve (SAM) with mild to moderate MR, and aortic valve calcification with limited leaflet excursion. Thickness of basal septum was 18 mm, while that of the middle septum was 12 mm and posterior wall 13 mm. The LV was hyperkinetic of ejection fraction ≥ 60% without any wall motion abnormality. Color Doppler echocardiography revealed mosaic flow occupying from the LVOT to the aortic valve. The continuous Doppler echocardiography described a late-systolic peaking dagger-shaped profile with a 6.0 m/s of peak jet velocity (Fig. 1). However, a precise determination of the severity of AS was difficult because it was impossible to discriminate the AS velocity from the LVOTO velocity. To eliminate the dy-

### Table 1. Laboratory data at referral

| variable                        | value | unit        |
|---------------------------------|-------|-------------|
| White-blood cell count          | 5300  | per mm³     |
| Red-blood cell count            | 3.69×10⁶ | per mm³   |
| Hemoglobin                      | 11.1  | g/dl        |
| Hematocrit                      | 34.1  | %           |
| Platelet                        | 2.63×10⁴ | per mm³   |
| Prothrombin-time international normalized ratio | 1.02 |
| Activated partial-thromboplastin time | 29.8 | sec        |
| Fibrinogen quantity             | 403   | mg/dl       |
| Fibrin degradation products     | 7.5   | ug/ml       |
| Total protein                   | 6.6   | g/dl        |
| Albumin                         | 3.5   | g/dl        |
| Aspartate aminotransferase      | 14    | IU/l        |
| Alanine aminotransferase        | 12    | IU/l        |
| LDH                             | 264   | IU/l        |
| Alkaline phosphatase            | 217   | IU/l        |
| Creatinine kinase               | 53    | IU/l        |
| Urea nitrogen                   | 12    | mg/dl       |
| Creatinine                      | 0.59  | mg/dl       |
| Estimated glomerular filtration rate | 74.0 | ml/min/1.73m² |
| Sodium                          | 141   | mEq/l       |
| Potassium                       | 4.4   | mEq/l       |
| Chloride                        | 107   | mEq/l       |
| C reactive protein              | 0.27  | mg/dl       |
| LDL cholesterol                 | 147   | mg/dl       |
| HDL cholesterol                 | 71    | mg/dl       |
| Hemoglobin A1c                  | 5.1   | %           |
| Qualitative troponin T          | Negative |
| B type natriuretic peptide      | 401   | pg/ml       |
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Fig. 1. Echocardiography on admission. A: Two-dimensional transthoracic echocardiography in systole shows upper septal hypertrophy (double arrows) and calcific aortic valve (AV) with limited opening (single arrow). B: Apical long axis view by color Doppler echocardiography revealed mosaic flow extending from the left ventricular outflow tract (LVOT) towards the AV and mild mitral regurgitation (double arrows). C: A zoomed image of LVOT shows systolic anterior motion of the mitral valve (single arrow) and aortic valve calcification with limited leaflet excursion (double arrows). D: The continuous wave Doppler echocardiography shows a dagger-shaped Doppler spectrum peaking in late systole and peak flow velocity across LVOT and AV of approximately 6.0 m/s. However, it was difficult to discriminate each flow from the other. Ao: aorta, LA: left atrium, LV: left ventricle, MR: mitral regurgitation.

Dynamic LVOTO, we performed landiolol (short acting beta-blocker) and cibenzoline stress echocardiography with simultaneous recordings of both LV and aortic pressure measurements in the cardiac catheterization laboratory (Fig. 2). In direct pressure measurement, extremely fine 0.014 mm PressureWire (Aeris™, Abbott Vascular, Illinois) was used to avoid any influence of the diameter of the catheter on the stenosis. At baseline, TTE showed SAM and MR. Continuous Doppler echocardiography showed a late-systolic peaking dagger-shaped Doppler profile, and the peak flow velocity across the aortic valve and LVOTO was 5.7 m/s. Pressure recording showed a peak instantaneous pressure gradient of 130 mmHg between the LV and the aorta. Intravenous landiolol administration did not produce any reduction of LVOTO and the pressure gradient. Next, we infused intravenous cibenzoline as bolus of 70 mg. After the injection of cibenzoline, SAM and MR were gradually decreased and finally abolished, resulting in the reduction of the peak flow velocity (2.0 m/s) and the peak instantaneous pressure gradient (30 mmHg) (Fig. 3). This finding indicated that the AS was not hemodynamically significant. Therefore, we could make a decision of watchful waiting regarding AS in this patient. Her exertional dyspnea subsided after the administration of oral cibenzoline therapy.

Human rights statements and informed consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from this patient to be included in the study.
We reported the utility of cibenzoline (Na+ channel-blocking agent) stress echocardiography to reliably estimate AS in patients with coexistent LVOTO. To the best of our knowledge, this case was the first study to demonstrate that cibenzoline could discriminate aortic valve (AV) gradient from LVOTO gradient with simultaneous measurements by catheter and echocardiography.

**Aortic stenosis and left ventricular outflow obstruction**

The prevalence of the LVOTO in patients with AS is reported to be approximately 10% [10]. Age has been reported to be one of the factors associated with upper septal hypertrophy [11]. Hence, the number of patients with concomitant LVOTO and AS is predicted to increase along with the aging of the population [1]. Accurate evaluation of the true severity of AS is quite difficult if it coexists with LVOTO due to hypertrophic obstructive cardiomyopathy or upper septal hypertrophy [7, 9, 10, 12]. Careful assessment is required to distinguish the flow across the aortic valve from the flow through LVOTO in a Doppler echocardiographic examination [5, 13], but it is sometimes difficult to separate these flows and to define which is the main component of the pressure gradient [8–10], as shown in Fig. 1, where the Doppler flow profile of AS and that of LVOT were mixed in this case.

**Fig. 3.** Pressure and echocardiography recording before and after intravenous cibenzoline. The upper panels (A–C) show before, and the lower panels show after injection of cibenzoline (D–F). A: Apical long axis view by color Doppler shows mitral regurgitation (MR) (double arrows). B: The peak flow velocity across the LVOT is 5.7 m/s. C: Simultaneous cardiac catheterization study shows that the peak (double headed arrow) and mean pressure gradients (red-colored area) between the left ventricle and the ascending aorta were 138 mmHg and 45 mmHg, respectively. D: After the injection of cibenzoline, color Doppler echocardiography shows a reduction of MR (double arrows). E: The peak flow velocity across LVOT was decreased to 2.0 m/s. F: Pressure study revealed that the peak (double headed arrow) and mean pressure gradients (red-colored area) were 30 mmHg and 17 mmHg respectively. Thus, the pressure gradient was remarkably reduced. Ao: aorta, AoP: aortic pressure, LA: left atrium, LV: left ventricle, LVP: left ventricular pressure, MR: mitral regurgitation.
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Effect of cibezoline on left ventricular outflow tract obstruction

Cibenzoline has a negative inotropic property and has been reported to be effective in the reduction or elimination of dynamic LVOTO in patients with hypertrophic cardiomyopathy and in those with upper septal hypertrophy [12, 14–16]. Gaillard et al reported that the presence of concomitant asymmetrical septal hypertrophy (ASH) may cause an overestimation of the hemodynamic severity of AS in an in-vitro study, and suggested that the extent of overestimation is more enhanced in less-severe AS [17]. This finding can support our results that cibenzoline clarified that an apparently severe AS was actually less than moderate. This in-vitro study by Gaillard et al and our results may imply that even if the flow across the aortic valve can be distinguished from the flow through obstruction in Doppler examination, the values of the parameters related to AS might be unreliable. Further, the Bernoulli equation can sometimes be suspect in a situation of coexistent AS and LVOTO, due to the basic assumption of this equation [18]. Therefore, the influence of LVOTO should be eliminated as much as possible for accurate determination of the severity of AS. Our case clearly showed that cibenzoline stress echocardiography has the potential for accurately determining the severity of AS in a patient with dynamic LVOTO.

Study limitations

There are some concerns to be addressed in this case report. First, landiolol did not work to reduce LVOTO. One of the possible reasons is that the negative inotropic effect of ladiolol is not enough to attenuate LVOTO compared to cibenzoline. Furthermore, a previous study demonstrated the effectiveness of a Na+ channel blocking agent to reduce LVOTO in patients with resistance to beta-blocker [19].

Second, it is not clear how long the effectiveness of cibenzoline would continue and whether cibenzoline would have benefited this patient in terms of long-term prognosis. This patient could survive for a few years without any side effects.

Another concern is that it was difficult to measure the pressure between aortic valve and LVOT because the pressure wire was too soft to be fixed at the point due to turbulence.

Finally, clinical studies should be conducted to elucidate the usefulness of cibenzoline stress echocardiography in the assessment of AS.

Conclusion

Cibenzoline stress echocardiography was useful for reliable evaluation of AS severity in patients with coexistent LVOTO and AS, resulting in proper decision-making.

Conflict of Interest

Yasufumi Nagata, Masaaki Takeuchi, Kyoko Otani, Shinjo Sonoda, and Yutaka Otsuji declare that they have no conflict of interest in this study.

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左室流出路狭帯を合併した大動脈弁狭窄症の重症度評価におけるシベンゾリン負荷心エコーの有用性

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要　旨：左室流出路狭帯は時に大動脈弁狭帯症に合併する。しばしば両者の狭帯を分離することができないため、大動脈狭帯症の真の重症度を正確に評価することが困難である。症例は外傷性血気胸で入院となった75歳女性。心エコー図検査により大動脈弁狭帯症と左室流出路狭帯を認めた。ドプラーエコーでは収縮後期をピークとするダガー型の血流波形を認め、左室流出路と大動脈弁を通過する最高血流速度は6.0 m/sであったが、両者の最高血流を分離することが困難であった。正確な大動脈弁狭帯症の重症度評価のため、ランジオロール（短時間作用型βブロッカー）とシベンゾリン（ナトリウムチャネルブロッカー）を用いた負荷心エコーを行い、同時にカテーテル検査により左室圧と大動脈圧を測定した。ランジオロールは無効であったが、シベンゾリンにより左室流出路狭帯は消失した。シベンゾリン負荷心エコー検査により大動脈弁狭帯症の重症度は中等度以下と評価され、適切な治療方針の決定が可能となった。本症例によって、シベンゾリン負荷心エコーは左室流出路狭帯を合併した大動脈弁狭帯症の重症度評価に有用である可能性が示された。

キーワード：大動脈弁狭帯症、左室流出路狭帯、シベンゾリン、負荷心エコー図検査。

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