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Editorial

Editorial: Cibenzoline for left ventricular outflow tract obstruction in tako-tsubo cardiomyopathy and hypertrophic cardiomyopathy

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Some patients with tako-tsubo cardiomyopathy (TCM) develop cardiogenic shock or cardiac rupture due to left ventricular outflow tract (LVOT) obstruction [1–4]. LVOT obstruction is reported to occur in 10–25% of patients with TCM [5,6]. The exact mechanism of TCM is unknown. The trigger is frequently, but not always, an intense emotional or physical stress. The pathogenesis is not well understood but a number of theories exist; catecholamine drive, oxidative stress, estrogen deficiency, transient coronary artery spasm, or genetic predisposition. Catecholamine concentrates such as epinephrine and nor-epinephrine levels have been noted to be high during the acute phase of TCM, and excessive catecholamine levels appear to have a major role in the pathology of this disorder [4,7].

A study showed that out of 136 consecutive patients with TCM, 13 patients developed dynamic obstruction to LVOT (gradients, 54 ± 48 mmHg) due to systolic anterior motion (SAM) of the mitral valve and mitral–septal contact, and in seven patients, following the intravenous administration of inotropic agents for hypotension [3]. A systematic analysis of the literature demonstrated LVOT obstruction in 25% of patients with TCM, all of whom presented with septal bulge associated with SAM of the mitral valve and mitral regurgitation. This morphology of the ventricular septum is mostly present in elderly patients and appears to be an important factor for LVOT obstruction in TCM [7,8].

LVOT obstruction is also a common characteristic of hypertrophic cardiomyopathy (HCM). Up to one-third of patients with HCM will have obstruction under basal (resting) conditions (defined as gradients ≥30 mmHg). Another one-third or more of patients will have labile, physiologically provoked gradients (<30 mmHg at rest and ≥30 mmHg with physiologic provocation) [9,10].

Outflow obstruction usually occurs in HCM by virtue of mitral valve SAM and mitral–septal contact. In HCM, the mitral leaflets are anteriorly positioned with extension of leaflet tips past the point of coaptation into the outflow tract. The papillary muscles are anteriorly malpositioned and can be inserted directly onto the mitral leaflet. These geometric papillary muscle changes, in combination with mitral leaflet elongation, lead to less posterior leaflet tethering and thus provide sufficient leaflet mobility to result in SAM [10–12]. Although the mechanism of the outflow tract gradient in HCM was initially thought to be caused by systolic contraction of the hypertrophied basal ventricular septum encroaching on the LVOT, most recent studies have demonstrated that given the mitral anatomy in HCM, the predominant mechanism of SAM is related to drag on the mitral valve leaflet, generated by blood flow acceleration across the septum during ventricular systole, 'pushing' the leaflets into the LVOT [10–12].

As opposed to a fixed stenosis in aortic stenosis, subvalvular obstruction is dynamic and fluctuates significantly based upon changes in numerous clinical factors, including fluctuations in volume status, autonomic nervous activity, diurnal variation, pharmacotherapy, exercise, and physical position during assessment [10–12].

To decrease pressure gradient of LVOT obstruction in TCM, treatment with a β-blocker, a calcium channel blocker such as verapamil or diltiazem, or an α-adrenoceptor agonist such as phenylephrine will be usually considered. Volume expansion will be also considered. These treatments will be useful in preventing acute complications such as cardiogenic shock due to LVOT obstruction, ventricular arrhythmias, or ventricular rupture [1,2].

The use of β-blockers for LVOT obstruction in TCM has been specifically advocated due to the possible abnormal response to excessive catecholamines. Administration of β-blockers would be reasonable when coronary spasm is not suspected on initial presentation, because excess catecholamines may be involved in the pathophysiology. It is necessary to take care of worsening heart failure or coronary spasm after initiation of therapy [1].

In HCM patients with LVOT obstruction who develop symptoms, β-blockers are the mainstay of pharmacologic therapy and the first-line agents because of their negative inotropic effects and their ability to attenuate adrenergic-induced tachycardia [10]. Although verapamil can also be considered, caution should be exercised in its administration to patients with marked resting gradients and advanced heart failure. Left ventricular (LV) filling can be improved by these drugs, although basal gradients are not usually mitigated significantly [13]. β-Blockers are most effective in blunting gradients provoked with exercise. Disopyramide is the most reliable drug for reducing outflow gradients at rest in HCM, although long-term use may be limited by parasympathetic side effects [13].

Hamada et al. proposed to use cibenzoline for the reduction of LVOT gradient in HCM. Unlike disopyramide, cibenzoline has little anticholinergic activity; therefore, this drug can be easily adapted

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to long-term use. In addition to the reduction in LV pressure gradient, cibenzoline can improve LV diastolic dysfunction, and induce regression of LV hypertrophy in patients with HCM [14]. A decrease in intracellular Ca^{2+} concentration through the activation of the Na^{+}/Ca^{2+} exchanger associated with cibenzoline therapy is likely to be closely related with the improvement in HCM-related disorders. It is possible that cibenzoline can prevent the progression from typical HCM to end-stage heart failure. One factor for the reduction of pressure gradient may be a suppression of LV overcontraction, and the other important mechanism may be LV reverse remodeling by cibenzoline therapy [14].

In this issue, Tomofuji et al. [15] report a case with TCM demonstrating a LVOT pressure gradient with 72 mmHg and considered to be a high risk for cardiac rupture. β-Blockers were contraindicated for the patient because of bronchial asthma. Intravenous cibenzoline administration resulted in successful attenuation of the patient's LVOT obstruction. The present case suggests that cibenzoline might be effective for the treatment of LVOT obstruction in TCM, especially in those contraindicated for β-blocker therapy.

β-Blockers are the first-line drugs for the treatment of LVOT obstruction in TCM and HCM. In case β-blockers are contraindicated due to bronchial asthma or coronary artery spasm or β-blockers are ineffective, other drugs such as verapamil for both conditions or disopyramide for HCM will be considered. Cibenzoline is an alternative drug for HCM, and the effects and safety have been well established. Tomofuji et al. have shown that cibenzoline is also effective for LVOT obstruction in TCM when β-blockers or other drugs are contraindicated or ineffective [15].

The mechanisms of LVOT obstruction in TCM and HCM have similarity but are not identical. LVOT obstruction in TCM is acute and transient, and sometimes life threatening. LVOT obstruction in HCM is chronic, dynamic, and contributes to the debilitating heart failure-related symptoms that may occur in HCM and is also a determinant of outcome. Although more clinical experience will be required, cibenzoline could be a new option for clinical management of LVOT obstruction in TCM.

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