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A short-acting beta-blocker, landiolol, attenuates systolic anterior motion of the mitral valve after mitral valve annuloplasty

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Abstract
Here, we describe three patients with severe hemodynamic instability after mitral valve annuloplasty (MVP) who were treated successfully using a new ultra-short-acting beta-blocker, landiolol hydrochloride. When systolic anterior motion (SAM) of the mitral valve occurs after MVP, left ventricular outflow tract obstruction (LVOTO) and mitral regurgitation (MR) often lead to hemodynamic collapse. Treatment of SAM is very difficult, and transfusion, or the reduction/discontinuation of catecholamine or vasopressor administration, is often ineffective. In our three patients, landiolol hydrochloride decreased the heart rate, markedly attenuated SAM, and improved the hemodynamics. We recommend that landiolol be administered before further surgical manipulation is considered in patients with SAM after MVP.

Key words Landiolol hydrochloride · Systemic anterior motion of the mitral valve (SAM) · Mitral valve annuloplasty (MVP)

Introduction

It is known that systolic anterior motion (SAM) of the mitral valve can occur when a patient is weaned from extracorporeal circulation during mitral valve annuloplasty (MVP) for mitral regurgitation (MR). Subsequent to the occurrence of SAM, left ventricular outflow tract obstruction (LVOTO) and MR often develop, leading to severe circulatory collapse. However, it is very difficult to treat severe SAM quickly during surgery. Here, we report three patients in whom SAM (resulting in circulatory collapse) developed after MVP, and in whom landiolol hydrochloride, a novel beta-blocker, markedly alleviated SAM and improved the hemodynamics.

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Case 1

A 66-year-old man, weighing 53 kg, with a height of 151 cm, had upper abdominal pain, and thorough testing confirmed moderate MR; thus, MVP was indicated. Preoperative echocardiography confirmed moderate MR accompanied by prolapse of the medial scallop of the posterior leaflet. The ejection fraction was 65.3%, and the posterior leaflet was also elongated.

As preanesthetic medication, 10 mg morphine hydrochloride was intramuscularly injected. Anesthesia was induced by the intravenous injection of 4 mg midazolam, 250 μg fentanyl, and 8 mg vecuronium, and was maintained with 40%–100% oxygen and continuous infusion of propofol (6 $mg \cdot kg^{-1} \cdot h^{-1}$). Intravenous fentanyl (total, 1000 μg) was periodically administered [1]. For patient monitoring, five-lead electrocardiography, invasive arterial pressure monitoring, pulmonary arterial pressure measurement, central venous pressure measurement, pulse oximetry, capnometry, and transesophageal echocardiography (TEE) were performed. Quadrangular resection of the posterior leaflet of the mitral valve was performed. Because the preoperative assessment suggested an elongated posterior leaflet, ring annuloplasty was not performed, and the patient was weaned from cardiopulmonary bypass (CPB) without catecholamine.

After the patient's separation from CPB, TEE monitoring confirmed that SAM, and LVOTO and MR occurred (Fig. 1). As indicated in Table 1, severe circulatory collapse developed. Hypovolemia was suspected, and transfusion was performed, after which noradrenaline was administered, but the patient's condition did not improve. Subsequently, landiolol hydrochloride administration was initiated, at 125 $\mu g \cdot kg^{-1} \cdot min^{-1}$. After 3 min of landiolol administration (Fig. 2), TEE confirmed the disappearance of SAM, LVOTO, and MR, and the hemodynamics improved substantially (Table 1). The landiolol hydrochloride dose was then reduced

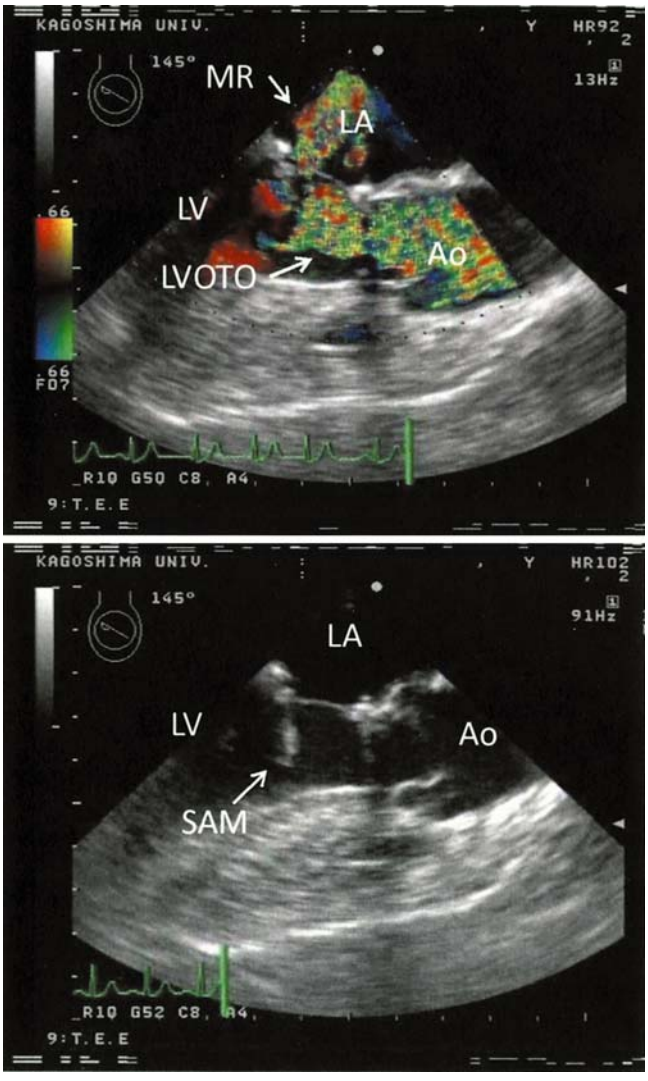

Fig. 1. Transesophageal echocardiography mid-esophageal long-axis view before landiolol hydrochloride administration, showing systolic anterior motion (*SAM*), left ventricular outflow tract obstruction (*LVOTO*), and mitral regurgitation (*MR*). *LA*, left atrium; *LV*, left ventricle; *Ao*, aorta

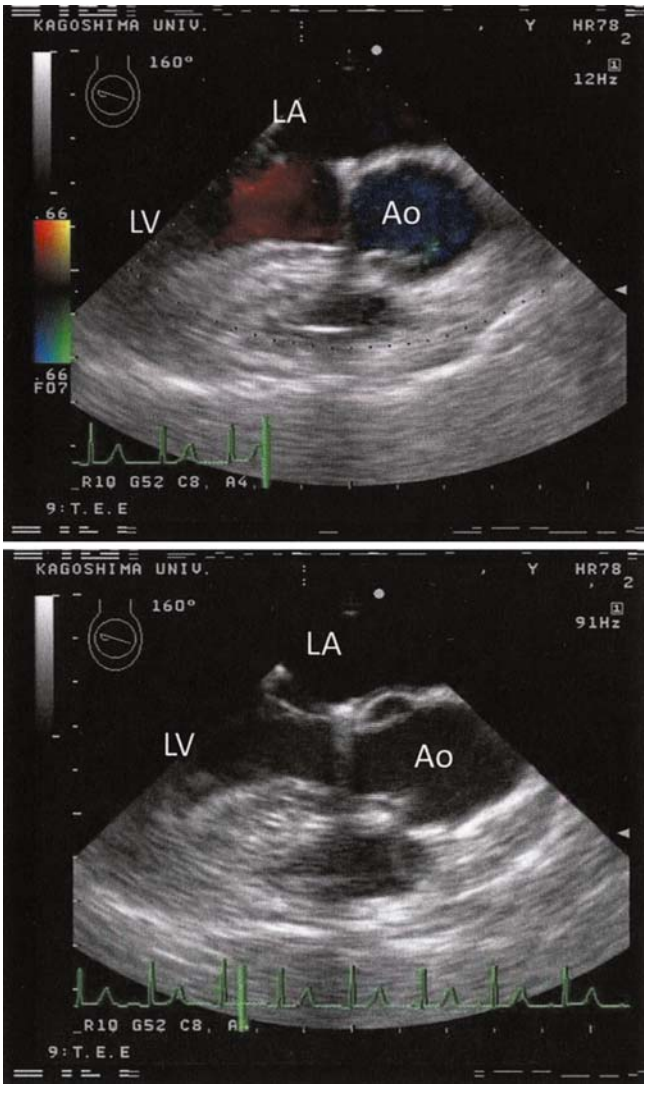

Fig. 2. Transesophageal echocardiography mid-esophageal long-axis view after landiolol hydrochloride administration, showing no residual left ventricular outflow tract obstruction or mitral regurgitation. *LA*, Left atrium; *LV*, left ventricle; *Ao*, aorta

to 10–40 $\mu g \cdot kg^{-1} \cdot min^{-1}$, but SAM did not appear and the hemodynamic decompression was not exacerbated. Low-dose landiolol was administered at the end of surgery upon the patient's arrival at the intensive care unit (ICU). As the patient's hemodynamic data remained within normal limits, landiolol was discontinued, uneventfully, after 5 h of administration.

Case 2

A 57-year-old woman, weighing 58 kg, with a height of 165 cm, had dyspnea on exertion, and thorough testing confirmed severe MR; thus, MVP was indicated. The ejection fraction was 66.7%, and the posterior leaflet was also elongated. With regard to past medical history, the patient was suspected of having had rheumatic fever. Preanesthetic medication and anesthesia were performed as described for case 1. Triangular resection of the posterior leaflet of the mitral valve and valve ring suturing were performed, dopamine and dobutamine were infused at a rate of 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and the patient was then weaned from CPB. As in case 1, TEE monitoring confirmed SAM, LVOTO, and MR, and severe circulatory failure developed (Table 1). Firstly, dopamine and dobutamine were stopped. Secondly, hypovolemia was suspected, and transfusion was performed, after which noradrenaline was administered; however, neither treatment improved the situation. Landiolol hydrochloride administration was then initiated, at

Table 1. Hemodynamics before and after landiolol administration

	Case 1	Case 2	Case 3
MAP (mmHg)			
Before landiolol	51	50	58
After landiolol	76	86	84
HR (bpm)			
Before landiolol	126	120	118
After landiolol	78	72	70
CI ($l \cdot min^{-1} \cdot m^{-2}$)			
Before landiolol	1.6	2	2.2
After landiolol	3.3	3.6	3.8
SV (ml)			
Before landiolol	19	27	33
After landiolol	63	82	95
MPAP (mmHg)			
Before landiolol	32	28	31
After landiolol	20	18	20
PCWP (mmHg)			
Before landiolol	22	21	22
After landiolol	8	7	6
Sv_{O_2} (%)			
Before landiolol	59	63	62
After landiolol	79	80	81

MAP, mean arterial blood pressure; HR, heart rate; CI, cardiac index; SV, stroke volume; MPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; Sv_{O_2}, mixed venous O_2 saturation

125 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and after 5 min, TEE confirmed the disappearance of SAM, and the hemodynamics improved (Table 1). The landiolol hydrochloride dose was then reduced to 10–40 $\mu g \cdot kg^{-1} \cdot min^{-1}$, as in case 1.

Case 3

A 62-year-old man, weighing 71 kg, with a height of 162 cm, exhibited cardiac murmur, and thorough testing confirmed moderate MR; thus, MVP was indicated. The ejection fraction was 71.5%, thickening of the ventricular septum was absent, and the posterior leaflet was elongated. Preanesthetic medication and anesthesia were performed as described for case 1. Triangular resection of the posterior leaflet of the mitral valve was performed. Valve ring suturing was performed, and dopamine and dobutamine were infused at a rate of 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$; the patient was then weaned from the extracorporeal circulation (CPB). Ten min after the weaning from the CPB, TEE monitoring confirmed SAM, LVOTO, and MR. Dopamine and dobutamine were stopped, transfusion was performed, and noradrenaline was administered, but the patient's condition did not improve. Subsequently, landiolol hydrochloride administration was initiated, at 125 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and after 3 min, TEE confirmed the disappearance of SAM, LVOTO, and MR (Table 1). The landiolol hydrochloride dose was then reduced to 10–40 $\mu g \cdot kg^{-1} \cdot min^{-1}$, but SAM did not appear and the hemodynamic decompression was not exacerbated.

Discussion

In the three patients in the present study, treatment with landiolol hydrochloride markedly stabilized the hemodynamic decompression caused by SAM following MVP. SAM is a well-known complication that follows MVP, and its incidence has been reported at 2%–14% [2–4]. As SAM increases the likelihood of MR and LVOTO, and these complications often occur together in MVP, there is a high risk of severe circulatory collapse during surgery. SAM following MVP is reported to be caused by such factors as an elongated posterior leaflet of the mitral valve, nondilating left ventricle, and valve ring sliding when a small artificial valve ring is used [5–7]. In SAM, the valve coaptations for the anterior and posterior leaflets of the mitral valve are displaced anteriorly. Insufficient ventricular volume increases the rate of blood flow from the narrow left ventricle, thus resulting in venturi effects. The anterior leaflet of the mitral valve is also drawn towards the ventricular septum, thus shortening the distance between the two tissues. At this time, the force pushing the mitral valve may also be involved. However, landiolol decreases the heart rate, and is thus used to treat SAM and LVOTO. Subsequently, hemodynamics are improved and valve replacement surgery can be avoided. TEE is useful in diagnosing SAM and in determining the appropriate time for landiolol administration [8, 9]. Other beta-blockers, such as propranolol (long-acting and potently cardiodepressive) and esmolol (short-acting and less cardiodepressive), have also been considered for administration [10]. However, landiolol, an ultrashort-acting β1-selective adrenoceptor antagonist, has a shorter plasma half-life, approximately 4 min, as compared with esmolol (9 min) and propranolol, and has a potency ratio (β1/β2) of 255 when compared with that of esmolol, at 33 [11]. Because hemodynamics are unstable when a patient is being weaned from extracorporeal circulation, drugs that can strictly control the effects are more desirable. Therefore, for the treatment of SAM during cardiac surgery, a continuous infusion of landiolol is recommended, because it has a relatively short action and favorable potency ratio.

In the present patients, the preoperative posterior leaflet of the mitral valve was elongated, at 19, 15, and 17 mm, respectively; the normal length of the posterior leaflet is 12.8 ± 1 mm [12]. Generally, if the posterior leaflet is long, to avoid SAM during surgery, either no artificial valve ring is used, or a slightly larger artificial valve ring than artificial valve ring is employed, or a sliding technique that narrows the width of the posterior

leaflet is used [5, 13]. Due to the high risk of SAM occurrence when an artificial valve ring is not used, a quadrangular resection of the posterior leaflet of the mitral valve was performed in case 1, and a slightly larger artificial valve ring than artificial valve ring was used in cases 2 and 3.

Nevertheless, if circulatory collapse due to SAM occurs, together with LVOTO and MR, both medical and surgical treatments are available. Brown et al. [2] compared medical and surgical treatments for SAM following MVP and reported that the vital prognosis was more favorable with medical treatment, because SAM tended to occur most frequently during the intraoperative period. SAM was sufficiently ameliorated to ensure that further surgery was not required. Furthermore, the clinical outcomes of patients with SAM were comparable to the current norms for mitral valve repair [2]. Therefore, even if circulatory dynamics can be maintained despite postoperative SAM, it is desirable to avoid repeated surgery. It is possible that SAM can be medically treated with transfusion to increase left ventricular capacity, with the reduction/discontinuation of catecholamine administration to suppress the rate of outflow tract flow, or with vasoconstrictors to diminish the intraventricular pressure gradient [2]. Nakagawa et al. [14] reported that angiotensin receptor antagonists also ameliorated intraventricular obstruction.

In the present patients, although neither volume replacement nor cessation of catecholamine was effective for the treatment of SAM, landiolol hydrochloride eliminated SAM and quickly resolved the circulatory collapse. Transfusion did not attenuate SAM, thus suggesting that the SAM was not induced by hypovolemia after CPB. Noradrenaline was administered in all patients. Dopamine and dobutamine were administered in cases 2 and 3. Although dopamine and dobutamine were stopped, SAM was not attenuated; the beta-blocker landiolol recovered the hemodynamics. These results suggest that sympathetic nervous system stimulation, particularly beta-adrenergic stimulation, caused the SAM that was observed in our patients. It appears that surgical and CPB-induced stresses may activate sympathetic nerves and increase circulating catecholamine levels, resulting in hypercontractility, leading to SAM.

In conclusion, when additional volume expansion fails in the treatment of SAM that occurs after MVP, landiolol can be administered before further surgical manipulation is considered.

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