Production of systolic anterior motion of the mitral valve in dogs

SHUGO SAKurai, M.D., HIROMItU TANaka, M.D., HISAKazu YOSHIMura, M.D., SHOICHIRO NAKAO, M.D., AND MINORu TAHARA, M.D.

ABSTRACT Production of an experimental preparation of systolic anterior motion (SAM) of the mitral valve was attempted for the purpose of clarifying its causal factors. Fourteen thoracotomized dogs under pentobarbital anesthesia were administered dobutamine, and the echocardiogram, left ventricular pressure, and aortic pressure of each were simultaneously recorded. In two of the dogs in which SAM was produced, two-dimensional echocardiograms were also obtained. Although SAM was absent in all 14 dogs before the administration of dobutamine, it appeared in nine of them after the drug was given. In seven of these dogs, the magnitude of SAM and outflow pressure gradient varied in a dose-dependent manner. No signs of asymmetric septal hypertrophy were observed in any of these dogs. SAM tended to occur even when there was no reduction in pre-ejection period when narrowing of the left ventricular outflow tract was observed. On the two-dimensional echocardiograms, the position of coaptation of the mitral valve was shifted closer to the base of the anterior leaflet in the presence of dobutamine-induced SAM than before the drug was administered. Although the left ventricular cavity became narrow, it was not completely obliterated. This study demonstrates that experimental preparations of SAM can be produced by the administration of dobutamine with a relatively high success rate in normal dogs, and that experimental SAM is accompanied by an outflow tract pressure gradient.


SINCE Shah et al.\(^1\) and Popp and Harrison\(^2\) observed systolic anterior motion (SAM) of the mitral valve echocardiographically in patients with hypertrophic obstructive cardiomyopathy, several causal factors of SAM have been proposed. Pridie and Oakley\(^3\) suggested that SAM and mitral incompetence result from abnormal traction of the mitral valve by contraction of the papillary muscles. Wigle et al.\(^4\) and Henry et al.\(^5\) have ascribed SAM to the Venturi effect and Roger\(^6\) has proposed that SAM is caused by anterosuperior displacement of the papillary muscle during systole, which results in the forward and upward displacement of the mitral leaflets. Shah et al.\(^7\) have theorized that SAM is caused by increased free edge of the mitral valve, since the edge is relatively long for the area of the valve.

These observations were made in patients with asymmetric septal hypertrophy (ASH), but several investigators\(^8\)–\(^11\) have reported SAM in those without ASH. In such patients small ventricular size, abnormal ejection dynamics, and hypercontractile cardiac states have been suggested as causes of SAM.

Although many investigators have participated in the search for the causal factors of SAM, no attempts at producing an experimental preparation of the disorder have been reported. In the present study we address this issue.

Materials and methods

Fourteen mongrel dogs (body weight 14 to 30 kg) were anesthetized intravenously with pentobarbital (25 mg/kg), and an endotracheal tube was inserted in each. After initiation of controlled room air respiration, a median thoracotomy was performed.

Two catheters (Microtip manometer; Miller) were inserted, one from the carotid artery to the ascending aorta, and the other from the apex of the left ventricle into the left ventricular cavity. A flat sensor (3.0 MHz, 5 mm in diameter) was placed directly on the right ventricular free wall to allow echocardiographic examination. Aortic blood flow was determined with a magnetic flowmeter (MF-27, Nippon Koden) and a blood flow probe for determination of large vessel flow was attached to the aortic root. Signals of aortic pressure, left ventricular pressure, and aortic flow along with those of echocardiograms were fed into a sonocardiograph (SSL-51U, Toshiba) and simultaneously re-
corded with a strip-chart recorder (Model OR-01A) at a paper speed of 100 mm/sec.

The left ventricular outflow tract (LVOT) pressure gradient was recorded continuously while the catheter was drawn from the left atrium to the left ventricular apex (figure 1).

After control values were obtained, recordings were repeated while dobutamine (20 µg/min) was continuously administered intravenously for 1 to 2 hr. When SAM was detected, a process of gradually regulating, suspending, and resuming the administration of drug was repeated.

The thickness of the intraventricular septum (IVS) was measured on echograms at the peak of the R wave of the electrocardiogram (ECG) in the diastolic phase and at the time point before drug administration at which the IVS was thickest in the systolic phase. The degree of systolic thickening of the septum was expressed as the systolic minus the diastolic thickness divided by the latter. The thicknesses of the IVS and the left ventricular posterior wall (LVPW) were determined after the hearts had been removed and fixed in formalin at the section immediately above the papillary muscles.

The distance from the C point on the mitral valve to the IVS was measured to determine the diameter of the LVOT, and preejection period was determined as the time from the onset of the R wave of ECG to the point at which left ventricular pressure exceeded aortic pressure. Preejection period was used in the present study as an approximate index of left ventricular function, since comparisons between fast heart rates were involved and the heart rate was primarily determined by the dosage of dobutamine given.

The systolic pressure gradient between left ventricular pressure and aortic pressure refers only to that between the left ventricular inflow tract (LVIT) and the aorta, which reaches a peak in mid-systole and lasts until end-systole, and not to that seen only at early systole. Measurement sites were specified for other pressure gradients. The pressure gradient used was the difference between the peak values of the two pressures (left ventricular and aortic).

Two-dimensional echocardiograms were obtained from two dogs with SAM with a sonolyergraph (SSH-11A, Toshiba). The images were recorded on 8 mm movie film and each exposure was studied.

Results

**Induction of SAM.** Table 1 lists data on the presence or absence of SAM and hemodynamic indexes before and after the administration of dobutamine. The post-drug left ventricular pressure and pressure gradient are the values obtained while the catheter was in place in the LVIT. Before dobutamine neither SAM nor the systolic pressure gradient was echographically observable in any of the dogs (figure 2, A). SAM appeared in nine of the 14 dogs at various postdrug intervals (30 to 120 min) (figure 2, B to D). In two (Nos. 8 and 9) of the nine dogs in which SAM was observed, no systolic pressure gradient was present between left ventricular pressure and aortic pressure, nor was the mitral leaflet in contact with IVS. In these two dogs, a left ventricular pressure–aortic pressure gradient appeared only in the early systole. This pressure gradient was also found in dogs without SAM and on predrug recordings (figure 1, A, table 1). In the other seven dogs (Nos. 1 to 7), SAM of various dose-dependent magnitudes (ranging from that without mitral leaflet–IVS contact to that with contact in early systole) was observed (figure 2, B to D). The SAM in these dogs was accompanied by various systolic pressure gradients, and the maximal gradient ranged from 30 to 154 mm Hg (table 1). After repeated administration of dobutamine over 4 to 5 hr, SAM was induced within 5 min of a dose of the drug smaller than 20 µg, and always disappeared with its cessation. When SAM reached the ventricular septum, a dip in the aortic pressure waveform that approximately coincided with the point of contact and a rapid decrease in aortic flow were observed. These phenomena became more evident when the mitral-septal contact occurred earlier in systole (figures 2 and 3). Although in the dogs showing no SAM-septal contact or SAM an interventricular pressure gradient between the LVIT and the apical region was noted while withdrawing the catheter from the left atrium to the left ventricle, no recognizable dip in the aortic pressure waveform was observed (see figure 6).

**Thicknesses of IVS and LVPW.** The thicknesses of the IVS and LVPW were measured echocardiographically in hearts removed at autopsy from 14 dogs (Nos. 1 to 14) (table 2). Echocardiographic measurements were as follows: The thickness of the IVS was 7 ± 0.6 mm (mean ± SD) in diastole and 12 ± 1.2 mm in systole. Systole wall thickening of the IVS was 58 ± 11.9% (table 2). Since the LVPW was not clearly visualized, its thickness was not measured. Measurements of thickness from the autopsied hearts were 12 ± 1.9 mm for the IVS and 13 ± 2.0 mm for the LVPW. The ratio of IVS to LVPW thickness was 0.92 ± 0.11.

**SAM in relation to LVOT and preejection period.** LVOT before administration of dobutamine in nine dogs with SAM was 16.8 ± 2.39 mm (mean ± SD), but decreased to 9.9 ± 2.33 mm when the systolic pressure gradient was maximal after the drug was given (table 2).
1). When LVOT was relatively wide, SAM (with and without a pressure gradient) tended to appear in association with a decrease in preejection period, but when narrowing of the LVOT occurred, it appeared even without the decrease (figure 4).

**Systolic pressure gradient and its site.** In the seven dogs in which mitral-septal contact was observed, a gradient between left ventricular pressure and aortic pressure appeared as soon as the catheter entered the left ventricle (figure 5); in the two dogs without SAM-septal contact, an interventricular pressure gradient was observed between the LVIT and the apical region (figure 6). Two-dimensional echocardiograms from two dogs exhibiting both mitral-septal contact and a dip in the aortic pressure waveform revealed no obliteration of LVIT, despite a severe narrowing of the left ventricular cavity (figure 7).

**Findings on the two-dimensional echocardiograms.** The length of the anterior leaflet of the mitral valve of dog 6 in figure 7 was about 16 mm during diastole, and the sum of the length of the anterior leaflet and that of SAM during systole was about 16 mm.

In dog 4 in figure 8 the position of coaptation of the mitral valve in the presence of SAM was closer to the

**TABLE I**

Echocardiographic and hemodynamic data obtained before and after infusion of dobutamine

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>BW (kg)</th>
<th>RR interval (msec)</th>
<th>AoP (mm Hg)</th>
<th>LVP (mm Hg)</th>
<th>PEP (msec)</th>
<th>LVOT (mm)</th>
<th>RR interval (msec)</th>
<th>AoP (mm Hg)</th>
<th>LVP (mm Hg)</th>
<th>PG (mm Hg)</th>
<th>PEP (msec)</th>
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Mean 410.0 83.0 19.0 267.0 38.0 12.0
SD 58.2 11.6 4.1 24.0 5.0 4.3

Data after dobutamine infusion represent those at maximum pressure gradient.

BW = body weight; AoP = aortic pressure; LVP = left ventricular pressure; PG = pressure gradient; PEP = preejection period.
The pressure measurements we obtained while withdrawing the catheter from the left atrium to the left ventricle, the two-dimensional echocardiographic findings in two dogs, and the fact that the dip in the aortic pressure waveform nearly coincided with the SAM-septal contact suggest that experimentally induced SAM caused LVOT pressure gradients similar to those seen in humans. Furthermore, aortic pressure and aortic flow waveforms observed during the SAM-septal contact closely resembled those observed in idiopathic hypertrophic subaortic stenosis. In two dogs of a different series of similar experiments, cavity obliteration extending to the LVIT was noted. In those dogs, however, no clear dip in the aortic pressure waveform or SAM-septal contact was observed. Cavity obliteration to the inflow tract appears to be more frequent in the absence of severe SAM, in which the mitral-septal contact occurs in early systole.

The aortic flow waveform in patients with the obstructive form of hypertrophic cardiomyopathy, characterized by a rapid flow during early systole and a subsequent sudden reduction in flow, is known to differ from that observed in those with the nonobstructive form of the disease. On the other hand, Murgo et al. observed no difference in the left ventricular emptying rate calculated from aortic flow and results of left ventricular cineangiography in patients with the obstructive and nonobstructive forms of hypertrophic cardiomyopathy.

### TABLE 2

<table>
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<tr>
<th>Dog No.</th>
<th>D (mm)</th>
<th>S (mm)</th>
<th>S−D (mm)</th>
<th>S−D (%)</th>
<th>IVS (mm)</th>
<th>IVS/LVPW</th>
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D = diastole; S = systole.
cardiomyopathy, and therefore suggested that SAM does not impede the LVOT. In the present study, however, aortic flow decreased rapidly after the onset SAM-septal contact. This tendency was more evident, with the contact becoming coincident with peak aortic flow, when the contact occurred earlier in systole (figure 3). These changes in aortic flow as well as in aortic pressure and the two-dimensional echograms indicate an impedance of the LVOT by SAM. The mean pressure gradient reported by Murgo et al. in their group with obstructive hypertrophic cardiomyopathy was relatively low (51 mm Hg), and the values varied widely among the patients, two of whom had gradients below 20 mm Hg. The absence of a difference in the rate of left ventricular emptying in the patients with obstructive and those with nonobstructive disease may be related to these factors. These investigators compared the rate of left ventricular emptying between the groups with and without a pressure gradient by use of a parameter defined as the ratio of forward flow time/systolic ejection period. In the same report, prolongation of both systolic ejection period and forward flow time was noted in the group with a pressure gradient. The validity of a comparison of these parameter values is doubtful. If SAM does not impede the LVOT, the cause of the prolongation of the above-mentioned time indexes in the group with obstructive disease seems inexplicable. The obstructive form of hypertrophic cardiomyopathy is known to be accompanied by mitral regurgitation, the extent of which is also considered to have an effect on the emptying rate.

Narrowing of the LVOT has been regarded as an important factor in the SAM observed in humans. In the present study, the LVOT was narrow when SAM was present, and SAM tended to occur even without a shortening of preejection period (after small doses of dobutamine) when narrowing of the LVOT was observed, indicating the importance of this narrowing in experimentally induced SAM. The close association between SAM and the narrowing of the LVOT implies two possible mechanisms of SAM. First, narrowing of the LVOT associated with narrowing of the left ventricular cavity may induce a Venturi effect. Second, narrowing of the LVOT may result from abnormal coaptation of the mitral valve at the onset of systole, and SAM may occur as the increased mitral free edges are carried to the outflow tract by the
blood flow. In the latter case, the Venturi effect is not considered to be a key factor in SAM.

Our finding, by two-dimensional echocardiography, that the position of mitral coaptation shifted closer to the base of the anterior mitral leaflet after administration of dobutamine might support the second mechanism. We could not determine in the present experiments, however, whether the abnormal mitral coaptation resulted from the Venturi effect or from other foregoing factors, such as narrowing of the mitral ring or abnormal displacement of the papillary muscles.

Shah et al. observed that the mitral valve is long in relation to the diameter of the mitral ring, and speculated that this disproportionate length of the leaflets might be responsible for SAM. Our findings on two-dimensional echocardiograms of experimental SAM resemble those observed in patients with SAM reported by Shah et al.

The anterior mitral leaflet was reported to be longer in patients with hypertrophic cardiomyopathy than in normal individuals. More recently SAM of the posterior leaflet was observed in hypertrophic cardiomyopathy patients. This phenomenon, not considered to be rare, was ascribed to abnormal coaptation of the mitral valve due to the malformed posterior leaflet. Involvement of such malformation in the SAM of patients with hypertrophic cardiomyopathy appears to be possible, although it may be excluded as the cause of the SAM produced in our experiments.

There have been a number of reports on SAM without ASH, and it was suggested that small ventricular size, a hypercontractile cardiac state, and abnormal ejection dynamics were causal factors. Our finding that SAM accompanied by an LVOT pressure gradient may occur under hypercontractile cardiac conditions or when the ventricular size is small may contribute to clarification of the cause of SAM and the relationship between SAM and hemodynamics in patients without ASH.

In our experiments, SAM was produced in some dogs at relatively long intervals (about 2 hr) after administration of dobutamine. Once SAM was observed, it disappeared with cessation of dosing but reappeared soon after resumption of administration at small doses. Since the experiments were conducted under thoracot-

**FIGURE 7.** Echocardiograms from long-axis view (dog 6). Echograms from end-diastole (A) and mid-systole (B) are shown on the top and are schematized on the bottom. The shadowed areas of the schemata represent the mitral valve and its SAM (possibly including the chordae tendineae). L represents the length of the anterior mitral leaflet during diastole, L, is the distance from the base of the anterior mitral leaflet to coaptation of the valve, and L2 the extent of SAM. See text for detailed discussion. These panels were prepared from 8 mm movie films.
omy, it seems likely that the animals became increasingly hypovolemic, and that the resultant narrowing of the left ventricle facilitated the occurrence of SAM.

SAM was not observed in five dogs. We could not assess whether the absence of SAM was the result of differences in the sizes of the animals (or the hearts), the structure of their mitral complexes, or other factors. SAM might have been induced if the experiments had been continued longer.

Although no notable changes were observed in left atrial pressure associated with the appearance of SAM, further studies with atrial phonocardiography and contrast echocardiography will be needed to clarify whether experimental SAM is accompanied by mitral regurgitation.

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