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# 僧帽弁逸脱症候群の心音図：体位変換，薬剤負荷試験ならびに心エコー図法との対比

# Phonocardiographic findings of mitral valve prolapse syndrome: Comparative study of phonocardiography at rest, on standing, and after amyl nitrite inhalation with ultrasono-cardiotomography

石田健次郎　Kenjiro ISHIDA
松本　幸平　Kohei MATSUMOTO
織田　明伸　Akinobu ODA
横田　慶之　Yoshiyuki YOKOTA
小林　克也　Katsuya KOBAYASHI
前田　和美　Kazumi MAEDA
猪尾　力　Tsutomu INOH
福崎　恒　Hisashi FUKUZAKI

**Summary**

Comparative study of phonocardiograms at rest, on standing, and after amyl nitrite inhalation with ultrasonic finding was done in 40 cases of mitral valve prolapse syndrome (MVPS). At rest, heart murmur suggesting so-called "innocent murmur" was observed in 17.5%, while there were neither systolic clicks nor murmurs (silent MVPS) in 10% of the cases examined. Postural change to the standing produced various responses of the murmur and clicks. On the contrary, amyl nitrite inhalation produced the shift of the murmur to early systole ad the increase in its amplitude with moving clicks forth in the majority of cases. Mitral valve prolapse (MVP) was classified into prolapses of anterior

神戸大学医学部　第一内科
神戸市生田区楠町 7-13（〒650）

Department of Internal Medicine, Division I, Kobe University School of Medicine Kusunoki-cho 7-13, Ikuta-ku, Kobe, 650

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alone, posterior alone, or both leaflets according to the ultrasono-cardiotomographic findings. There were no significant differences among each group except for the less prevalent incidence of systloic clicks in the group of posterior MVP. After amyl nitrite inhalation, approximatley one-thirds of the patients revealed the finding of the shifted aortic component of the second heart sound ($A_2$) forth, at least 40 msec apart from the end of the T wave of the electrocardiogram, which was designated as an early $A_2$. It was considered that this phenomenon was probably related to the augumented mitral regurgitation and/or prolongation of the corrected QT interval (QTc). We conclude that it is important to confirm the diagnosis with ultrasono-cardiotomography (UCT) and perform phonocardiography using amyl nitrite, whenever MVPS is suspected.

**Key words**
Mitral valve prolapse syndrome (MVPS) Phonocardiogram Ultrasono-cardiotomography (UCT) Standing Amyl nitrite

Phonocardiographic finding of mid-systolic click-late systolic murmur has been recognized for many years[1,2], and mitral valve prolapse syndrome (MVPS) was thought as one of the most probable underlying etiology[3~5]. Development of echocardiography has exposed this syndrome, consisting of various phonocardiographic manifestations. This report details phonocardiographic characteristics at rest, on standing, and after amyl nitrite inhalation in MVPS, whose diagnosis was confirmed by ultrasono-cardiotomography (UCT) and/or left ventriculography.

## Material and Methods

Totally 40 cases of MVPS, 24 males and 16 females, with the age ranging from 16 to 59 years old were studied. They were hospitalized patients or follow-up cases at the outpatient clinic of the Department of Medicine, Division I, Kobe University Hospital. The diagnosis was confirmed by UCT and/or left ventriculography. Ten normal subjects with the age ranging from 21 to 31 years old consisted the control group, and they had no abnormality in each of history, physical examination, electrocardiogram, chest X-ray and echocardiogram.

Phonocardiograms (PCG) were taken using contact microphone (MA 250, Fukuda Co., Ltd.) and multichannel polygraph recorder (MCM 8000, Fukuda Co, Ltd) with multiple filters of low, medium and high frequency. These were simultaneously recorded with electrocardiogram (EKG) on the ink-jet writing papers using Mingograph. Both echocardiography (UCG) and UCT were performed using Toshiba SSL-51H and UCT was obtained by mechanical sector scanning. UCT was recorded on 8 mm cine-films as well as polaroid films. All of the 40 cases underwent supine phonocardiography at rest, UCG, and UCT. Postural change to standing was attempted in 35 patients and amyl nitrite inhalation test in 38 patients, respectively. Patient inhaled amyl nitrite for 30 seconds under close observation with electrocardiographic and phonocardiographic monitoring.

## Results

1) As shown in **Fig. 1**, phonocardiographic findings in supine position were various: a) 17 of 40 cases (42.5%) revealed only systolic murmur, b) 18 patients (45%) showed both

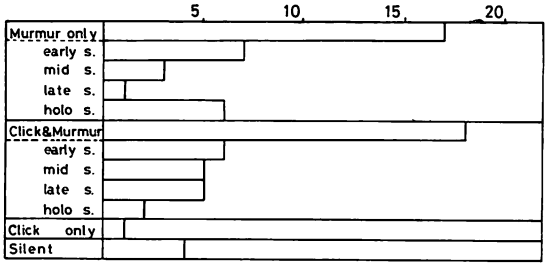


**Fig. 1. PCG findings of MVPS at rest.**

Various patterns ranging featured by silent type to click and murmur type are observed.

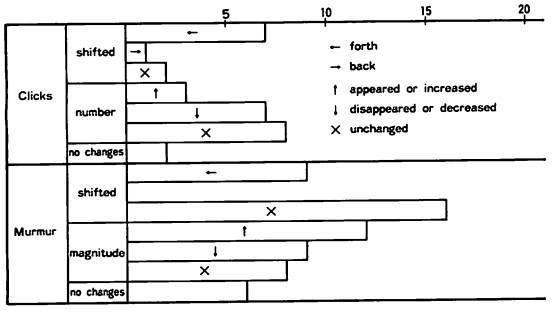


**Fig. 2. Effects of standing on clicks and murmur.**

Uniform changes are not observed. No changes indicate unchanged in number, location and magnitude.

systolic clicks and systolic murmur, c) one case (2.5%) presented only click, d) neither clicks nor murmur (silent MVP) was observed in 4 cases (10%). Seven out of 17 cases with systolic murmur alone demonstrated only soft and short systolic murmur in early systolic phase. Clicks with systolic murmur or holosystolic murmur which was regarded as typical findings of MVPS were observed in 60% in this series.

2) As **Fig. 2** demonstrates, behavior of systolic clicks on standing was a) shifted clicks forth in 7 cases, b) shifted clicks back in one case, which revealed no alteration of the murmur, c) increased number of clicks or newly developed clicks in 3 cases, d) decreased number or disappearance of clicks in 7 cases. Alterations of the systolic murmur on standing were a) shifted murmur forth in 9 cases (no case showed shifted murmur back), b) accentuation or newly developed murmur in 12 cases, c) diminution or disappearance of the murmur in 9 cases.

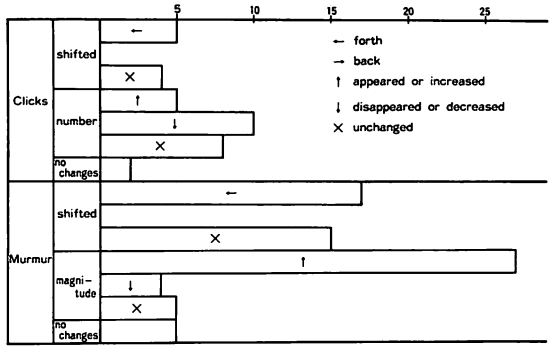


**Figure 3. Effects of amyl nitrite on clicks and murmur in MVPS.**

No clicks are shifted back and murmur is increased in most cases.

3) Amyl nitrite inhalation produced the following phonocardiographic changes (**Fig. 3**): a) shifted clicks forth in 5 cases (no cases showed shifted clicks back), b) increased number or newly developed clicks in 5 cases, c) decreased number or disappearance of clicks in 10 cases, d) shifted murmur forth in 17 cases, e) altered

**Table 1. PCG findings at rest correlating with location of MVP assessed by UCT**

| | Click<br>Click+M | Murmur only | | | | | Silent | total |
|---|---|---|---|---|---|---|---|---|
| | | early s | mid s | late s | holo s | total | | |
| A | 12 | 3 | 2 | 1 | 2 | 8 | 1 | 21 |
| AP | 6 | 2 | | | 2 | 4 | 2 | 12 |
| P | 1 | 2 | 1 | | 2 | 5 | 1 | 7 |
| total | 19 | 7 | 3 | 1 | 6 | 17 | 4 | 40 |

A: MVP of anterior leaflet, AP: MVP of both leaflets, P: MVP of posterior leaflet, Clicks are less prevalent in P.

**Table 2. Effects of standing correlating with location of MVP**

| | Clicks | | Murmur | |
|---|---|---|---|---|
| | shifted | number | shifted | magnitude |
| A | ←4 →1 /6 | ↑2 ↓6 /13 | ←7 /16 | ↑8 ↓6 /18 |
| P | ←1 /1 | /1 | /5 | ↑2 ↓1 /5 |
| AP | ←2 /3 | ↑1 ↓1 /4 | ←2 /4 | ↑1 ↓3 /6 |
| total | 8 /10 | 10 /18 | 9 /25 | 21 /29 |

No significant differences are shown among the groups.

**Table 3. Effects of amyl nitrite inhalation correlating with location of MVP**

| | Clicks | | Murmur | | early $A_2$ |
|---|---|---|---|---|---|
| | shifted | number | shifted | magnitude | |
| A | ←3 /6 | ↑2 ↓7 /12 | ←11 /21 | ↑15 ↓2 /21 | 5/18 |
| P | ←1 /1 | /1 | ←3 /6 | ↑5 ↓1 /6 | 3/6 |
| AP | ←1 /2 | ↑3 ↓3 /6 | ←3 /9 | ↑7 ↓1 /9 | 4/6 |
| total | 5 /9 | 15 /23 | 17 /36 | 31 /36 | |

No significant differences are shown among the groups.

magnitude of the murmur 31 out of 38 cases, (diminished in 4 and increased in 27, respectively).

4) As shown in **Table 1, 2,** and **3,** phonocardiographic findings at rest, on standing and after amyl nitrite inhalation were compared with classification of the prolapsed mitral valve (anterior, posterior and both leaflets) assessed by

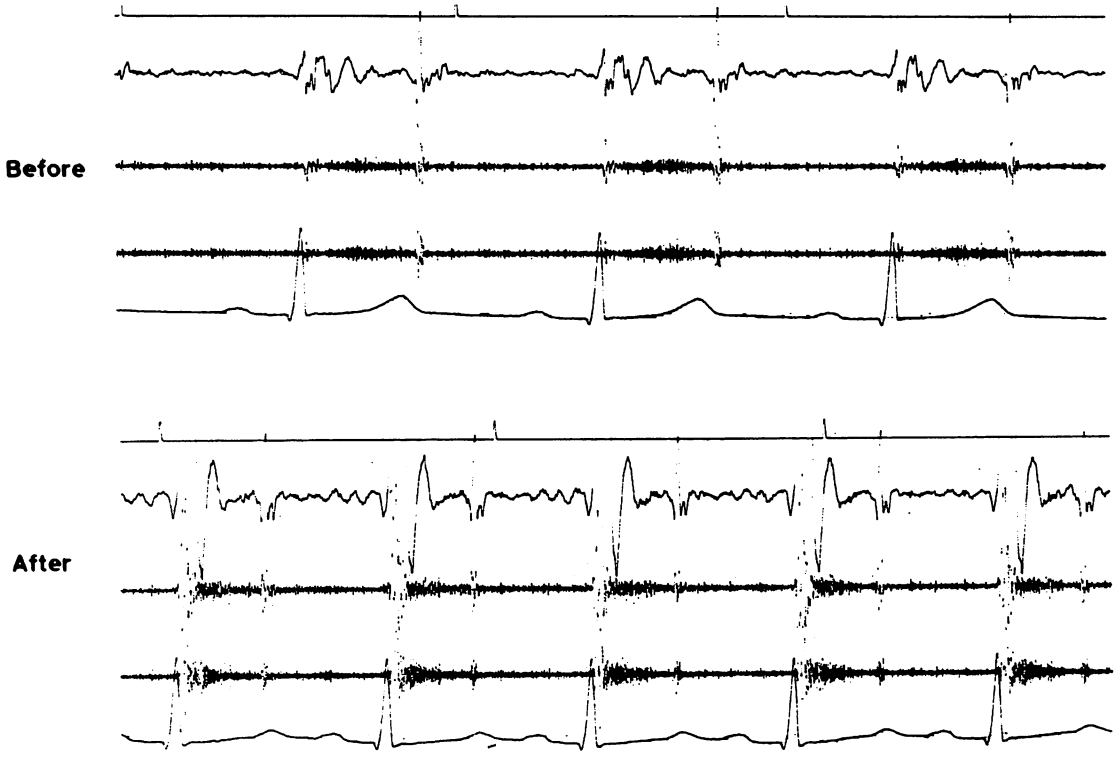


**Fig. 4. PCG indicating early $A_2$ after amyl nitrite inhalation in MVPS.**
Aortic component of the second heart sound is located before the peak of the T wave after amyl nitrite inhalation.

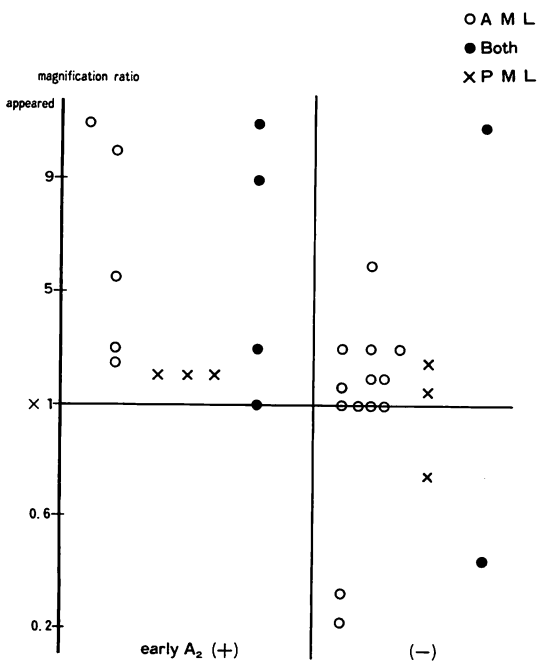


**Fig. 5. Electromechanical dissociation (early $A_2$) correlating magnification ratio of murmur following amyl nitrite.**

Magnification ratio is calculated from the amplitude of the wave through medium pitch filter. The upper three points are cases of MVPS that show the appearance of murmur but a case without early $A_2$ shows only faint murmur (Levine 1/6).

UCT. There were no significant differences among each group in phonocardiograms at rest, on standing, and after amyl nitrite inhalation except that the incidence of clicks was less prevalent in cases of posterior MVP.

5) **Fig. 4** illustrates the phonocardiogram after amyl nitrite inhalation in a case of MVPS, demonstrating $A_2$ located before the peak of the T wave of EKG. It was observed in our study that approximately one-thirds of MVPS revealed the $A_2$ occurred 40 msec or more before the end of the T wave. We designated here his phenomenon as electro-mechanical dissociation, related with early apperrance of the $A_2$ (early $A_2$). As shown in **Fig. 5**, none of the patients with early $A_2$ following amyl nitrite inhalation showed decreased intensity of the murmur, while all of the cases except one with markedly accentuated murmur more than 5 times presented the findings of early $A_2$. There was a case without early $A_2$ revealing appearrance of the murmur, but this murmur was faint (Levine's grade 1/6) and of short duration. In the majority of cases with early $A_2$, the murmur was shifted forth and the duration became longer, and substantial number of patients, namely more than a half, showed holosystolic murmur at the loading test. As indicated in **Table 4**, QTc was within normal limits at rest in the group with early $A_2$ as well as in the normal group without early $A_2$, but it was abnormally prolonged after amyl nitrite inhalation in all groups. There were no statistically significant differences between normal group and group without early $A_2$ both before and after loading test. However, significant difference ($p<0.005$) was present when these two groups were compared with the group with early $A_2$. This was supported by the evidence of different prolongation of QTc in these groups after loading test.

## Discussion

Though MVPS had been originally considered as a synonym of click and murmur syndrome, various phonocardiographic manifestations of this syndrome were subsequently reported with developed laboratory tests, especially angiocardiography and echocardiography[6]. From our study, MVPS was felt as the syndrome with wide phonocardiographic spectra ranging from silent cases to either cases with typical click and murmur, or cases with holosystolic murmur, or

**Table 4. Corrected QT interval before and after amyl nitrite inhalation in normal subjects and patients with MVPS**

| | Before-After |
|---|---|
| early $A_2$ (+) group | $P < 0.001$ |
| (−) group | $P < 0.001$ |
| normal group | $P < 0.001$ |

| | | Before | | | After | | |
|---|---|---|---|---|---|---|---|
| | | normal group | MVPS with early $A_2$ group | MVPS without early $A_2$ group | normal group | MVPS with early $A_2$ group | MVPS without early $A_2$ group |
| QTc | $\bar{X}$ | 0.373 | 0.410 | 0.378 | 0.444 | 0.491 | 0.433 |
| | SD | 0.022 | 0.020 | 0.025 | 0.019 | 0.025 | 0.015 |
| | P | <0.001 NS <0.005 | | | <0.001 NS <0.001 | | |

MVPS with early $A_2$ group shows significant prolongation of QTc after amyl nitrite inhalation.

cases with murmur only and cases with click alone. It was also noted that these phonocardiographic findings were not constant and 17.5% of the studied MVPS showed soft murmur of Levine's grade 1/6 to 2/6 with short duration which had been traditionally thought as an innocent murmur. Thus we felt obvious limitation of performing routine supine phonocardiography just once to detect this syndrome, because severity of the prolapse in the same case was not always uniform, but changeable under different conditions[7,8]. It has been thought that both clicks and murmur shifted forth due to decrease in end-diastolic volume (EDV) of the left ventricle[8,9] and murmur was accentuated right after standing[7,10]. However, we observed that location of the murmur was unchagned in many cases, while click was shifted back in a case. It was also noted that changes in intensity of the murmur was various, namely unchanged in 8 cases, accentuated in 12 cases, diminished in 9 cases. Four cases of silent MVP and 7 cases of so-called functional murmur showed no significant changes on standing. We considered that standing posture not only produced reduction in EDV, but also affected on mode of cardiac contraction. For example, it was well known that standing posture prolonged pre-ejection period[11], and thus it might be an explanation why uniform response to produce MVP earlier systolic phase was not always seen on standing. On the contrary, many of the patients showed clicks shifted forth after amyl nitrite inhalation. The murmur was also accentuated in most cases. Only 4 patients with presumably large mitral regurgitation demonstrated decrease in amplitude of the murmur.

Three of 6 cases, whose murmur was considered as innocent previously, turned to be holosystolic after amyl nitrite inhalation. Two of 4 silent MVPS revealed clearly developed systolic murmur. Amyl nitrite inhalation diminishes EDV[8,12], increases heart rate[8,12], increases maximum velocity of the circumferential fiber shortening and induces hyperkinetic state, which is probably more useful in obtaining clinical informations. MVPS is common[13], known to be generally benign in it's longterm natural history[14], and there are many asymptomatic cases. However, sudden deaths[15~18], marked mitral valve regurgitation[19], and abrupt onset of chordal rupture[20] were sporadically reported even though it was not well known, which of these MVPS would be complicated with.

It is also suggested that sudden death in MVPS could be resulted from serious arrhythmias, especially ventricular tachycardia and fibrillation, possibly related with prolonged QT interval[17,21]. We reported in this study that 30% of cases with MVPS showed early $A_2$ after amyl nitrite inhalation, which revealed prolongation of QTc as well as increased intensity of the regurgitant murmur. At present, this mechanism of prolonged QTc is unknown, even though it might be postulated that papillary muscle is excessively extended, severe enough to produce ischemia which alters the process of repolarization. Explanations of early $A_2$ after amyl nitrite inhalation would be reduction in resistance of the left ventricular ejection resulting from increased mitral regurgitation[22], and prolongation of QTc. Therefore, patients with early $A_2$ after amyl nitrite inhalation will probably show the similar findings of increased regurgitation due to more marked prolapse with hyperkinetic state, induced not only by amyl nitrite inhalation but also by sudden strenous exercise. If ventricular premature beats are coupled with prolonged QTc in MVPS, it might cause the R on T phenomenon resulting in fatal ventricular tachycardia and fibrillation, as one of the possibilities, even though this may be extremely unusual.

Posterior MVP appeared to be slightly less prevalent in this study, compared with previously reported studies. We postulate that this would be resulted from 1) anatomical characteristic of the short posterior leaflet which is hard to be detected even with UCT, and 2) uncertainty of the left ventriculography to identify location of the prolapsed mitral valve. There were no significant differences in phonocardiographic findings at rest and on standing as well as amyl nitrite inhalation test among the groups of anterior, posterior and both leaflet prolapses assessed by UCT, even though the clicks were less prevalent in posterior prolapse. These findings couldn't detract the clinical usefulness of UCT for diagnosis of MVPS. From these findings, we conclude that it is absolutely important to confirm diagnosis by UCT and perform amyl nitrite inhalation test with phonocardiography, whenever MVPS is suspected.

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