The Effect of Amyl Nitrite on the Mitral Valve Echocardiogram in Presumably Healthy Young Adults*

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We analyzed the use of amyl nitrite as a provocative factor in the diagnosis of mitral valve prolapse in a population of healthy young adults. Sixty-five men and 11 women underwent continuous M-mode echocardiographic and phonocardiographic monitoring before, during and after the administration of inhaled amyl nitrite. All of the 76 subjects had normal baseline echocardiograms, and all had a satisfactory hemodynamic response to amyl nitrite. Mitral valve prolapse, defined by echocardiography and phonocardiography, was not provoked in any of the subjects. Therefore, we concluded that, although this technique may be difficult, significant false-positive results should not occur if adherence to strict diagnostic criteria takes place.

P rimary mitral valve prolapse, a term coined by Barlow,¹ is a disorder with a wide spectrum of clinical manifestations and may be common among male as well as female populations. One of the major difficulties in evaluating this disorder has been the lack of a universally agreed upon “gold standard” by which the results of testing can be compared.² Currently, the major cardiac diagnostic tests (phonocardiography,³ M-mode⁴ and 2D echocardiography,⁵ and left ventricular angiography⁶) that are used to evaluate the mitral valve all have their own criteria for the diagnosis of prolapse. Discrepancy has arisen when these techniques have been used in the same patients to determine what might be a practical gold standard.⁷⁻⁹ Some of this discrepancy is resolved when more precise and rigid criteria for prolapse are applied.⁶ In an effort to improve the sensitivity of these tests, notably M mode echocardiography, close attention should also be paid to specificity before these tests are applied more widely in diagnostic screening.

The use of amyl nitrite to provoke mitral valve prolapse is just such an example. The effect of amyl nitrite on the systemic circulation,¹⁰ the left ventricle,¹¹ and mitral valve prolapse¹² has been previous-
normalities noted on physical examination or echocardiogram, (3) a poorly defined mitral valve recording because of either poor visualization of one or both leaflets or of excessive angulation of the transducer, and (4) the use of any medication likely to influence data that was not stopped at least 72 hours prior to the study.

After excluding 16 subjects, four of whom had mitral valve prolapse detected by the baseline studies (Table 1), amyl nitrite was administered to the 76 remaining subjects. Baseline blood pressure (right arm lying) and heart rate (ECG) were recorded. After warming of the expected, unusual odor, a 0.2-ml vial of amyl nitrite, wrapped in gauze, was broken and held about 3 inches from the subject's nose. The subject then inhaled deeply three times. Subjects were continuously monitored with ECG, phonocardiogram (fourth left intercostal space at midclavicular line), and M mode echocardiogram (mitral valve). Blood pressure was recorded at 30, 90, 180 sec after amyl nitrite administration. The criteria for an adequate hemodynamic response to amyl nitrite were a heart rate increase of at least 20 beats per minute or a decrease in mean arterial pressure of 20 mm Hg, or 25 percent of the resting values. These criteria are based on previous recommendations and research.10 12,17 Mean arterial pressure (MAP) was calculated from the formula:

\[
\text{MAP} = \text{diastolic} + \frac{1}{3} (\text{systolic-diastolic}).
\]

Echocardiograms and phonocardiograms were recorded continuously until either the heart rate and blood pressure had returned to baseline values or three minutes had elapsed (Fig 1).

Each study was evaluated independently by two experienced observers who were blinded to the names of the subjects. Any discrepancy between the two readings was resolved by consensus. The criteria used to determine the presence of mitral valve prolapse are those described by Markiewicz et al,14 which include smooth pansystolic hammering or late systolic posterior motion deviating more than 2 mm from the drawn CD line. For the purpose of this study, equivocal readings (<2 mm of systolic posterior motion) were considered normal.

Numerical data are expressed as the mean ± SD. Statistical analysis used the paired t test.

RESULTS

Patient Population

Table 1 shows how the study population was derived from the total medical student list. Also shown are respective distribution by sex for each group. There was no significant difference between the percentages of men and women in the total student group and the final study group.

Baseline Studies

Early systolic ejection murmurs unassociated with any other abnormal auscultatory findings were found in 25 subjects (32 percent). No systolic clicks, late systolic murmurs, or thoracic skeletal deformities were noted in any of the 76 subjects studied.

All subjects had normal resting echocardiograms, which included left ventricular posterior wall and septal thickness, left ventricular systolic and diastolic dimensions, percent shortening of the minor axis, left atrial dimension, aortic root, and mitral valve. In addition, no clicks or late systolic murmurs were recorded on phonocardiography.

Amyl Nitrite

All 76 patients experienced some symptoms, including temporal pounding, palpitations, dizziness, and flushing. However, there were no untoward effects.

Table 1—Derivation of Study Population from Medical Students

<table>
<thead>
<tr>
<th>Population Characteristics</th>
<th>Men, No. (%)</th>
<th>Women, No. (%)</th>
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</thead>
<tbody>
<tr>
<td>Total students considered</td>
<td>335 (78)</td>
<td>74 (22)</td>
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<tr>
<td>Students randomly selected</td>
<td>140 (77)</td>
<td>32 (23)</td>
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<tr>
<td>Agreed to study</td>
<td>92 (85)</td>
<td>14 (15)</td>
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<tr>
<td>Exclusion to AN*</td>
<td>16 (81)</td>
<td>3 (19)</td>
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<tr>
<td>Technical</td>
<td>10 (8)</td>
<td>2</td>
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<tr>
<td>Other heart disease</td>
<td>2 (2)</td>
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<tr>
<td>Mitral valve prolapse</td>
<td>4 (3)</td>
<td>1</td>
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<tr>
<td>Final AN Study</td>
<td>76 (85)</td>
<td>11 (15)</td>
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*AN = amyl nitrite.
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Figure 2. Occasional late systolic apparent posterior motion of the mitral valve, which we did not consider as prolapse. Measured 1.5 mm, possibly reflection of earlier systolic anterior motion (SAM). Also note early systolic murmur and third heart sound.

The average baseline heart rate was 67±12 beats per minute (range, 44 to 95) and mean arterial pressure was 92±9 mm Hg (range, 58 to 111). After amyl nitrite inhalation, average heart rate was 98±15 beats per minute (range, 60 to 133), and mean arterial pressure was 70±9 mm Hg (range, 48 to 87). The increase in heart rate (48 percent) and the decrease in mean arterial pressure (24 percent) were both significant (\( P < 0.001 \)). Seventy-three of the 76 subjects achieved the minimum criteria for an adequate hemodynamic response. Of the three who failed to achieve the

criteria, all had resting bradycardia (56, 44, and 50 beats per minute, respectively) and had an increase of 18, 16, and 15 beats per minute, respectively.

Analysis of all 76 M-mode echocardiograms revealed no evidence of new mitral valve prolapse at any time throughout the duration of recording, particularly at the point where the heart rate was 20 to 30 beats above the baseline. Seventy-three subjects had normal C-D segments and three had equivocal readings. An example of one of these readings is seen in Figure 2. No new clicks were recorded. However, it was common for a new systolic ejection murmur (Fig 1) or accentuation of a systolic ejection murmur (Fig 3) to occur. These early systolic flow murmurs are noted often following amyl nitrite and should not be confused with the murmurs of mitral regurgitation. A few of the subjects had artifacts noted that resembled prolapse but did not meet the strict criteria (Fig 2 and 4).

DISCUSSION

There has been no systematic study with a defined protocol of the effect of amyl nitrite on mitral valve prolapse in terms of either sensitivity or specificity. Likewise, previous studies have not been helpful in determining the need for routine use of amyl nitrite in patients who are thought to have mitral valve prolapse.16,17

We studied a group which, although not randomly selected, did represent a medical school student population. This population was predominantly male but, based on the results of recent series studying men,15,19 mitral valve prolapse, determined echocardiographically, appears in men and women with a similar frequency. The echocardiographic in-

Figure 3. A, Small systolic murmur. Heart rate, 50 beats per minute; third sound present. B, Note increase in systolic murmur with amyl nitrite. Heart rate increased to 85; test considered normal.

CHEST, 81: 4, APRIL, 1982

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Cidence of prolapse in our group (4/80 or 5 percent) certainly agrees with a combined prevalence from previous series involving about 1,000 patients (6.6 percent).

Comments concerning difficulties with the amyl nitrite maneuver are pertinent. Amyl nitrite as an inhalant is difficult to titrate such that a heart rate increase of only 20 to 30 beats per minute occurs. Careful titration is not as essential with hemodynamic or phonocardiographic recordings as with echocardiograms. When the heart rate goes above 100 beats per minute, the ability to recognize the usual mitral valve landmarks decreases progressively, and one must wait until the heart rate decreases to a point where an interpretable echo appears. In addition, the longer the transducer is held in one position, the greater the opportunity for hand fatigue with slight movement or angulation of the probe. Any excessive angulation of the probe may alter the results significantly, as shown by Markiewicz et al and as noted in Figure 4.

A further question concerning this maneuver rests in the significance of an amyl nitrite-induced pattern of prolapse. In young patients with auscultatory and other objective data supporting the diagnosis, it is clear that this, in all probability, represents the syndrome of primary mitral valve prolapse. Those patients with or without suggestive symptoms and no other objective criteria should not be categorized in the same subgroup. Recent pathologic studies of the mitral valve apparatus have revealed “a spectrum of normality” rather than specific abnormalities in apparently healthy individuals. These findings relate to deficiencies of chordal distribution that may predispose the mitral valve to various conditions including prolapse. The maneuver may be uncovering a preprolapse condition or a tendency that labels those patients as candidates for more clinically obvious prolapse later in their lives. This question cannot be answered without further identification and long-term follow-up of these patients.

We concluded that, if the amyl nitrite maneuver is used to provoke echocardiographic mitral valve prolapse in a patient with suggestive clinical findings, particular attention should be paid to technical details in the performance and interpretation of the test. In this way, an individual will not be incorrectly labeled with an entity that is of unknown, long-term significance and that may entail the unnecessary use of medication. Mitral valve prolapse, as best as we can determine, cannot be induced by the use of amyl nitrite in a patient whom we consider clinically normal.

ACKNOWLEDGMENT: We wish to express our sincerest appreciation to Lucille Bruner for technical assistance in obtaining the echocardiograms and to Becky Foulk for assisting in obtaining the study subjects.

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