Hemodynamic Effects of Methoxamine in Mitral Valve Disease

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The hemodynamic effects of methoxamine (Vasoxyl) in man have not previously been reported in detail. Since this drug is frequently used as a therapeutic agent, an investigation of its effects on the circulation seems warranted.

Methoxamine is a potent sympathomimetic drug producing elevation of total systemic vascular resistance. The present study was designed to evaluate the circulatory effects of this agent on patients with mitral valve disease as well as on healthy subjects. It was anticipated that the hemodynamic response of the patients with predominant mitral insufficiency to the increase in systemic vascular resistance might be different characteristically from that in patients with predominant mitral stenosis or no mitral valve lesion.

Gorlin and associates have described the hydraulic relationship whereby mitral regurgitant flow in patients with mitral insufficiency is determined by mitral regurgitant area, the systolic ejection period and the pressure gradient between the left ventricle and left atrium during systole.1,2 Other workers have demonstrated increments in left atrial pressure and mitral regurgitant flow following aortic constriction or levarterenol infusion in animals with experimental mitral insufficiency.3-7 Braunwald et al. described significantly greater increase in left atrial mean and V peak pressures during levarterenol infusion in patients with mitral insufficiency than in those without this lesion.7 They discussed the mechanisms and diagnostic usefulness of these findings and suggested that equipressor doses of methoxamine might be expected to produce greater changes in left atrial pressure than levarterenol, since methoxamine has a minimal effect on myocardial contractility.8-12

The purposes of this paper are: (1) to report the hemodynamic effects of methoxamine in patients with no mitral valve disease or predominant mitral stenosis; (2) to compare these effects with those found in subjects with predominant mitral insufficiency; (3) to discuss the physiologic mechanisms involved in the hemodynamic response to methoxamine; and (4) to emphasize the usefulness of changes in pulmonary "capillary" pressure during methoxamine infusion in the diagnosis of mitral insufficiency.

Methods

Twenty-two patients were studied and divided into 3 groups as follows: Group I includes 4 patients without evidence of cardiovascular disease of hemodynamic significance. Group II is composed of 12 patients in whom the diagnosis of "pure" or predominant mitral stenosis was confirmed at surgery. Four of these patients had tiny posterior regurgitant jets not considered to be of hemodynamic significance. Group III includes 6 patients with the diagnosis of predominant mitral insufficiency; 4 were confirmed at operation, 1 inadvertently created at operation (case 15, 17), and 1 established by retrograde left ventriculography in another institution.

Right heart catheterization was carried out 2 to 3 hours after a light breakfast. All subjects received 200 to 400 mg. methyprylon (Noludar) by mouth as premedication. The technic used in this laboratory for determination of cardiac output according to the direct Fick principle and for measurement of blood pressures have been described in detail in a previous publication.13 Formulae for the calculation of resistances and mitral valve area.
Figure 1

Relationship of the increment in pulmonary "capillary" V peak pressure (Δ "PC"v) to that of systemic arterial systolic pressure (Δ FA S) during methoxamine infusion.

Hemodynamic data are summarized in table 1. During methoxamine infusion systemic arterial systolic pressure increased 20 mm. Hg or more in all but one subject. Systemic arterial mean pressure and total systemic vascular resistance also increased significantly in most patients. Effective cardiac index and heart rate decreased significantly or remained unchanged and arteriovenous oxygen difference increased in all patients. Total pulmonary and "left heart" resistances increased significantly in most instances.

No consistent change was observed in oxygen consumption, arterial oxygen saturation or pulmonary artery-pulmonary "capillary" mean pressure gradient.

Characteristic of patients with mitral insufficiency (Group III) were significant increments in pulmonary artery mean, pulmonary "capillary" mean and pulmonary "capillary" V peak pressures which were observed in all patients in Group III with but one exception each. Changes in these parameters were variable in patients in Groups I and II. Furthermore, the increments in total pulmonary and "left heart" resistances were usually greater in patients with mitral insufficiency than in those without this lesion. Significant increment in pulmonary vascular resistance occurred in 4 of the 6 patients with mitral insufficiency, but was inconsistent in subjects in the other groups.

The relationship between the increment in pulmonary "capillary" V peak pressure and that of systemic arterial systolic pressure during methoxamine infusion is shown in figure 1. In patients with mitral insufficiency, the increment in "PCv" exceeded 50 per cent of the increment in FA S in all but 1 patient. In the absence of this lesion, it exceeded 20 per cent in only 3 subjects and in none was greater than 50 per cent. An arbitrary value of 35 per cent for ΔV/ΔFA S × 100 separates patients with mitral insufficiency from...
METHOXAMINE IN MITRAL VALVE DISEASE

Table 1

| Statistical Analysis of the Hemodynamic Data Before and During Methoxamine Infusion* |
|-------------------------------------|-----|-----|-----|
|                                     | C  | M   | C   | M   | C   | M   |
| Vo2                                 | 137 ± 10.4 | 152 ± 4.7 | 132 ± 7.9 | 151 ± 4.7 | 132 ± 7.9 | 151 ± 4.7 |
| Cardiac index (L/M2/min.)            | 4.39 ± 0.4 | 3.08 ± 0.4 | 6.60 ± 0.5 | 4.87 ± 0.5 | 7.40 ± 0.7 |
| Heart rate (beats/min.)             | 3.11 ± 0.5 | 2.17 ± 0.5 | 3.08 ± 0.4 | 1.98 ± 0.5 | 2.88 ± 0.4 | 1.92 ± 0.3 |
| Stroke index (ml/beat)              | 33 ± 6.6 | 36 ± 7.6 | 56 ± 3.3 | 55 ± 2.6 | 85 ± 8.8 | 61 ± 7.1 |
| Pulmonary artery mean pressure (mm. Hg) | 39 ± 6.6 | 40 ± 6.6 | 42 ± 6.6 | 40 ± 3.4 | 34 ± 3.0 | 32 ± 5.4 |
| Femoral artery systolic pressure (mm. Hg) | 10 ± 1.2 | 13 ± 1.8 | 36 ± 3.8 | 36 ± 4.1 | 30 ± 2.9 | 44 ± 5.8 |
| Femoral artery diastolic pressure (mm. Hg) | 5 ± 1.1 | 9 ± 1.8 | 22 ± 2.1 | 25 ± 1.6 | 20 ± 2.4 | 30 ± 4.9 |
| Femoral artery mean pressure (mm. Hg) | 5 ± 0.7 | 5 ± 1.8 | 14 ± 2.5 | 12 ± 3.4 | 10 ± 0.6 | 13 ± 4.2 |
| Total systemic resistance (dynes-sec/cm²) | 120 ± 6.9 | 180 ± 12.7 | 117 ± 5.5 | 159 ± 5.7 | 115 ± 5.8 | 148 ± 8.5 |
| Total pulmonary resistance (dynes-sec/cm²) | 68 ± 4.9 | 90 ± 10.4 | 65 ± 3.7 | 76 ± 3.5 | 64 ± 3.4 | 75 ± 5.2 |
| Pulmonary vascular resistance (dynes-sec/cm²) | 84 ± 6.5 | 118 ± 10.7 | 79 ± 3.4 | 99 ± 3.8 | 79 ± 4.5 | 95 ± 3.3 |
| **LHR** | 78 ± 10 | 104 ± 37 | 282 ± 77 | 338 ± 130 | 191 ± 34 | 379 ± 132 |

*Mean ± standard error.

Group I. No mitral valve disease.

Group II. Predominant mitral stenosis.

Group III. Predominant mitral insufficiency.

Vo2 = Oxygen consumption (ml./M²/min. STPD).

Cardiac index (L/M²/min.).

Heart rate (beats/min.).

Stroke index (ml./M²/beat).

Arterial blood oxygen saturation (%).

Pulmonary artery mean pressure (mm. Hg).

Pulmonary 'capillary' mean pressure (mm. Hg).

Pulmonary 'capillary' V peak pressure (mm. Hg).

Femoral artery systolic, diastolic, and mean pressures (mm. Hg).

Total systemic resistance (dynes-sec/cm²).

Total pulmonary resistance (dynes-sec/cm²).

Pulmonary vascular resistance (dynes-sec/cm²).

**LHR** = 'Left heart' resistance (dynes-sec/cm²).

Discussion

To the best of our knowledge this is the first detailed report of the hemodynamic effects of methoxamine in man. Based upon our findings, the sequence of circulatory changes occurring during methoxamine infusion may be as depicted in figure 3.

The increase in total systemic vascular and
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Figure 2
Femoral arterial (FA) and pulmonary "capillary" ("PC") pressures during methoxamine infusion in E.S. (case 15 and 17) before and after inadvertent creation of mitral insufficiency during mitral commissurotomy.

"left heart" resistances was an almost uniform finding. The increment in total pulmonary resistance was largely due to an elevated "left heart" resistance. The changes in pulmonary vascular resistance and pulmonary artery to pulmonary "capillary" pressure gradient were inconsistent.

The significant decrease in cardiac index and increase in "left heart" resistance in most patients indicate that any possible positive inotropic action of methoxamine was insufficient to counteract the effect of the increased systemic vascular resistance.

In mitral insufficiency, the level of pulmonary "capillary" mean pressure is a reflection primarily of left ventricular diastolic pressure and rises as would be expected during elevation of systemic resistance by methoxamine. The increase in amplitude of pulmonary "capillary" V waves may also contribute to this elevation of mean pressure. The failure of pulmonary "capillary" mean pressure to increase in most patients with mitral stenosis despite similar elevation of systemic pressures and resistance is explicable by the decline in mitral valve flow rate that results from bradycardia and decreased cardiac output. In addition, the increase in amplitude of the V waves in patients with mitral stenosis is usually slight.

Increase in V wave amplitude in patients with mitral insufficiency probably results from an increase in mitral regurgitant stroke volume resulting from bradycardia and increased left ventricular systolic pressure. The pressure-volume characteristics of the left atrium and pulmonary venous bed undoubtedly also play a role in determining V wave amplitude.

The behavior of pulmonary "capillary" V peak pressure in our patients during methoxamine infusion is similar to that described by Braunwald et al. for left atrial V waves during levaterenol infusion. An elevation of "PC", greater than 35 per cent of the elevation of systemic artery systolic pressure was found usually, but not always, to indicate the presence of hemodynamically significant mitral insufficiency. It is suggested that study of pulmonary "capillary" pressure records during methoxamine infusion may permit the diagnosis of mitral insufficiency without recourse to left heart catheterization.

Figure 3
Schematic representation of the hemodynamic changes during methoxamine infusion. MI = Mitral insufficiency; MS = Mitral stenosis.

In most cases, the increase in pulmonary "capillary" mean pressure is a reflection of the increased resistance to blood flow in the pulmonary circulation. The changes in systemic arterial pressure and resistance are also important in determining the pressure-volume characteristics of the left heart.

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METHOXAMINE IN MITRAL VALVE DISEASE

Summary

The hemodynamic changes following elevation of systemic arterial pressure and total systemic resistance by methoxamine were studied by right heart catheterization in 18 patients with mitral valve disease and 4 patients with no significant cardiovascular abnormality. This is the first detailed report of the circulatory effects of this drug in man. Changes in oxygen consumption, arterial oxygen saturation, stroke index and pulmonary artery to pulmonary “capillary” mean pressure gradient were insignificant. Forward cardiac index and heart rate decreased significantly while arteriovenous oxygen difference increased markedly in all groups of patients. The hemodynamic mechanisms involved in the changes observed during methoxamine infusion are discussed. Characteristic of patients with mitral insufficiency were significant increments of pulmonary arterial mean, pulmonary “capillary” mean, and pulmonary “capillary” V peak pressures. These subjects also had significantly greater increments in “left heart” resistance than patients without mitral insufficiency. An elevation of pulmonary “capillary” V peak pressure of 35 per cent or more of the elevation of systemic arterial systolic pressure was found to be a useful index of the presence of mitral insufficiency. Study of the pulmonary “capillary” pressure records during methoxamine infusion may obviate the necessity of left heart catheterization in the detection of significant mitral insufficiency.

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Summary in Interlingua

Le alteraciones hemodynamic que occorriu post le effectuation de un elevate tension systemic-arterial e de un augmento del total resistentia systemica per le administration de methoxamine esseva studiati per catheterismo dextero-cardiae in 18 patientes con morbo de valvula mitral e in 4 patientes sin significative abnormalitate cardiovascular. Isto es le prime detalhi reporto del effectos circulatori del mentionata droga in humanos. Le alterationes del consumption de oxygeno, del saturation oxygenic arterial, del indice de pulsos, e del gradienti medii del tension inter arteria pulmonar e “capillares” pulmonar non esseva significativi. Le indice cardia e le frequentia del corde declinau significativemente durante que le differencia arterio-venose de oxygeno montava marcatemente in omne le gruppos de patientes. Le mecanismos hemodynamic interessante in le alterationes observate durante le infusion de methoxamine es discutiti. Constatationes caracteristiche de patientes con insufficientia mitral esseva le significative aumentos del tension media pulmo-arterial, del tension media pulmo-“capillar” e del tension maximal “capillar” de unha V. Jete patientes etiam habeva significative plus marcate augmentos del resistentia “sinistro-cardiac” que le patientes sin insufficientia mitral. Esseva constatata que un augmento del tension sistolic systemico-arterial es utile como indice del presente de insufficiencia mitral. Le studio del registration del tension pulmo-“capillar” durante le infusion de methoxamine va possibilemente render innecessari le application de catheterismo sinistro-cardiae in le detection de grados significative de insufficientia mitral.

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Hemodynamic Effects of Methoxamine in Mitral Valve Disease
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