During intravenous infusion of a vasoressor agent (norepinephrine or methoxamine), the "V" wave of the left atrial pressure or of the pulmonary artery wedge pressure in patients with predominant mitral insufficiency was significantly increased. This change presumably reflects augmentation of the degree of regurgitation in these patients and is most likely the outcome of an acutely increased systemic resistance and left ventricular systolic pressure. In contrast, during the infusion of a vasoressor agent, no significant change in the "V" wave was observed in patients with predominant mitral stenosis.

Korner and Shillingford have demonstrated that in a circulatory model a decrease in the forward flow and/or increase in "central" volume lengthen the various time components of the dilution curves. The introduction of valvular insufficiency further lowers the peak concentration and prolongs the downslope of the dilution curve. They have shown similar findings in patients, and their observations have been confirmed by other workers.

It was postulated that the effects of acutely increased systemic resistance, when allowance is made for any change in cardiac output and "central" blood volume, should further lower the peak concentration and prolong the downslope of the indicator-dilution curves in patients with predominant mitral insufficiency, but not in patients with predominant mitral stenosis. This postulation was tested in 16 patients with mitral valvular disease. The purpose of this paper is to describe overall changes in time-concentration components and contour of indicator-dilution curves before and during intravenous infusion of methoxamine in these patients. Based upon the changes in the dilution curves, attempts were made to differentiate predominant mitral stenosis from predominant mitral insufficiency.

Methods

The technique of obtaining radioisotope (radioactive iodinated [I131] human serum albumin)-dilution curves from a systemic artery was briefly described in a previous paper. Subsequently, the following modifications were made in order to inscribe multiple curves: (1) A plastic tube for blood sampling was passed through a hole drilled along the diameter of the crystal of a scintillation counter. (2) Arterial blood was continuously sampled through a Cournand needle and the plastic tube attached to a syringe mounted on a Colson constant flow system. The rate of withdrawal was 0.8 to 1 ml per second. (3) The radioactivity of the blood was summed for each second and dilution curves were inscribed on a 1-milliampere direct-writing recorder (Rectirtet).

Thus, the method was made quite similar to that described by MacIntyre, Pritchard, et al. and a detailed report of the technique and studies has been published elsewhere.

In order to assess the validity of our method, cardiac output was determined nearly simultaneously by Fick procedure and radioisotope-dilution curves in a series of 36 patients with mitral valvular disease.

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*Obtained from Gilford Instrument Laboratory, Inc., Oberlin, Ohio.
†Obtained from Texas Instruments, Inc., Houston, Texas.
vular disease. In 30 patients, the values by the two methods agreed within 15 per cent, although in 6 patients a greater deviation was observed, which was particularly evident in those with mitral insufficiency. However, no systematic error was found. In 18 patients, successive determinations of the cardiac output by radioisotope-dilution curves were made 15 to 20 minutes apart, in order to show the reproducibility of the results. No significant difference between the first and second determination was observed.

Right-heart catheterization was performed according to the usual procedure. A No. 18 gauge Cournand needle was inserted into the femoral artery for sampling of arterial blood and recording the arterial pressure. With the patient at rest, an indicator-dilution curve was inscribed from the femoral artery after rapid injection of a weighed quantity of radioisotope through the cardiac catheter into the main pulmonary artery. The catheter was always flushed with 5 ml. of normal saline.

Methoxamine* (Vasoxyl) diluted with 5 per cent dextrose in water to a concentration of 1 mg. per 10 ml. was administered at a rate of about 1 mg. per minute through the cardiac catheter. The total dose ranged from 5 to 40 mg., depending upon the response of the patients' systemic pressure. During methoxamine infusion, blood pressure was recorded at frequent intervals through the arterial needle. When the systemic artery systolic pressure had risen appreciably (16 to 66 mm. Hg) above the control level and ventilation was stable, a further dilution curve was inscribed.

The formulas for the calculation of the total and "central" blood volumes have been mentioned in a previous paper. The total blood volume was estimated before, as well as during, methoxamine infusion, and these values were used respectively for the calculation of cardiac output during each period by the dilution technique. The definitions and symbols of the time components of the dilution curves were those proposed by Wood and Swan. The formula described by Korner and Shillingford was used to derive the reciprocal of the downslope (1/S). The spread time (Tₐ) indicates the width of the curve in seconds at a height of one-tenth of peak concentration.

Since the downslope of the dilution curve is affected by cardiac output and "central" blood volume as well as by valvular insufficiency, we have attempted to eliminate, as far as possible, the effect of changes in the two former determinants resulting from methoxamine infusion. In our calculation, based upon the work of Newman and others, we have assumed that the reciprocal of the logarithmic downslope (1/S) varies inversely as the cardiac output and directly as the "central" blood volume.

Thus, assuming no increase in regurgitant flow, the approximate expected value of 1/S during methoxamine infusion was estimated by simple proportion according to the following formula:

\[
\frac{1}{S} \text{ (expected)} = \frac{1}{S} \text{ (control)} \times \frac{\text{C.O.} \text{ (methoxamine)}}{\text{C.O.} \text{ (control)}} \times \frac{\text{CBV} \text{ (methoxamine)}}{\text{CBV} \text{ (control)}}
\]

Since CBV = C.O. X Tₘ, the above formula may be simplified to:

\[
\frac{1}{S} \text{ (expected)} = \frac{1}{S} \text{ (control)} \times \frac{Tₘ \text{ (methoxamine)}}{Tₘ \text{ (control)}},
\]

where C.O. = cardiac output; CBV = "central" blood volume; Tₘ = mean transit time from the pulmonary artery to the femoral artery; (control) = values obtained prior to methoxamine infusion; (methoxamine) = values obtained during methoxamine infusion.

It is well known that the Tₘ is altered mainly by changes in forward cardiac output and "central" blood volume, and affected to a much less extent by changes in the magnitude of regurgitant flow. Hence, during methoxamine infusion, a value of 1/S appreciably higher than the calculated "expected" value, allowing for changes in cardiac output and "central" blood volume, would suggest that there had been a significant increase in valvular regurgitation.

Sixteen patients ranging in age from 27 to 52 years were studied. They were divided into two groups on the basis of clinical and hemodynamic findings. The presence of a left-to-right intracardiac shunt was excluded by right-heart catheterization.

Group 1 included nine patients with predominant mitral stenosis. All of them had a loud first mitral sound and an apical rumbling diastolic murmur. An opening snap was heard in all but one patient. At operation a tight mitral stenosis was found in all nine patients, and a tiny regurgitant jet was felt in two.

Group 2 consisted of seven patients with predominant mitral insufficiency. All these patients had a loud apical pansystolic murmur transmitted to the axilla, and enlargement of both the left atrium and left ventricle. A definite regurgitant jet was palpated in each patient at operation.

Results

The cardiac output, blood volumes, and time-concentration components derived from the indicator-dilution curves before and during methoxamine infusion are presented in

Circulation Research, Volume IV, March 1959
During methoxamine infusion the following changes were observed:

**Forward Cardiac Output**

There was a significant decrease (more than 13 per cent) in the forward cardiac output in 13 of 16 patients. Although in both groups the decrease was statistically significant, no significant difference was found between the two groups of patients.

**Total and "Central" Blood Volumes**

There was no significant change in the total or "central" blood volume in either group. The same was true of the ratio of the "central" blood volume to the total blood volume.

**Time-Concentration Components**

1. The appearance time (T_A) and the mean transit time (T_M) were prolonged in all patients. The changes were statistically significant in both groups. However, the changes in T_A and T_M in one group were not significantly different from those in the other. The build-up time (T_B) was prolonged in eight patients and remained unchanged, or decreased slightly, in the remaining eight. The change in this parameter was statistically insignificant in either group.

2. Although there was a uniform prolongation of the disappearance time (T_D) in patients of both groups, the changes in T_D were significantly greater in patients with mitral insufficiency than in those with mitral stenosis (P < 0.05).

3. As shown in figure 3, the change in the ratio of spread time (T_S) to appearance time (T_A) likewise effected an excellent separation between the two groups. It decreased in all patients with mitral stenosis but increased in all with mitral insufficiency.

**Contour of the Dilution Curves**

In patients with mitral stenosis, the change in the contour of the dilution curves was manifested by a slight broadening of the base and little alteration of the overall configuration. The least concentration (C_L) and the concentration of systemic recirculation (C_R) were easily identified (fig. 4). In contrast, in patients with mitral insufficiency, the dilution curves during methoxamine infusion were characterized by a reduction in peak concentration and a disproportionate prolongation of the downslope. Furthermore, neither C_L nor C_R was identifiable (fig. 5).
Table 1
Forward Cardiac Output, Blood Volumes, and Time Components Derived from the Indicator-Dilution Curves Before and During Methoxamine Infusion

<table>
<thead>
<tr>
<th>Case</th>
<th>Periods of study</th>
<th>Cardiac index (L/min./M.²)</th>
<th>Blood volume (mL/M.²)</th>
<th>Time components (seconds) *</th>
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<td></td>
<td></td>
<td></td>
<td>TCV*</td>
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<td>P value**</td>
<td>&lt;0.01</td>
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</table>

**"CBV" = "central" blood volume; Tₐ = appearance time; Tₘ = build-up time; Tₙ = disappearance time; Tₘ = mean transit time from pulmonary artery to systemic artery.

1C = control period; M = period during methoxamine infusion.

‡ = same patient studied before and six months after mitral valvulotomy.

§ = average difference between two periods.

|S.E.| standard error.

*The symbol "P" indicates the probability that this observed difference is a chance occurrence. A difference with a chance probability of 0.05 or less is considered to be significant.

Circulation Research, Volume IX, March 1961
MITRAL VALVULAR DISEASE

The ratio of spread time ($T_s$) to the appearance time ($T_a$) before and during methoxamine infusion in two groups of patients. During methoxamine infusion, the ratio ($T_s/T_a$) decreased in all patients with mitral stenosis, but increased in those with mitral insufficiency.

Of special interest were the indicator-dilution curves recorded in one patient (E.S.) before, and six months after, mitral valvulotomy. Preoperatively, the contour of the dilution curve was consistent with that seen in predominant mitral stenosis. At operation a tight mitral stenosis with a tiny regurgitant jet was found. Unfortunately, after fracture of the mitral valve, moderately severe mitral insufficiency was inadvertently produced. The surgeon was able to feel a much more pronounced regurgitant jet upon completion of the operation. Postoperatively, there were also progressive clinical signs of mitral insufficiency. Six months after operation, dilution curves showed features of predominant mitral insufficiency (fig. 6). As reported in a separate paper, changes in the pulmonary artery wedge pressure during methoxamine infusion in the same patient prior to surgery were consistent with predominant mitral stenosis, and after surgery were typical of predominant mitral insufficiency.

Discussion

In the present study, we found that during methoxamine infusion the changes in the contour of the dilution curves, particularly the...
Indicator-dilution curves following injection of I\(^{131}\) human serum albumin into the pulmonary artery (hereinafter referred to as PA curves) recorded before (A) and during (B) methoxamine infusion in a patient with predominant mitral stenosis. Note the similarity of the two curves with the exception of prolongation of appearance time, mean transit time, and disappearance time (T\(_D\)). There is no reduction in peak concentration (C\(_P\)). The least concentration (C\(_L\)) and the peak of systemic recirculation (C\(_R\)) are easily identified.

In a patient with predominant mitral insufficiency, the pulmonary artery curve during control period (A) showed some prolongation of T\(_D\). During methoxamine infusion (B) note the disproportionate prolongation of the downslope. Neither C\(_L\) nor C\(_R\) can be identified.

downslope, and in 1/S showed a sharp difference between the patients with mitral stenosis and those with mitral insufficiency.

When allowance was made for changes in 1/S caused by altered forward cardiac output and "central" blood volume, using the equation previously described, the distinction was even more marked. In patients with mitral stenosis, there was little or no discrepancy between the actual or "expected" values of 1/S during methoxamine infusion. In those with mitral insufficiency, the actual value invariably exceeded the "expected" value by amounts ranging from 20 to 98 per cent. Therefore, it may be reasonable to assume that in the latter patients augmentation of valvular insufficiency during each stroke is an important factor in increasing the value of 1/S during methoxamine infusion.

Hoffman and Rowe,\(^{16}\) working on a circulatory model, have demonstrated that distortion of the indicator-dilution curves produced by valvular insufficiency depends not only on...
the amount of backflow, but also on the dilution of the regurgitant indicator. The latter is largely influenced by the force, shape, and direction of the regurgitant jet, and by the volume and elasticity of the proximal chamber entered by the jet. It is possible that in our patients with mitral insufficiency, the increased total systemic resistance and left ventricular systolic pressure during methoxamine infusion may augment not only the amount of the regurgitant stroke volume, but also the force and direction of the regurgitant jet.

The ratio of spread time to appearance time has been found by Shillingford to be a reliable and useful index for assessing the severity of mitral insufficiency. In his experience, a ratio of 3.2 or greater usually indicates some degree of valvular insufficiency. In general, the greater the ratio, the more severe the insufficiency. The results of our present studies showed that during methoxamine infusion, the delay in appearance time was proportionately more pronounced than the spread time in patients with mitral stenosis, but that the reverse was true in those with mitral insufficiency. Since there was relatively little change in the build-up time in both groups, the ratio of spread time to appearance time therefore reflected indirectly the change in the disappearance time or downslope of the curve.

During methoxamine infusion, all patients with mitral stenosis showed a consistent decrease in the ratio $T_s/T_A$ to a value less than 3.0. In contrast, the ratio $T_s/T_A$ uniformly increased in all patients with mitral insufficiency, and in five of seven patients the value was greater than 3.2. By studying the changes in the time-concentration components and the contour of the indicator-dilution curves during intravenous methoxamine infusion, differentiation between predominant mitral stenosis and predominant mitral insufficiency may be made with reasonable accuracy, and left-heart catheterization may thus be obviated. However, accurate quantitation of the regurgitant blood flow is not possible by the present method.

Summary

This report describes the time-concentration components and the contour of indicator-dilution curves recorded from the femoral artery after injection of radioactive iodinated (I$^{131}$) human serum albumin into the pulmonary artery before and during methoxamine infusion in nine patients with predominant mitral stenosis, and seven patients with predominant mitral insufficiency.

During methoxamine infusion, the changes were as follows: (a) The forward cardiac output was uniformly reduced in both groups. The changes in the total and "central" blood volumes were inconsistent in both groups. In all cases, there was prolongation of the appearance and mean transit times. (b) There was a significantly greater prolongation of the reciprocal of the downslope and the disappearance time in patients with mitral insufficiency than in those with mitral stenosis. By means of a simple formula, we allowed for alteration in forward cardiac output and "central" blood volume during methoxamine infusion, and a satisfactory discrimination between mitral stenosis and mitral insufficiency was achieved by comparing the change in $1/S$.

(c) Comparison of the ratio of spread time to appearance time ($T_s/T_A$) before and during methoxamine infusion also effected an excellent separation between the two groups. It is postulated that the characteristic changes of the indicator-dilution curves during methoxamine infusion in patients with mitral insufficiency were due to augmentation of regurgitant stroke volume, increase in the force of the regurgitant jet, or both.

Acknowledgment

We wish to express our thanks and appreciation to Dr. Arthur Button, Assistant Professor of Radiation Biology and Scientist (Statistics), Atomic Energy Project, University of Rochester, for his help on the statistical aspects of this study. We are indebted to Mr. Raymond Quick, Physicist-in-Chief, Department of Radiology, for his aid and advice on the scintillation equipment. The technical assistance of Mrs. Garland Kleinstuber and the secretarial aid of Miss Irene Subrani and Miss Jean Pittinaro are gratefully acknowledged.
References


Indicator-Dilution Curves During Methoxamine Infusion in Patients with Mitral Valvular Disease

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