Action of Bradykinin on Human Pulmonary Circulation

Observations in Patients with Mitral Valvular Disease

By Flavio M. de Freitas, M.D., Eduardo Z. Faraco, M.D., Decio F. de Azevedo, M.D., and Isaac Lewin, M.D.

BRADYKININ acts as a powerful vasodilator upon the systemic circulation. Contradictory reports, however, have been published concerning its effect on the pulmonary vascular bed. In different studies carried out in various animal species, the drug has been reported as eliciting either dilatation or constriction of the pulmonary vessels.

Gersmeyer and Spitzbarth observed a rise in pulmonary arterial pressure when a single dose of bradykinin was intravenously injected into intact man. In an earlier publication from this laboratory, a decrease in pulmonary vascular resistance was noted in eight of 10 patients with normal pulmonary vascular pressures receiving a continuous intravenous infusion of synthetic bradykinin.

Since a functional component of vasoconstriction is admitted in most cases of pulmonary hypertension, patients with high pulmonary vascular pressures may serve, within certain limits, as a suitable material for assessing the action of a vasodilator agent on the lesser circulation.

The aim of the present investigation was to evaluate the hemodynamic alterations observed in patients with pulmonary hypertension secondary to rheumatic heart disease during the intravenous administration of bradykinin.

Method

Of the 21 patients studied, 10 were male and 11 female. Ages ranged from 14 to 52 years and averaged 30 years. All patients had pulmonary hypertension secondary to a mitral valve lesion (pure stenosis in 15 cases, and combined stenosis and insufficiency in six). Tricuspid insufficiency was present in five patients, and pulmonary insufficiency in one. Diagnosis was surgically confirmed in every case. The level of the systolic pulmonary arterial pressure was more than 80 mm Hg (range, 87 to 131 mm Hg) in nine patients, between 50 and 80 mm Hg in eight, and less than 50 mm Hg (range, 44 to 47 mm Hg) in four patients. None of the patients was in cardiac failure at the time of the study, and 11 were receiving maintenance digitalis therapy. Normal sinus rhythm was present in 19 patients, and atrial fibrillation in two.

During cardiac catheterization, patients were in the fasting state and had been premedicated with 100 mg of secobarbital and 50 mg of butabarbital, orally. Equipment and procedures used for the execution of right and left heart catheterization, as well as for the recording of pressures and dye curves were described in detail in previous reports. Synthetic bradykinin (0.1 mg/ml) was delivered into the bloodstream at a constant rate from a motor-driven syringe connected to a vinyl tubing (0.028 inch, outside diameter) which had been percutaneously introduced into a peripheral vein.

The routine outlined below was observed in each study. As soon as the diagnostic procedures carried out during cardiac catheterization were completed, the tip of the right heart catheter was placed in the pulmonary artery just downstream from the pulmonic valve. The transseptal left heart catheter was pulled back from the left ventricle and located just upstream from the mitral valve. While the patient breathed quietly, pressures from the pulmonary artery, left atrium, and a peripheral systemic artery were simultaneously recorded during 10 to 12 respiratory cycles. Mean pressures were electronically integrated.

*Synthetic bradykinin was kindly supplied by Sandoz, Brasil, S. A.
In cases of pure mitral stenosis, a known amount of indocyanine dye was rapidly injected into the circulation through a large-bore catheter which had been previously introduced into the inferior vena cava via the left femoral vein. A pair of dye curves was then obtained by the simultaneous sampling of blood from the pulmonary artery and left atrium, at an equal flow rate, through two cuvette densitometers of similar characteristics. These curves were used for the calculation of the cardiac output and pulmonary blood volume in accordance with the method described in preceding papers from this laboratory.\textsuperscript{15, 16} For the calculation of the mitral valve flow, the cardiac output, in milliliters per minute, was divided by the product of the mean duration of the ventricular filling period, in seconds, and the heart rate per minute. The ventricular filling period was measured from the left atrial pulse pressure curve and was considered to be the time elapsed between the peak of the V wave and the beginning of the C wave (Z point). Since it is known that the peak of the V wave may occur 0.01 to 0.1 second earlier than the opening of the mitral valve,\textsuperscript{17} the ventricular filling period was probably overestimated. The average of measurements carried out over 10 or more diastolic intervals was used for the calculations. All figures for flow and volumes were referred to body surface area in square meters.

In patients with a double mitral lesion, no attempt was made to compute the pulmonary blood volume because of the errors involved in the process used for that purpose in presence of mitral regurgitation.\textsuperscript{15} In these cases, cardiac output was determined from a single indicator curve, dye being injected into the left atrium and sampled from a peripheral systemic artery. Results for cardiac output obtained from indicator-dilution curves in these patients were checked against cardiac output determined by the Fick principle and considered satisfactory when agreeing within a range of ±10%. For obvious reasons, mitral valve flow was not calculated in patients with mitral insufficiency.

After the control data had been recorded in duplicate, the infusion of bradykinin was started, and the dose per minute increased gradually until a stable reduction of the systemic arterial pressure or an increase of the heart rate or both were obtained. At this point, a steady rate of drug infusion was maintained and the procedures carried out in control period were repeated. The average final dose of bradykinin given to the 21 patients was equal to 0.98 \( \mu g \)/kg/min with a range of 0.75 to 1.42 \( \mu g \)/kg/min. As previously reported,\textsuperscript{8} this dose induced circulatory changes with minimum or no unpleasant side effects. The mean total amount of drug injected was 1.26 mg (range, 0.95 mg to 1.75 mg). The period of infusion varied from 12 to 18 minutes and averaged 14 minutes.

The pulmonary vascular and the total peripheral resistances were calculated by well-known formulae, and expressed in mm Hg/liter/minute. The average intravascular pressure in the pulmonary circuit (which is simply the sum of the mean pulmonary arterial and the mean left atrial pressures divided by two) was used as a crude estimation of the transmural pressure in the pulmonary vessels.\textsuperscript{18} Since all mean intravascular pressures were measured during various respiratory cycles, the pressure outside the walls of the vessels was averaged out. Moreover, the pressure outside the vessels was considered small as compared to the average intravascular pressure.\textsuperscript{19}

Student's t-test was used in the statistical analysis. The data obtained were arranged according to the paired technique, since each patient served as his own control. The percentage change on the following pairs of variables was examined for possible correlations: cardiac output versus mean pulmonary arterial pressure, cardiac output versus mean left atrial pressure, mitral valve flow versus mean left atrial pressure, and average intravascular pressure versus pulmonary vascular resistance.

Results and Discussion

The mean results, the statistical significance of the differences between the values obtained during control and test periods, and the individual directional changes are listed in table 1.\textsuperscript{*}

Bradykinin elicited an appreciable fall of the systemic vascular resistance (mean change, \(-38\%\)) simultaneously with a decrease of the mean systemic arterial pressure (\(-19\%\)) and an increase of the cardiac output (\(+37\%\)) in all cases studied. It can be concluded that the alterations suffered by these variables were essentially identical to those observed in patients with no cardiac valvular lesions submitted to a similar investigation, as reported in a preceding paper.\textsuperscript{8} In the present series, the rise in cardiac output derived mainly from a rise in heart rate (\(+24\%\)), since the modifications of the stroke volume were generally of low magnitude (\(+10\%\)). However, in the pre-

\*An additional table containing the individual data of all patients may be obtained from the authors on request.
vvious study, both heart rate and stroke volume contributed importantly to the increase in cardiac output. This minor difference in behavior between two distinct groups of patients is understandable, since one would expect that adjustments of the cardiac output taking place in patients with advanced mitral disease could be more easily accomplished through changes in heart rate than in stroke volume.

The increase in blood flow was coincident, in the pulmonary circulation, with a rise of the mean arterial pressure (+20%) and of the venous (left atrial) pressure (+36%), in 19 and all patients, respectively. The cyclic respiratory variations of the intravascular and intracardiac pressures remained unchanged during control and test periods, but the respiratory rate increased slightly in all cases. No modifications of the systemic arterial blood oxygen saturation were observed. Except for the rise in pulmonary vascular pressures, these results are also similar to those previously observed in this laboratory.

A positive correlation coefficient \( r = +0.688 \) \( (P<0.01) \) was found, when the per cent changes in cardiac output were compared with the per cent changes in mean left atrial pressure, in all cases (fig. 1). Likewise, when the per cent increments in the flow through the mitral valve were correlated with the per cent increments in mean left atrial pressure, in the 15 patients with pure mitral stenosis, a significant coefficient \( (r = +0.747, P<0.01) \) was encountered (fig. 1). In contrast, the correlation coefficient computed from the comparison of the changes in cardiac output with the changes in mean pulmonary arterial pressure was very low and not significant \( (r = +0.322) \). These findings may well be explained by the relatively fixed resistance represented by the ostium of the stenotic mitral valve, which would require for a rise in flow through it a proportional increase of the left atrioventricular filling pressure gradient and, consequently, of the pulmonary venous-left atrial pressure. The same would not occur with the pulmonary arteriovenous pressure gradient and the pulmonary arterial pressure,

![Figure 1](image_url)

(A) Correlation between the per cent increases in cardiac output (CO) and in mean left atrial pressure (MLAP) in the 21 patients studied. (B) Correlation between the per cent increases in mitral valve flow (MVF) and in mean left atrial pressure in 15 patients with pure mitral stenosis.
the changes in which would be related to the changes in diameter of the small pulmonary vessels, responsible for the major portion of the pulmonary vascular resistance. Since this resistance is essentially variable both by passive (mechanical) and active modifications in the caliber of the vessels, the amount of variation would depend largely on the degree of structural and functional alterations of the vascular walls present in each case.

During bradykinin infusion, the pulmonary vascular resistance fell in 19 of the 21 cases studied (mean change, $-22\%$). Since the transmural pressure in the pulmonary vascular bed, as evaluated from the average intravascular pressure, rose in all patients ($+25\%$), the fall in resistance could be attributed to a passive distention of the small pulmonary vessels. The diverse degree of structural and functional alterations of the vascular walls in the different patients, as mentioned before, was probably the main reason for the observed failure of the individual increases in average intravascular pressure to correlate with the corresponding decreases in pulmonary vascular resistance ($r = +0.199$).

In most patients with pure mitral stenosis, no appreciable modifications of the pulmonary blood volume was noted while bradykinin was being injected, in spite of the important rise of the pulmonary intravascular pressures. This fact leads to the conclusion that the pulmonary vascular system behaved as a compartment of low distensibility, during the action of bradykinin. This conclusion is only valid for the pulmonary vascular bed as a whole (left atrium included), since the method employed to measure the pulmonary blood volume was not designed to detect different changes in volume or eventual shifts of blood from one to another of the various pulmonary vascular segments.

As could be expected from experiments carried out in intact animals or man, the modifications in resistance and capacity observed in the pulmonary vascular bed must have represented the net effect of passive response due to changes in transmural pressure and active variations in pulmonary vascular distensibility. The results discussed above provide no clear evidence of a direct effect of bradykinin upon the lung vessels. Actually, when the transmural pressure rises, as occurred

---

**Table 1**

### Hemodynamic Effects of Bradykinin in Twenty-one Patients with Mitral Valve Disease

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control (C) mean ± SD</th>
<th>Bradykinin (Br), mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>2.41 ± 2.32</td>
<td>3.29 ± 3.75</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>90.0 ± 14.2</td>
<td>111.3 ± 17.1</td>
</tr>
<tr>
<td>Stroke index (ml/beat/m²)</td>
<td>27.2 ± 8.8</td>
<td>30.0 ± 10.4</td>
</tr>
<tr>
<td>Pulmonary arterial pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>79.2 ± 29.9</td>
<td>91.9 ± 29.4</td>
</tr>
<tr>
<td>Diastolic</td>
<td>38.4 ± 12.2</td>
<td>46.8 ± 12.8</td>
</tr>
<tr>
<td>Mean</td>
<td>53.3 ± 17.5</td>
<td>64.2 ± 16.7</td>
</tr>
<tr>
<td>Mean left atrial pressure (mm Hg)</td>
<td>22.9 ± 7.3</td>
<td>31.2 ± 9.4</td>
</tr>
<tr>
<td>Average intravascular pressure (mm Hg)</td>
<td>38.1 ± 11.4</td>
<td>47.6 ± 12.0</td>
</tr>
<tr>
<td>Pulmonary vascular resistance (mm Hg/L/min)</td>
<td>10.5 ± 9.0</td>
<td>8.2 ± 6.7</td>
</tr>
<tr>
<td>Pulmonary blood volume* (ml/m²)</td>
<td>337.1 ± 39.5</td>
<td>345.2 ± 39.2</td>
</tr>
<tr>
<td>Mitral valve flow* (ml/diast sec/m²)</td>
<td>68.7 ± 21.7</td>
<td>97.3 ± 32.9</td>
</tr>
<tr>
<td>Systemic arterial pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>124.0 ± 11.4</td>
<td>100.4 ± 22.5</td>
</tr>
<tr>
<td>Diastolic</td>
<td>70.2 ± 8.4</td>
<td>55.5 ± 14.6</td>
</tr>
<tr>
<td>Mean</td>
<td>88.7 ± 10.0</td>
<td>71.8 ± 15.0</td>
</tr>
<tr>
<td>Total peripheral resistance (mm Hg/L/min)</td>
<td>26.5 ± 10.7</td>
<td>16.3 ± 8.2</td>
</tr>
<tr>
<td>Arterial oxygen saturation (%)</td>
<td>95.6 ± 1.2</td>
<td>95.8 ± 1.5</td>
</tr>
</tbody>
</table>

*Pulmonary blood volume and mitral valve flow were computed only in the 15 patients with pure mitral stenosis.
in this study, a fall in pulmonary vascular resistance is compatible with either a decrease or increase of the vascular wall tone.\textsuperscript{18, 20} Though some active pulmonary vasodilatation induced by the drug could have been anticipated,\textsuperscript{8} the reduction observed in systemic vascular resistance and arterial pressure probably triggered a reflex neurohumoral mechanism with release of catecholamines\textsuperscript{2, 8, 10, 21} which could be responsible for a counteractive decrease in distensibility of both the small\textsuperscript{18, 20, 22} and large\textsuperscript{20, 23, 24} pulmonary vessels. This effect would be an additional reason for the relatively small decrease occurring in pulmonary vascular resistance, in most patients, and for the minor changes noted in pulmonary blood volume, notwithstanding the appreciable rise in the pulmonary intravascular pressures.

Although the above possibilities are based on previous research, they remain a matter for further investigation. Meanwhile, the conclusion which can be drawn from the present work is that whatever may have been the direct effect of bradykinin on the pulmonary vascular bed it was sufficiently small to be overshadowed by secondary effects, either passive or active, consequent upon the action of the drug on the systemic vessels and heart.

Summary

Twenty-one patients with pulmonary hypertension secondary to rheumatic mitral valve disease were submitted to right and left heart catheterization and received a continuous intravenous infusion of synthetic bradykinin (average dose, 0.98 µg/kg/min).

The drug elicited an appreciable fall of the systemic vascular resistance simultaneously with a decrease of the mean systemic arterial pressure and an increase of the cardiac output in all cases. The rise in cardiac output derived mainly from an increase in heart rate, since the modifications of the stroke volume were generally of low magnitude.

In the pulmonary circulation, the increase in blood flow was coincident with a rise of the mean arterial and venous (left atrial) pressures in 19 and all patients, respectively. The pulmonary vascular resistance fell in 19 patients, but no appreciable modifications were noted in pulmonary blood volume.

The changes in the lesser circulation were interpreted as expressing secondary effects, either mechanical or reflex, consequent to the
action of bradykinin on the systemic vessels and heart rather than a direct effect of the drug on the pulmonary vessels.

Acknowledgment

The authors are grateful to Mr. Plinio Degani and Mrs. Vera Petersen for their technical assistance in the development of this work.

References

Action of Bradykinin on Human Pulmonary Circulation: Observations in Patients with Mitral Valvular Disease

FLAVIO M. DE FREITAS, EDUARDO Z. FARACO, DECIO F. DE AZEVEDO and ISAAC LEWIN

Circulation. 1966;34:385-390
doi: 10.1161/01.CIR.34.3.385

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1966 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/34/3/385