General Circulatory Alterations Induced by Intravenous Infusion of Synthetic Bradykinin in Man

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BRADYKININ is an endogenous polypeptide with great biologic activity. It was first described by Rocha e Silva et al., and thus named for the slow contraction it causes on the isolated intestine. Using a combination of chromatography and electrophoresis, Elliott et al., in 1960, isolated the pure substance. The synthesis of bradykinin by Boissonnas et al. made possible its widespread use in a variety of investigations. The identity between natural and synthetic bradykinin seems to be established. Effects of this drug have been described on capillary permeability, on smooth muscle, on systemic and pulmonary blood vessels and circulation, and locally, on tissues, causing pain, edema, and migration of leukocytes.

Both in animals and in man, bradykinin has a powerful vasodilatory action. The general hemodynamic effects induced by a continuous intravenous administration of bradykinin have not been studied by cardiac catheterization except in the dog. This investigation was undertaken to study the circulatory alterations occurring during a constant-rate intravenous infusion of bradykinin in man submitted to simultaneous right- and left-heart catheterization.

Material and Methods

The studies were performed in ten male patients, aged 21 to 47 years (table 1). All had given informed consent for these experiments. Six patients were considered to have essential arterial hypertension and had either normal or slightly elevated pulmonary arterial pressure, but none was in cardiac failure at the time of study. They had been hospitalized at least ten days prior to the study and treated with bed rest and low sodium diet, but no hypotensive drugs. Four patients had no detectable cardiovascular disease (table 1). All ten patients were in normal sinus rhythm.

The experiment was always performed with the patient in basal conditions, in supine position, on a fluoroscopic table. Thirty minutes before the procedure was started, all patients received phenobarbital (100 mg. orally) and meperidine (100 mg. intramuscularly). Right-heart catheterization was performed by the conventional technic. A modification of the Ross transseptal technic was used for the catheterization of the left atrium. The brachial artery was cannulated with a Cournand needle. A polyethylene catheter was introduced percutaneously through an antecubital or the left femoral vein, and was advanced into the superior or inferior vena cava. This catheter was left in place for the subsequent infusion of the solution containing bradykinin.

Pressures were measured with Statham P23Db transducers connected to a cathode-ray photographic recording system (Electronics for Medicine, Inc.). The zero level for the recorded pressures was referred to a horizontal plane at the mid-axillary line of the patient lying in supine position. Mean pressures were obtained by electronic integration and were measured during at least three respiratory cycles. In order to determine the cardiac output by the Fick principle, the expired air was collected during five minutes in a Neoprene bag and immediately analyzed by the micro-Scholander technic for the determination of the oxygen consumption. At a midpoint of the expired air collection, blood samples were taken simultaneously from the brachial and pulmonary arteries, and oxygen contents were determined.

The solution of bradykinin (2.5 mg. per 100 ml. of physiologic saline) was administered through the polyethylene catheter placed in the

* Bradykinin was kindly supplied by Sandoz Brasil S.A.
superior or inferior vena cava, with use of a motor-driven syringe (infusion-withdrawal pump, Harvard Apparatus Company), at a constant rate of infusion.

During the control period, the following data were obtained, usually in duplicate: pressures in the brachial artery, the pulmonary artery, and the left atrium; and the cardiac output by the Fick method. After these procedures had been completed, the intravenous injection of bradykinin was started. The rate of infusion was gradually increased until a dose was reached sufficient to provoke fall of the brachial arterial pressure or an increase in ventricular rate, which was continuously monitored on the oscilloscope. Usually a dose large enough to elicit unpleasant side effects was avoided. In fact, only three patients complained of slight sensation of warmth in the face and limbs. In one of these patients a visible reddening of the face and neck was noted. All three patients received doses exceeding 1 mg./Kg./min. As soon as the final rate of infusion was established and the circulatory conditions of the patient were judged to be stable, the same procedures carried out in the control period were repeated.

The peripheral total resistance (PTR), pulmonary vascular resistance (PVR), and the average intravascular pressure (AIP) in the pulmonary circulation were calculated as follows:

\[
PTR = \frac{\overline{SA}}{C.O.} \times 80
\]
\[
PVR = \frac{\overline{PA} - \overline{LA}}{C.O.} \times 80
\]
\[
AIP = \frac{\overline{PA} + \overline{LA}}{2}
\]

In the above formulae, \(\overline{SA}\), \(\overline{PA}\), and \(\overline{LA}\) are the mean systemic arterial, mean pulmonary arterial, and mean left atrial pressures in mm. Hg, respectively. C.O. is the cardiac output in liters per minute. The results for resistances were expressed in dynes sec. cm.\(^{-5}\) The changes in average intravascular pressure were used, as an approximation, to estimate changes in transmural pressure in the pulmonary vessels. Transmural pressure is defined as the difference in pressure between the intravascular pressure and the pressure on the outside of the vessel wall. Since all mean pressures were measured during at least three respiratory cycles, the pressure outside the vessel walls would be averaged out. It should be pointed out that any change in pulmonary blood flow, pulmonary blood volume, or in pulmonary arterial or left atrial pressure could only alter the pulmonary vascular resistance through changes in transmural pressure.\(^{18}\)

Left ventricular work (LVW) was calculated in kilogram-meters per minute per square meter of body area, by the formula:

\[
LVW = \frac{(\overline{SA} - \overline{LA}) \times C.I.}{100}
\]

in which \(\overline{SA}\) and \(\overline{LA}\) are the mean systemic arterial and mean left atrial pressures in cm. H\(_2\)O, respectively. C.I. is the cardiac index in liters per minute per square meter of body area.

The tension-time index was used to estimate, indirectly, changes in the myocardial oxygen consumption and was calculated from the planimetric integrated area under the systolic portion of the arterial pressure pulse.\(^{19}\)

**Results and Discussion**

Data from all patients are summarized in table 1. In the same table, the mean differences between the control period and the period corresponding to the administration of bradykinin, as well as the respective standard deviations and \(p\) values, are tabulated.

The systemic arterial pressure decreased significantly during the intravenous infusion of the drug. This decrease in pressure was accompanied by a simultaneous and equally significant increase of the cardiac output, with no consistent change in total oxygen consumption. Therefore, the present investigation has confirmed that bradykinin has a vasodilatory effect on the systemic circulation, since the calculated total peripheral resistance fell appreciably in all patients.

The fall in resistance could explain not only the decrease in pressure but it could also be responsible for a compensatory increase of the cardiac output. As is already known, a lowered pressure acting upon the arterial stretch receptors elicits a reflex acceleration of the heart rate. In addition, a drop in pressure would offer less resistance to ventricular ejection and could allow an increase of the stroke volume. Furthermore, as was experimentally demonstrated by Saraff et al.\(^{20}\) a decrease of pressure in the carotid sinus reflexly augments the ventricular contractility at any given filling pressure, thus permitting a more complete systolic empty-
Circulatory Effects of Bradykinin in Ten Patients

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Mean difference (D-C): -6.6 -14.07 +2.00 +17.1 +13.6

± standard deviation
P values

* Figures are the mean of two controls.

Key to abbreviations: AH, arterial hypertension; Diab., diabetes mellitus; PU, peptic ulcer; BSA, body surface area (M²); C, control period; D, during bradykinin infusion; Br., bradykinin (μg/Kg/min.); VO₂, oxygen consumption (ml/min/M²); A-V Diff, arterio-venous difference (ml/L); CI, cardiac index (L/min/M²); HR, heart rate

ing. These effects would be enhanced by the catecholamines discharged from the adrenal medulla in response to a lowering of the pressure in the carotid sinus region. Since the increased cardiac output noted in these experiments was coincident with a significant elevation of both the heart rate and the stroke volume, the above-mentioned compensatory mechanisms could have been operative during bradykinin administration. Further support for this interpretation could be found in the secondary rise of the systemic blood pressure following an initial fall determined by a single intravenous injection of bradykinin. Moreover, bradykinin might have a direct releasing action upon the catecholamines stored in the vascular walls or the suprarenal medulla, and its hypotensive effects can be potentiated by sympatholytic agents phenoxybenzamine (Dibenzyline) and by catecholamine-depleting drugs (reserpine). During bradykinin infusion, the left ventricular work either increased or decreased (table 1), depending on whether the rise of the cardiac output was proportionally greater or lesser than the fall of the systemic arterial pressure. Coincident with the rise or fall of the left ventricular work, the tension-time index increased or decreased. Since the tension-time index correlates well with the myocardial oxygen consumption, the results obtained suggest that there was no appreciable modification of the mechanical efficiency of the left ventricle during bradykinin administration.

In the pulmonary circulation, no significant change in pressures was noted either in the arterial or the venous side (left atrium). The respiratory variations of the intravascular and
intracardiac pressures, as well, were about the same during control period and bradykinin infusion. The pulmonary vascular resistance, however, decreased significantly, since the measured flow increased. Since the average intravascular pressure did not undergo any appreciable change, the fall in resistance could not be attributed to any passive mechanical effect, but may be ascribed to active vasodilatation of the pulmonary vessels that would include newly opened parallel vascular channels. The vasodilatation of the pulmonary vascular bed observed in this study, during bradykinin, cannot be interpreted as secondary to the effect of the drug upon the systemic circulation, since the decrease of the systemic pressure acting upon the arterial stretch receptors would tend to elicit a reflex constriction of the pulmonary vessels.

Though the present investigation had not been designed to study in detail the eventual respiratory alterations induced by bradykinin, a slight increase in the respiratory rate and in the volume of expired air per minute was noted in all patients, with no change of the tidal volume.

The duration of the effects of bradykinin was very brief: one to three minutes after the infusion was discontinued, the heart rate and the systemic blood pressure returned to levels similar to those of the control period, as could be observed by the oscilloscopic monitoring of these variables.

The results here reported indicate that the effects of bradykinin in man deserve a more extensive study. Eventually, bradykinin may prove of therapeutic value in emergencies where the acute reduction of high blood pressure levels is of primary importance.

**Summary**

The general hemodynamic effects induced by a continuous intravenous infusion of syn-

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**EFFECTS OF Bradykinin IN MAN**

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(beat/min.); SI, stroke index (ml./beat/M.²); SA, systemic arterial pressure (mm. Hg); PA, pulmonary arterial pressure (mm. Hg); LA, left atrial pressure (mm. Hg); AIP, average intravascular pressure (mm. Hg) in the pulmonary circulation; PTR, peripheral total resistance (dynes sec. cm.⁻⁵); PVR, pulmonary vascular resistance (dynes sec. cm.⁻⁵); LVW, left ventricular work (Kg./min./M.); TTI, tension-time index (mm. Hg sec./min.).
thetic bradykinin were studied in ten patients submitted to simultaneous right- and left-heart catheterization. A significant drop in systemic arterial pressure and in total peripheral resistance was observed, coincident with an increase of the cardiac output, heart rate, and stroke volume. There was no consistent change of the pulmonary arterial and left atrial pressures, but the pulmonary vascular resistance decreased significantly.

Acknowledgment

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