Influence of Beta-adrenergic Blockade on Immediate Hæmodynamic Effects of Angiocardiography

A. REALE, P. IMHOF, AND M. MOTOLESE

From the Clinica Chirurgica, University of Rome Medical School; the Biological Department, CIBA, Basle; and the Istituto di Patologia Medica e Metodologia Clinica, University of Rome Medical School

In our experience, the hæmodynamic reactions taking place within the first 60 seconds after intracardiac injection of contrast media are characterized by an increase in heart rate and a fall in systemic blood pressure, with changes in the morphology of the arterial pressure pulse reflecting peripheral vaso-dilatation. These early modifications, different from those observed at a later stage after the injection (Brown et al., 1965; Friesinger et al., 1965; Rahimtoola, Duffy, and Swan, 1966), are similar to the hæmodynamic effects of isoprorenaline or orciprenaline, substances that stimulate beta-adrenergic receptors specifically (Engelhardt, Hoefke, and Wick, 1961; Whalen et al., 1963). It is therefore suggested that the immediate hæmodynamic changes observed after the administration of contrast media are, at least in part, mediated by adrenergic beta-receptors. Consequently, it should be possible to counteract these effects with the aid of specific beta-adrenergic blocking agents.

SUBJECTS AND METHODS

Selective angiocardiography was performed with Angio-Conray* during left and/or right heart catheterization, before and after beta-receptor blockade in 17 patients with various congenital or acquired valvular lesions. In adult patients 40-50 ml. and in children 20-25 ml. contrast material were injected directly into the right or left ventricle. In each case the amounts of Angio-Conray and the site and the pressure of injection were kept the same throughout the study. In 7 patients angiocardiography was carried out twice before the administration of the beta-receptor-blocking agent; no difference was found between the first and the second control injection.

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* Sterile aqueous solution containing 80 per cent sodium salt of 5-acetylamino-2,4,6-tri-iodo-N-methylisophthalamic acid, corresponding to 48 per cent of iodine, and calcium bisodium ethylenediamine-tetracetae, and sodium bisulphate.

We used a new beta-receptor blocking agent, CIBA 39,089-Ba, which is 1-iso-propylamino-3- (o-allyloxyphenoxy) -2-propanol hydrochloride (CIBA Ltd., Basle, 1966). In order to demonstrate its specific beta-adrenergic blocking properties, infusions of orciprenaline in doses of less than 1 mg. were given to 8 subjects in a separate preliminary study; CIBA 39,089-Ba was administered as soon as a definite effect of orciprenaline was observed, while infusion of the latter drug was continued.

In all experiments intravenous doses of 2.5-10 mg. of CIBA 39,089-Ba were used. The following parameters were studied: left ventricular and brachial arterial pressures, heart rate and rate of change in the ventricular pressure (dp/dt). The first derivative of pressure was obtained by means of a Statham P23 Db transducer and of an R C differentiator with a time constant of 0.5 msec. The latter instrument has an output proportionately linear to input frequency within 5 per cent up to a maximum frequency of 75 cycles*. Measurement of dp/dt, however, is not always considered a sufficiently reliable index of myocardial contractility, since it is influenced by changes in ventricular preload and afterload. It has been suggested (Mason et al., 1965; Mason, 1966) that measurement of the time interval between the onset of contraction and the moment at which the maximum rate of contraction is reached (t-dp/dt) might overcome this difficulty. This parameter was studied in 7 patients. In 9 of them, left ventricular end-diastolic pressures were determined. Furthermore, the time of onset and the duration of arterial hypotension were measured as well as the time elapsing before heart rate, morphology of the arterial pressure pulse, and dp/dt returned to a steady state. When the injection was made into the right ventricle, the time of measurement was always referred to the appearance of contrast material in the left ventricle.

RESULTS

Demonstration of Beta-receptor Blocking Activity of CIBA 39,089-Ba. Orciprenaline administered to 8

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patients elicited an increase in heart rate and dp/dt values, whereas arterial diastolic pressure, t-dp/dt values, and left ventricular end-diastolic pressure decreased. CIBA 39,089-Ba consistently counteracted all these modifications, indicating that specific beta-receptor blockade was achieved. The response to CIBA 39,089-Ba even went beyond control values, since not only the effects of orciprenaline but also some of the endogenous sympathetic activities were blocked (Fig. 1).

**Influence of CIBA 39,089-Ba on Blood Pressure, Heart Rate, and Mechanical Performance of Myocardium under Basal Conditions.** Investigations in 17 patients (Fig. 2) revealed that beta-receptor blockade was followed by a slight but not statistically significant rise in systolic and diastolic blood pressure in the brachial artery. Heart rate, however, decreased significantly by an average of 22 beats a minute. The first derivative of the left ventricular pressure (dp/dt) decreased slightly in most cases and more in those patients with high control values (Fig. 3). The time interval between the onset of contraction and the maximum rate of contraction (t-dp/dt) measured in 7 patients, was slightly increased in most instances, remained unchanged in a few cases, but in no case did it decrease. The over-all changes, however, were statistically non-significant. Left ventricular end-diastolic pressure, which was measured in 9 patients, increased on the average significantly.

**Influence of CIBA 39,089-Ba on Circulatory Reactions due to Injection of Contrast Media.** After the injection of contrast material, brachial arterial pressure decreased in systole by 25 per cent and in diastole by 31 per cent. Beta-receptor blockade did not change this response significantly, the fall in blood pressure being 30 per cent in systole and 33 per cent in diastole (Fig. 4). The average increase of 22 beats a minute in heart rate due to injection of contrast material was identical before and after beta-receptor blockade though taking place at a lower level. In 11 out of 17 patients heart rate exceeded 120 beats a minute before blockade whereas after blockade it reached rates of more than 120 a minute in two instances only, and was never higher than 124 a minute (Fig. 5).
As far as dp/dt and t-dp/dt values are concerned, there was always an increase in peak dp/dt and a decline in t-dp/dt after control contrast injection, though the average differences were not statistically significant. After beta blockade the second injection of contrast medium elicited similar reactions with a trend, however, toward lower values of dp/dt and longer t-dp/dt (Fig. 4 and 6).

Left ventricular end-diastolic pressure decreased after control injection: this effect was even more pronounced after beta-receptor blockade, but in this situation, pre-injection values of left ventricular end-diastolic pressures were always higher than in the control studies.

The onset of the hypotensive reaction was somewhat delayed (9.1 ± 3.8→ 13.5 ± 4.5 sec.; p < 0.001) and the duration of the hypotensive phase slightly shorter after beta-receptor blockade (27.1 ± 10.7→ 22.1 ± 7.5 sec.; p < 0.05). The changes in the morphology of the arterial pressure pulse, consisting in a lower position of the dicrotic incisura along the descending limb of the curve and indicative of peripheral arterial dilatation, were usually less pronounced after beta-receptor blockade (Fig. 6). The return to pre-injection morphology of the arterial pressure pulse occurred sooner (81→ 66 sec.) and heart rate (Fig. 5) and dp/dt also reverted more rapidly to control values (91→ 72 sec.; 84→ 69 sec., respectively).

FIG. 3.—Influence of CIBA 39,089–Ba on the rate of change in the ventricular pressure (dp/dt).
FIG. 4.—Influence of CIBA 39,089–Ba on the circulatory reactions due to injection of contrast medium.

FIG. 5.—Simultaneous recordings of electrocardiogram, of left ventricular and brachial arterial pressures, and of the first derivative of the brachial arterial pressure: A = control, maximal hypotensive and tachycardic reaction; B = control, one minute after injection; C = after beta blockade, maximal hypotensive and tachycardic reaction; D = one minute after beta blockade (recording speed = 25 mm./sec.; time lines = 1 sec.).
In two instances vomiting occurred after the first injection of the contrast material but not after the second following beta-receptor blockade.

**DISCUSSION**

The present study was undertaken with the aim of investigating whether the immediate circulatory effects of angiocardiography are sustained by a stimulation of beta-adrenergic receptors. If this assumption were correct, the administration of a beta-adrenergic blocking agent should prevent the haemodynamic modifications due to the injection of contrast media and could thereby have a clinical application.

Our observations seem to confirm that the reactions taking place within the first minute after angiocardiography are quite similar to the effects of isoprenaline or orciprenaline. In fact, there is a consistent fall in systolic and diastolic blood pressure, peripheral arterial dilatation, and an increase in heart rate. A positive inotropic effect may be inferred from the changes in the first derivative of the ventricular pressure (dp/dt) and the parameter "time interval between the onset of contraction and the peak of the first derivative" (t-dp/dt). Although myocardial contractility is an extremely difficult parameter to measure in intact man, recent work (Mason *et al.*., 1965; Mason, 1966) suggests that the interval t-dp/dt, in combination with the peak dp/dt, does provide a useful approach to the assessment of the contractile state of the heart. An elevation of peak dp/dt accompanied by a decline in t-dp/dt reflects an increased contractility. This behaviour was consistently observed by us after contrast injection.

CIBA 39,089-Ba, a specific beta-adrenergic blocking agent, was shown to counteract the effect of orciprenaline upon heart rate, diastolic blood pressure, and the mechanical performance of the myocardium, but does not avoid the hypotension, nor the increase both in heart rate and in the contractile state of the heart produced by the injection of contrast media. These observations may indicate either that the beta-adrenergic stimulation elicited by the contrast material is excessive in respect to the dosage of the blocking agent used in this study, or that some other mechanism is involved in the circulatory modifications.

It must be emphasized that the changes in heart rate, dp/dt and t-dp/dt values, take place at a lower level after beta-receptor blockade and that pre-angiographic values are regained sooner. In particular, the severe degrees of tachycardia after beta-receptor blockade were not reached and there was a clinical impression that angiocardiography was somewhat better tolerated.

This consideration should be kept in mind in those patients undergoing angiocardiography in whom it is desirable, even for a short time, to avoid excessive cardiac acceleration and enhancement of cardiac performance.

**Fig. 6.**—Simultaneous recordings of electrocardiogram, of left ventricular and brachial arterial pressures, and of the first derivative of the left ventricular pressure: A = pre-injection, control; B = pre-injection, after beta blockade; C = maximal hypotensive reaction, control; D = maximal hypotensive reaction, after beta blockade (recording speed = 25 mm./sec.; time lines = 1 sec.).
SUMMARY

It is suggested that the haemodynamic modifications taking place within the first minute after intracardiac injection of contrast material are mediated by stimulation of the beta-adrenergic receptors. The influence of a new beta-adrenergic blocking agent, CIBA 39,089-Ba, upon these circulatory effects was tested in 17 patients undergoing diagnostic cardiac catheterization. The drug avoided neither the hypotension nor the increase in heart rate and in the contractile state of the heart produced by angiocardiography. This may indicate that the beta-adrenergic stimulation was excessive in respect of the dosage of the blocking agent used or that some other mechanism was involved. However, all circulatory modifications took place at a lower level and pre-angiographic values were regained sooner after beta blockade.

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