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Influence of monoamine oxidase inhibitor on contractility of isolated rat hearts

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MEIJLER, F. L., AND D. DURRER. *Influence of monoamine oxidase inhibitor on contractility of isolated rat hearts.* Am. J. Physiol. 202(6): 1152–1154. 1962.—Following the suggestion that monoamine oxidase inhibitor might interfere with potentiation of cardiac contractions, the influence of 1-iso-nicotinyl-2-isopropyl-hydrazide and 1-pivaloyl-2-benzyl-hydrazine on postextrasystolic increase of isotonic contractions in isolated perfused rat hearts was studied. It was found that monoamine oxidase inhibitor did not change the increase in contractility following an interpolated or a noninterpolated premature beat. The metabolic process by which cardiac muscle varies its contractility with varying cycle length remains unknown.

EXPERIMENTAL EVIDENCE has been presented that potentiation of myocardial contractility is caused by an increase in catecholamine release (1). Recently it has been stated that: "if the end-diastolic pressure and fiber length remain constant, the contraction of the ventricle varies directionally with the effective catecholamine stimulus" (2). Postextrasystolic increase of contractility in intact canine hearts can occur without changes in end-diastolic pressure or end-diastolic volume (3, 4). In a previous paper (5) it was demonstrated that postextrasystolic increase of isotonic contractions in isolated rat hearts cannot be explained by the Frank-Starling mechanism either. According to Whalen's observation (1) and Sarnoff's statement (2) changes in myocardial contractility which do not originate from changes in end-diastolic pressure or fiber length might depend on the amount of available catecholamines.

Kruta (personal communication) observed that rhythm-induced potentiation of contractility in isometric contracting mammalian auricular strips is not depressed by catecholamine inhibitor (reserpine). According to the papers of Resnick (6), Pletscher (7), and Randall and Bagdon (8) monoamine oxidase inhibitors alter the epinephrine metabolism in both human and animal subjects and cause a rise in the catecholamine content of the heart.

Since the Frank-Starling mechanism fails to explain rhythm-induced potentiation of contractility and reserpine does not prevent this kind of potentiation, it was thought possible that monoamine oxidase inhibitors might interfere with it. This paper deals with the study of the influence of monoamine oxidase inhibitors on isotonic contractions which follow a premature beat in isolated perfused rat hearts.

METHODS

Techniques for perfusing isolated mammalian hearts (9, 10), for controlling heart rate, eliciting premature beats (11, 5), and recording the isotonic contractions of the heart (5) were described in detail previously. The linearity of the recording system used warrants accurate reproduction of the apical movements during contraction. Contractility is expressed as recorded contraction height in arbitrary units of length.

After isolation the hearts were connected to the perfusion apparatus and for 15 min were allowed to contract at their own frequency. After 15 min, stimulation was induced at a rate of 3 cycles/sec; after 30 min the investigation was started.

Premature beats were elicited by stimuli of the same intensity (0.5–1.0 ma) and duration (1 msec) as the driving impulses after different delays (125-400 msec) following any 8th or 10th normal contraction at different basal rates (2-6 cycles/sec). At low driving frequencies (2-3.5 cycles/sec) the delay of the extra impulse was changed by steps of 25 msec; at high driving frequencies (3.5-6 cycles/sec) the delay was changed by steps of 10 msec. The stimuli for basal rate and premature beats were applied via the same electrodes, which were sewed on the right auricle. Interpolated premature beats were elicited by stimuli occurring early in the cardiac cycle.

Three groups of ten white rats of approximately 250 g were used for these experiments. The hearts of the first group of rats were perfused with a fluid which contained 1-iso-nicotinyl-2-isopropyl-hydrazide (Marsilid-Roche)

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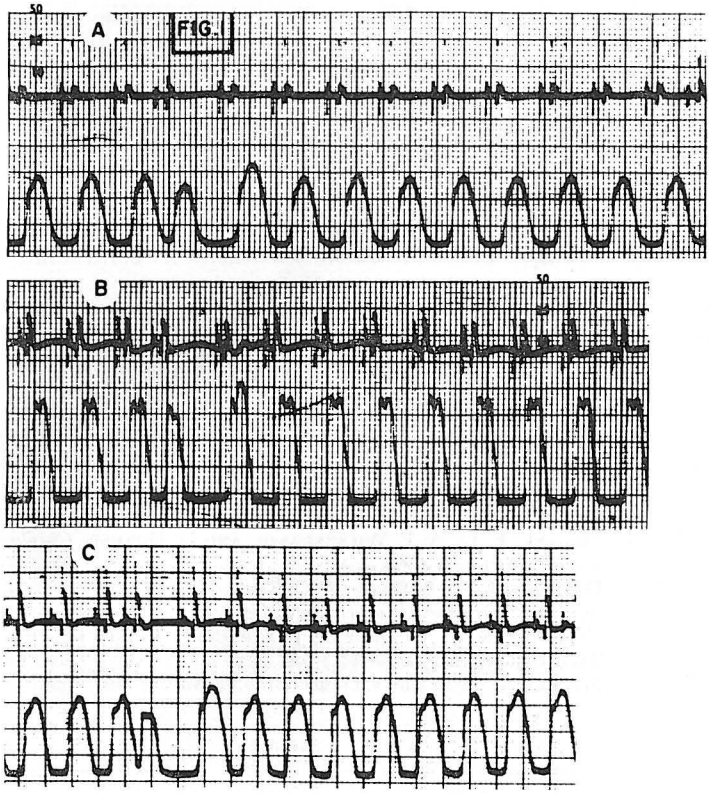

FIG. 1. ECG and apical displacement record of isolated rat hearts; paper speed: 25 mm/sec. *A:* record from heart perfused with Marsilid added to perfusion fluid; cycle length: 400 msec; delay of extra stimulus: 300 msec. *B:* record from heart of animal which received Tersavid intraperitoneally; cycle length: 360 msec; delay of extra stimulus: 250 msec. *C:* record from heart of control group; cycle length: 330 msec; delay of extra stimulus: 225 msec. Notice increase of postcompensatory contraction height without increase of cardiac length.

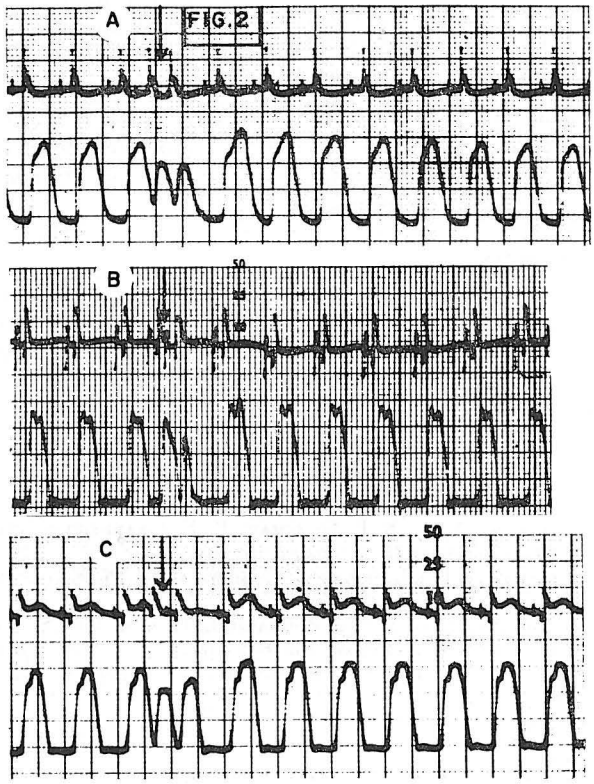

FIG. 2. ECG and apical displacement record of isolated rat hearts; paper speed: 25 mm/sec. Increase of contraction height following an interpolated premature beat. *A:* record from heart of *group 1* (Marsilid); cycle length: 360 msec; delay of extra stimulus: 200 msec. *B:* record from a heart of *group 2* (Tersavid); cycle length: 380 msec; delay of extra stimulus: 240 msec. *C:* record from a heart of *group 3* (control); cycle length: 390 msec; delay of extra stimulus: 200 msec. Notice difference in "postextrasystolic potentiation" between this figure and Fig. 1.

in a concentration of 100-300 mg/liter. The rats of the second group received 50 mg/kg 1-pivaloyl-2-benzylhydrazine (Tersavid-Roche) (5 mg/ml 0.9% NaCl) intraperitoneally daily for 3 days. After this period the hearts were isolated and perfused with a fluid without the addition of monoamine oxidase inhibitor. In the same way as in the first group premature beats were elicited and contractions recorded. The third group of rats, to which no monoamine oxidase inhibitor was administered, served as controls.

RESULTS

It was found that, in all hearts, at each stimulation rate and at each delay of the premature beat, an increase in amplitude of the contractions following an interpolated or a noninterpolated premature beat was present.

In Fig. 1 the records demonstrate that a postextrasystolic increase in amplitude of contraction following a compensatory pause is present in all three groups of rats: *A: group 1*, perfused with 100 mg/liter Marsilid in the perfusion fluid; *B: group 2*, treated by intraperitoneal injections of Tersavid; *C: group 3*, which served as a control.

It can be seen that the contraction pattern differs qualitatively in all three groups but, at a constant end-diastolic length, postextrasystolic contraction increase is present in each.

Fig. 2 demonstrates postextrasystolic increase of contractility following an interpolated premature beat (arrow): *A:* record derived from a heart of *group 1*; *B:* record derived from *group 2*; *C:* record from the control, *group 3*. The striking difference (5) between course of contractility following a premature beat and a compensatory pause (Fig. 1) and that following an interpolated premature beat (Fig. 2) is not altered by monoamine oxidase inhibitor either.

We have refrained from describing the differences in form of the contractions in the three groups.

During these experiments it was noticed that coronary perfusion rate was increased from approximately 10 ml/min in the control group, to two- to threefold in the group of hearts perfused with fluid containing Marsilid.

Coronary flow was not significantly altered in the

hearts of the injected group. Another feature noticed during these experiments was that all animals injected with Tersavid in the way described suffered from bronchopneumonia and showed degenerative changes in liver, spleen, and kidney tissue. We further noticed a decrease of survival time of the isolated hearts from approximately 6 hr in the control group to 1–2 hr in the first and second groups.

DISCUSSION

In previous studies it has already been demonstrated that, in isolated perfused rat hearts, postextrasystolic increase in contractility occurs without increase in end-diastolic intraventricular pressure (12) or cardiac length (5). Kruta's observations and these experiments indicate that, at a constant cardiac length, potentiation of myocardial contractility need not solely depend on catecholamine stimulus. We therefore think the statement that cardiac contractility does depend exclusively on catecholamine stimulus, the Frank-Starling mechanism, or both, may be an oversimplification. The metabolic process by which cardiac muscle varies its contractility with varying cycle length remains unknown.

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