The Effects of Coronary Vasodilators on Coronary and Systemic Circulation*

Experiments on the Hearts of Anesthetized Dogs

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The effects of coronary vasodilators, papaverine, iproveratril, dipyridamole and carbochromene on myocardium and coronary vessels and their resultant effects on systemic circulation were studied. Coronary flow, aortic pressure, cardiac output and cardiac work were determined before and after intracoronary administration of the drugs in the anesthetized open chest dogs continuously using electromanometer and electromagnetic flowmeter.

Each drug caused characteristic increase in coronary flow.

Papaverine, iproveratril and carbochromene caused transient fall in aortic pressure. Iproveratril and carbochromene decreased and dipyridamole increased cardiac output significantly. Papaverine caused some decrease. Iproveratril decreased and dipyridamole increased cardiac work significantly. Papaverine and carbochromene caused some decrease.

THE coronary vasodilators are used to increase oxygen supply to the heart by increasing the coronary blood flow in patients suffering from coronary diseases. The hearts of these patients show in many cases myocardial damages due to coronary insufficiency. Each coronary vasodilator has different pharmacologic actions both on coronary circulation and on systemic circulation. Therefore, knowledge of their hemodynamic effects not only on coronary circulation but also on systemic circulation should be important for judging the effectiveness from the standpoints of clinical view. In the present study the direct effects of the coronary vasodilators on myocardium and coronary vessels and their resultant effects on systemic circulation after the intracoronary administration in such small doses as to cause no changes in systemic hemodynamics when applied intravenously were studied. It is true that almost exhaustively many works on the pharmacology of coronary vasodilators are found

in the literatures, but simultaneous observations on coronary and circulatory changes followed by the intracoronary administration of coronary vasodilators are scanty. In this connection, we studied the effects of papaverine hydrochloride, iproveratril, dipyridamole and carbochromene both on coronary and systemic circulation by recording coronary blood flow, aortic blood flow, aortic blood pressure and heart rate simultaneously and cardiac work was calculated as described in the next paragraph.

METHOD

Experimental data were obtained from 16 adult mongrel dogs in weight from 10 to 20 kg anesthetized by intravenous sodium pentobarbital 30–40 mg/kg injection. Following the institution of general anesthesia, an endotracheal tube with inflatable cuff was inserted and animal was placed on positive pressure breathing of room air. Respiration was controlled by the extent of chest wall

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Fig. 1. The effect of intracoronary administration of papaverine hydrochloride 0.05 mg/kg on coronary blood flow, aortic blood flow and aortic blood pressure. The data were recorded at paper speed 2 mm/sec and 25 mm/sec. Blood pressure was measured in mmHg.
 mean CBF: electrically integrated curves of coronary blood flow
 CBF: phasic coronary blood flow. ABF: phasic aortic blood flow.
 ABP: phasic aortic blood pressure. O: calibrated zero level of each curve.

expansion and the persistence of arterial blood oxygenation.

The chest was opened through the third or the fourth left intercostal-space. After incising the pericardium, silk sutures were placed along the incision and to the thorax wall in order to prevent the expanding of lung over the anterior surface of the heart. The aorta was freed from the pulmonary artery for a distance of about 2 cm, and left descending coronary artery was freed from the heart wall about 10 mm at the nearest part to its origin. In order to administrate the drugs via intracoronary route, a polyethylene cannula of 0.7 mm in diameter was inserted through a arterial branch just near the probe of flowmeter. The probe of electromagnetic flowmeter was placed on the ascending aorta just distal to the coronary orifice and proximal to the first major aortic branch and the other probe of proper caliber was applied to the left descending coronary artery near its origin. To avoid distortion of the natural flow by applying probe, careful selection of its diameter and fixation of its proper position were necessary. Systemic arterial blood pressure was measured through a cardiac catheter inserted into

the ascending part of the aorta through the femoral artery.

The catheter was connected to the strain gauge electromanometer. The zero level in flow in both the ascending aorta and coronary artery was determined by the method described by IRIUCHI-JIMA.¹ After these procedures, all the experiments were performed when steady state of experimental animal was obtained. The coronary blood flow curves, aortic blood flow curves and aortic blood pressure curves were recorded before and after intracoronary administration of the coronary vasodilators at speeds of 2 mm/sec, and of 25 mm/sec. The recording at later speeds was repeated at 15 seconds, 30 seconds, 1 minute, 3 minutes, 6 minutes, 10 minutes and 20 minutes intervals to calculate the cardiac work, cardiac output and phasic coronary blood flow.

The coronary vasodilators which were studied in this experiments were papaverine hydrochloride, iproveratril, dipyridamole and carbochromene. In order to obtain adequate intracoronary doses of the drugs which were effective in producing a definite increase in coronary blood flow after intracoronary administration but producing

Fig. 2. Retrace of an original record obtained in the present experiments, showing phasic coronary blood flow, phasic aortic blood pressure, phasic aortic blood flow and schema of calculation of cardiac work.

a: onset of isometric contraction
b: onset of isometric relaxation
S: systolic coronary blood flow
D: diastolic coronary blood flow

$$W \doteq \int_0^v p dV = k \int_0^t p v dt = \sum_0^t p v \Delta t$$

no changes in the systemic circulatory state when injected intravenously, several pilot experiments were carried out at different doses of each drug. By these pilot experiments, we found these doses were 0.05 mg/kg of papaverine, 0.005 mg/kg of iproveratril, 0.02 mg/kg of dipyridamole and 0.05 mg/kg of carbochromene.

CALCULATION

1. Coronary blood flow

Mean coronary blood flow, stroke coronary blood flow, systolic coronary blood flow and diastolic coronary blood flow were measured from coronary blood flow curves by planimetry (Fig. 2).

2. Aortic blood pressure

Mean aortic blood pressure was measured

from aortic blood pressure curves by planimetry (Fig. 2).

3. Cardiac output

Aortic blood flow was used as approximate value of cardiac output, since the flowmeter did not include coronary flow. To obtain more precise stroke cardiac output, the area under the four aortic blood flow curves were measured by planimetry and the mean of these four was calculated (Fig. 2).

4. Heart rate

Heart rate was calculated from flow or pressure curves.

5. Cardiac work

Cardiac work was calculated from aortic blood flow curves and aortic blood pressure curves following the formula (1) (Fig. 2).

$$\text{Stroke work} \doteq \int_0^v p dV = k \int_0^t p v dt \dots\dots (1)$$

k: constant

p: aortic blood pressure during ejection

V: cardiac output per cardiac cycle

v: blood flow in aorta

t: ejection time

The value of p was measured from the pressure curve as a height from the level of zero. The value of v was measured from the flow curves as a height from the level of zero. The value of t was measured as one cardiac cycle. Calculations described above were carried out on two cardiac cycles and the mean was obtained. Stroke work of heart was timed by heart rate and thus cardiac work per minute was obtained.

RESULTS

In order to make a comparison among these experiments, the changes of all the observed hemodynamic parameters were expressed in percentage of the control periods. The mean and standard error of the mean for each observed value were calculated and statistical significance of changes compared with control values was tested by t-value. The results of each experimental group were summarized in Table I, II, III and IV.

Papaverine

1. Mean coronary blood flow

Papaverine caused a rapid and brief increase in mean coronary blood flow and the peak effect, $140.6 \pm 12.8\%$ ($p < 0.02$) was reached at 15 seconds after the injection. The increase lasted more than one minute. All dogs showed an in-

TABLE I PERCENT CHANGES IN CORONARY AND SYSTEMIC HEMODYNAMIC PARAMETERS AFTER THE INTRACORONARY ADMINISTRATION OF PAPAVERINE HYDROCHLORIDE 0.05mg/kg

	after the administration		
	15 sec	30 sec	1 min
MCBF	140.6 ± 12.8 <i>p</i> < 0.02	130.2 ± 6.7 <i>p</i> < 0.005	126.7 ± 6.7 <i>p</i> < 0.005
Stroke CBF	139.6 ± 10.5 <i>p</i> < 0.01	128.8 ± 6.9 <i>p</i> < 0.005	124.5 ± 6.5 <i>p</i> < 0.005
SCBF	94.6 ± 11.5 <i>ns</i>	102.6 ± 8.2 <i>ns</i>	107.1 ± 11.4 <i>ns</i>
DCBF	151.3 ± 12.5 <i>p</i> < 0.005	140.7 ± 8.2 <i>p</i> < 0.005	132.8 ± 8.2 <i>p</i> < 0.005
MABF	94.7 ± 2.4 <i>ns</i>	100.5 ± 2.9 <i>ns</i>	102.6 ± 2.6 <i>ns</i>
Stroke ABF	95.2 ± 2.3 <i>ns</i>	99.1 ± 3.2 <i>ns</i>	102.4 ± 1.8 <i>ns</i>
MABP	94.7 ± 4.0 <i>ns</i>	92.8 ± 2.5 <i>p</i> < 0.05	96.7 ± 1.0 <i>ns</i>
SABP	101.3 ± 1.7 <i>ns</i>	98.7 ± 1.1 <i>ns</i>	99.8 ± 1.6 <i>ns</i>
DABP	91.5 ± 3.4 <i>p</i> < 0.05	89.3 ± 4.1 <i>p</i> < 0.05	94.6 ± 2.7 <i>ns</i>
HR	100.9 ± 0.3 <i>p</i> < 0.02	101.3 ± 0.7 <i>ns</i>	100.0 ± 1.5 <i>ns</i>
W	91.5 ± 4.5 <i>ns</i>	90.0 ± 5.3 <i>ns</i>	95.0 ± 3.7 <i>ns</i>

The data were expressed in percentage compared with control level and mean values ± standard error of the mean were shown in the Table.

MCBF: mean coronary blood flow

MABF: mean aortic blood flow

SCBF: systolic coronary blood flow

DCBF: diastolic coronary blood flow

MABP: mean aortic blood pressure

SABP: systolic aortic blood pressure

DABP: diastolic aortic blood pressure

HR: heart rate

W: cardiac work

crease in mean coronary blood flow. The maximal effect was observed at 15 seconds in five dogs, at 30 seconds in three dogs and at one minute in two dogs after the injection. The maximal values ranged from 116.2% to 169.5%. Values of stroke coronary blood flow showed similar changes as those of mean coronary blood flow.

2. Phasic coronary blood flow

A dramatic increase of diastolic coronary blood flow appeared immediately after the injection and lasted more than one minute, with the peak effect, $151.3 \pm 12.5\%$ ($p < 0.005$), being reached at 15 seconds after the injection, while no changes of systolic coronary blood flow were detected.

Each dog showed an increase in diastolic coronary blood flow. The maximal effects were observed at 15 seconds in five dogs, at 30 seconds in two dogs and at one minute in one dog after the injection. The maximal values ranged from 116.0% to 205.1%.

3. Mean aortic blood flow

The changes in mean aortic blood flow after the injection of papaverine were not significant statistically.

4. Mean aortic blood pressure

Papaverine caused a decrease in mean aortic blood pressure with the peak effect, $92.8 \pm 2.5\%$ ($p < 0.05$), being reached at 30 seconds after the administration and the decrease returned to the

control level within one minute after the injection. Nine of ten dogs showed the maximal decrease in mean aortic blood pressure ranging from 72.7% to 98.6% within 30 seconds after the injection. In one dog mean aortic blood pressure increased and reached to the maximal value, 117.8% of the control level at 15 seconds after the injection.

5. Phasic aortic blood pressure

Papaverine caused a decrease in diastolic aortic blood pressure with the peak effect, $89.3 \pm 4.1\%$ ($p < 0.05$), being reached at 30 seconds after the injection, whereas no significant changes in mean value of systolic aortic blood pressure were observed. The values of the peak effect in diastolic aortic blood pressure ranged from 55.0% to

109.1%, and those in systolic aortic blood pressure ranged from 91.3% to 109.1%.

6. Heart rate

Papaverine caused a slight but significant increase in heart rate, with the peak effect, $100.9 \pm 0.3\%$ ($p < 0.02$) at 15 seconds after the injection. Seven of ten dogs showed an increase in heart rate in which the values of the peak effect ranged from 101.4% to 105.4% of the control level.

7. Cardiac work

Eight of ten dogs showed a decrease in cardiac work in which the values of the peak effect ranged from 64.5% to 94.4% of the control level. One dog showed no changes and one dog showed an increase in cardiac work.

TABLE II PERCENT CHANGES IN CORONARY AND SYSTEMIC HEMODYNAMIC PARAMETERS AFTER THE INTRACORONARY ADMINISTRATION OF IPROVERATRIL 0.005mg/kg

	after the administration				
	15 sec	30 sec	1 min	3 min	6 min
MCBF	122.7 ± 6.8 $p < 0.01$	124.3 ± 8.2 $p < 0.02$	124.2 ± 9.2 $p < 0.05$	109.1 ± 4.8 <i>ns</i>	96.3 ± 4.6 <i>ns</i>
Stroke CBF	121.3 ± 6.8 $p < 0.002$	122.8 ± 8.4 $p < 0.05$	122.2 ± 9.2 $p < 0.05$	108.8 ± 4.8 <i>ns</i>	95.4 ± 4.1 <i>ns</i>
SCBF	131.8 ± 15.9 <i>ns</i>	132.8 ± 15.9 <i>ns</i>	131.6 ± 11.5 $p < 0.05$	114.7 ± 7.6 <i>ns</i>	99.0 ± 3.3 <i>ns</i>
DCBF	121.3 ± 9.7 <i>ns</i>	122.2 ± 12.5 <i>ns</i>	121.1 ± 11.9 <i>ns</i>	106.8 ± 6.9 <i>ns</i>	94.6 ± 3.3 <i>ns</i>
MABF	93.3 ± 2.0 $p < 0.02$	98.0 ± 3.5 <i>ns</i>	96.8 ± 2.0 <i>ns</i>	98.9 ± 3.9 <i>ns</i>	99.8 ± 4.4 <i>ns</i>
Stroke ABF	93.1 ± 2.0 $p < 0.01$	96.6 ± 3.4 <i>ns</i>	95.2 ± 3.4 <i>ns</i>	98.5 ± 4.0 <i>ns</i>	99.5 ± 4.4 <i>ns</i>
MABP	96.6 ± 4.1 <i>ns</i>	94.7 ± 3.2 <i>ns</i>	97.9 ± 2.7 <i>ns</i>	95.6 ± 3.8 <i>ns</i>	96.7 ± 3.4 <i>ns</i>
SABP	93.1 ± 2.9 $p < 0.05$	93.0 ± 2.0 $p < 0.01$	96.1 ± 2.1 <i>ns</i>	95.8 ± 2.2 <i>ns</i>	94.3 ± 2.5 <i>ns</i>
DABP	92.1 ± 3.7 <i>ns</i>	95.4 ± 3.2 <i>ns</i>	97.1 ± 2.8 <i>ns</i>	98.1 ± 3.8 <i>ns</i>	95.0 ± 3.2 <i>ns</i>
HR	101.3 ± 0.2 $p < 0.01$	101.3 ± 0.5 $p < 0.05$	101.8 ± 0.3 $p < 0.001$	100.5 ± 0.3 <i>ns</i>	100.5 ± 0.4 <i>ns</i>
W	87.0 ± 4.5 $p < 0.05$	92.0 ± 5.2 <i>ns</i>	94.9 ± 5.1 <i>ns</i>	93.5 ± 4.6 <i>ns</i>	90.0 ± 5.9 <i>ns</i>

The data were expressed in percentage compared with control level and mean values $\pm$ standard error of the mean were shown in the Table.

MCBF: mean coronary blood flow

SCBF: systolic coronary blood flow

MABP: mean aortic blood pressure

DABP: diastolic aortic blood pressure

MABF: mean aortic blood flow

DCBF: diastolic coronary blood flow

SABP: systolic aortic blood pressure

HR: heart rate W: cardiac work

TABLE III PERCENT CHANGES IN CORONARY AND SYSTEMIC HEMODYNAMIC PARAMETERS AFTER THE INTRACORONARY ADMINISTRATION OF DIPYRIDAMOLE 0.02mg/kg

	after the administration					
	15 sec	30 sec	1 min	3 min	6 min	10 min
MCBF	135.7 ± 11.7 <i>p</i> < 0.02	127.5 ± 8.6 <i>p</i> < 0.02	128.3 ± 15.5 <i>p</i> < 0.05	126.3 ± 10.6 <i>ns</i>	128.3 ± 15.5 <i>ns</i>	116.8 ± 14.7 <i>ns</i>
Stroke CBF	136.2 ± 10.6 <i>p</i> < 0.02	126.2 ± 8.7 <i>p</i> < 0.02	127.4 ± 9.8 <i>p</i> < 0.02	126.9 ± 13.8 <i>ns</i>	121.6 ± 14.9 <i>ns</i>	116.6 ± 16.2 <i>ns</i>
SCBF	168.9 ± 30.6 <i>ns</i>	147.0 ± 34.0 <i>ns</i>	147.3 ± 29.1 <i>ns</i>	152.2 ± 42.1 <i>ns</i>	151.7 ± 47.6 <i>ns</i>	142.4 ± 49.6 <i>ns</i>
DCBF	133.7 ± 9.1 <i>p</i> < 0.005	133.0 ± 6.9 <i>p</i> < 0.02	125.0 ± 7.2 <i>p</i> < 0.01	124.6 ± 9.9 <i>p</i> < 0.05	117.8 ± 19.4 <i>ns</i>	114.8 ± 9.5 <i>ns</i>
MABF	104.9 ± 4.2 <i>ns</i>	104.7 ± 2.4 <i>ns</i>	105.2 ± 2.6 <i>ns</i>	104.3 ± 4.2 <i>ns</i>	104.7 ± 3.8 <i>ns</i>	100.2 ± 4.2 <i>ns</i>
Stroke ABF	105.2 ± 4.1 <i>ns</i>	104.0 ± 2.2 <i>ns</i>	105.4 ± 2.4 <i>p</i> < 0.05	104.0 ± 3.4 <i>ns</i>	104.0 ± 3.5 <i>ns</i>	99.5 ± 3.6 <i>ns</i>
MABP	97.6 ± 1.6 <i>ns</i>	100.4 ± 2.9 <i>ns</i>	98.6 ± 2.1 <i>ns</i>	98.6 ± 2.1 <i>ns</i>	98.9 ± 2.6 <i>ns</i>	97.5 ± 2.5 <i>ns</i>
SABP	100.0 ± 1.8 <i>ns</i>	101.0 ± 2.8 <i>ns</i>	99.7 ± 2.5 <i>ns</i>	100.9 ± 2.1 <i>ns</i>	99.2 ± 2.1 <i>ns</i>	96.4 ± 2.4 <i>ns</i>
DABP	99.1 ± 1.6 <i>ns</i>	100.3 ± 3.2 <i>ns</i>	97.9 ± 3.3 <i>ns</i>	99.4 ± 2.0 <i>ns</i>	97.5 ± 3.0 <i>ns</i>	95.9 ± 3.1 <i>ns</i>
HR	99.7 ± 0.5 <i>ns</i>	100.9 ± 1.0 <i>ns</i>	99.8 ± 1.0 <i>ns</i>	99.7 ± 1.0 <i>ns</i>	99.4 ± 0.6 <i>ns</i>	100.1 ± 0.9 <i>ns</i>
W	108.0 ± 1.5 <i>ns</i>	109.8 ± 4.6 <i>ns</i>	107.0 ± 3.4 <i>ns</i>	115.6 ± 5.5 <i>p</i> < 0.02	108.1 ± 5.4 <i>ns</i>	106.9 ± 5.4 <i>ns</i>

The data were expressed in percentage compared with control level and mean values ± standard error of the mean were shown in the Table.

MCBF: mean coronary blood flow
DCBF: diastolic coronary blood flow
MABP: mean aortic blood pressure
DABP: diastolic aortic blood pressure

SCBF: systolic coronary blood flow
MABF: mean aortic blood flow
SABP: systolic aortic blood pressure
HR: heart rate W: cardiac work

Iproveratril

1. Mean coronary blood flow

Iproveratril caused a prompt increase in mean coronary blood flow with the peak effect, 124.3 ± 8.2% (*p* < 0.02) at 30 seconds after the injection. The increase returned to the control level at six minutes after the injection. Nine of ten dogs showed an increase in mean coronary blood flow in which the values of the peak effect ranged from 112.2% to 196.3% within three minutes after the injection. One dog showed no changes in flow.

2. Phasic coronary blood flow

As presented in Table II, iproveratril caused an increase in coronary flow during systole and during diastole. Nine of ten dogs showed an increase

in systolic blood flow with the peak effect ranging from 109.6% to 257.2% being reached within one minute after the injection. One dog showed a decrease in systolic coronary blood flow. Eight of ten dogs showed an increase in diastolic coronary blood flow with the peak effect ranging from 111.1% to 226.1% being reached within one minute after the injection. Two dogs showed a decrease in diastolic coronary blood flow. Seven of ten dogs showed an increase in coronary flow both during systole and diastole.

3. Mean aortic blood flow

Iproveratril produced a decrease in mean aortic blood flow with the peak effect, 93.3 ± 2.0% (*p* < 0.02), being reached at 15 seconds after the injection. Nine of ten dogs showed a decrease in

mean aortic blood flow with the peak effect ranging from 83.8% to 97.9% within 30 seconds after the injection. One dog showed an increase in mean aortic blood flow. The changes in stroke aortic blood flow were similar to those in mean aortic blood flow.

4. Mean aortic blood pressure

Eight of ten dogs showed a decrease in mean aortic blood pressure with the peak effect ranging from 80.1% to 93.1% and two dogs showed an increase in mean aortic blood pressure.

5. Phasic aortic blood pressure

Iproveratril caused a decrease in systolic aortic blood pressure with the peak effect, $93.1 \pm 2.9\%$ ($p < 0.01$), being reached at 30 seconds after the injection. Eight of ten dogs showed a decrease in systolic blood pressure in which values of the peak effect ranged from 80.0% to 93.3% of the control level. Eight of ten dogs showed a decrease in diastolic aortic blood pressure in which the values of the peak effect ranged from 74.2% to 94.7% of the control level. Seven of ten dogs showed a decrease in both systolic and diastolic aortic blood pressure, and one dog showed a rise in both.

6. Heart rate

Iproveratril produced a slight but significant increase in heart rate lasting more than one minute with the peak effect, $101.8 \pm 0.3\%$ ($p < 0.001$), being reached at one minute after the injection. Nine of ten dogs showed an increase in heart rate and one dog showed a decrease.

7. Cardiac work

Iproveratril caused a decrease in cardiac work lasting more than six minutes with the peak effect, $87.0 \pm 4.5\%$ ($p < 0.05$) at 15 seconds after the injection. Nine of ten dogs showed a decrease in cardiac work with the peak effect ranging from 69.3% to 89.9%, and seven of those dogs showed the peak effect within one minute after the injection. One dog showed an increase in cardiac work.

Dipyridamole

1. Mean coronary blood flow

Dipyridamole produced a prompt increase in mean coronary blood flow, with the peak effect, $135.7 \pm 11.7\%$ ($p < 0.02$), being reached at 15 seconds after the injection. The increase in flow lasted more than ten minutes after the injection. All dogs showed an initial increase within one minute after the injection. Nine of ten dogs showed the peak effect ranged from 109.1% to 259.1% within three minutes after the admini-

stration. The effect of dipyridamole on stroke coronary blood flow was similar to that on mean coronary blood flow.

2. Phasic coronary blood flow

All dogs showed an increase in systolic coronary blood flow within three minutes after the injection. In one dog the increase was very profound and the value of the peak effect in systolic coronary blood flow was 568.9% of the control level at three minutes after the injection. In nine dogs the values of the peak effect in systolic coronary blood flow ranged from 112.9% to 241.3% of the control level, and were reached within three minutes in eight dogs and within six minutes in one dog after the injection. But six minutes after the injection, systolic coronary blood flow in five out of ten dogs decreased below the control level after the initial increase. Dipyridamole also caused an increase in diastolic blood flow lasting more than ten minutes, with the peak effect, $133.7 \pm 9.1\%$ ($p < 0.005$), being reached at 15 seconds after the injection. All dogs showed an increase in diastolic coronary blood flow, with the peak effect ranging from 106.8% to 202.3% being reached within three minutes in eight dogs and within six minutes in two dogs after the injection. But at six minutes after the injection, systolic coronary blood flow in five of ten dogs decreased below the control level after the injection.

3. Mean aortic blood flow

Eight of ten dogs showed an increase in mean aortic blood flow in which the values of the peak effect ranging from 105.3% to 120.4% of the control level.

4. Stroke aortic blood flow

Dipyridamole increased systolic aortic blood flow lasting more than six minutes with the peak effect, $105.4 \pm 2.4\%$ ($p < 0.05$), being reached at one minutes after the injection. Eight of ten dogs showed an increase in stroke aortic blood flow in which the values of the peak effect ranged from 105.3% to 136.6% of the control level.

5. Mean aortic blood pressure

The changes in mean aortic blood pressure were not significant statistically. Mean aortic blood pressure decreased in six dogs, increased in three dogs and showed no changes in one dog after the injection. The values of the peak effect ranged from 84.1% to 116.9% of the control level.

6. Phasic aortic blood pressure

No significant changed in both systolic and diastolic aortic blood pressure were observed.

TABLE IV PERCENT CHANGES IN CORONARY AND SYSTEMIC HEMODYNAMIC PARAMETERS AFTER THE INTRACORONARY ADMINISTRATION OF CARBOCHROMENE 0.05mg/kg

	after the administration						
	15 sec	30 sec	1 min	3 min	6 min	10 min	20 min
MCBF	99.5 ± 7.1 ns	104.6 ± 4.7 ns	106.8 ± 6.9 ns	113.6 ± 7.5 ns	124.5 ± 11.6 ns	120.2 ± 8.9 p < 0.05	123.3 ± 18.6 ns
Stroke CBF	98.9 ± 7.1 ns	103.7 ± 4.3 ns	107.7 ± 5.6 ns	114.9 ± 8.2 ns	123.6 ± 12.0 ns	123.3 ± 11.7 ns	108.0 ± 29.8 ns
SCBF	98.4 ± 12.8 ns	98.6 ± 5.6 ns	105.5 ± 6.6 ns	110.6 ± 9.3 ns	123.2 ± 13.2 ns	122.6 ± 14.2 ns	103.4 ± 32.0 ns
DCBF	98.4 ± 4.7 ns	104.6 ± 4.3 ns	107.7 ± 6.1 ns	116.8 ± 7.9 ns	129.4 ± 11.8 p < 0.05	123.3 ± 10.6 ns	130.9 ± 14.8 ns
MABF	88.5 ± 2.6 p < 0.005	89.6 ± 2.8 p < 0.01	96.6 ± 2.2 ns	96.6 ± 2.8 ns	91.1 ± 3.5 p < 0.05	93.5 ± 3.2 ns	91.0 ± 4.8 ns
Stroke ABF	88.0 ± 2.6 p < 0.05	91.8 ± 2.8 p < 0.02	95.3 ± 2.4 ns	95.6 ± 1.7 p < 0.05	90.7 ± 2.8 p < 0.01	92.5 ± 3.0 p < 0.05	91.0 ± 4.0 ns
MABP	97.1 ± 1.9 ns	94.4 ± 2.2 p < 0.05	98.0 ± 1.4 ns	99.3 ± 2.2 ns	98.3 ± 2.3 ns	97.4 ± 2.0 ns	99.0 ± 3.0 ns
SABP	98.4 ± 1.4 ns	98.1 ± 1.6 ns	99.9 ± 1.6 ns	102.2 ± 2.4 ns	100.9 ± 2.3 ns	100.1 ± 2.0 ns	100.6 ± 1.5 ns
DABP	99.1 ± 1.2 ns	97.5 ± 3.3 ns	101.0 ± 1.7 ns	101.4 ± 2.7 ns	101.2 ± 2.8 ns	99.7 ± 2.4 ns	100.6 ± 4.2 ns
HR	100.6 ± 0.3 ns	100.5 ± 0.6 ns	100.2 ± 0.4 ns	99.3 ± 2.0 ns	100.9 ± 0.7 ns	101.2 ± 0.9 ns	99.1 ± 3.8 ns
W	98.5 ± 3.0 ns	93.4 ± 4.1 ns	99.8 ± 4.6 ns	95.6 ± 4.6 ns	97.3 ± 5.3 ns	97.8 ± 3.8 ns	93.8 ± 3.3 ns

The data were expressed in percentage compared with control level and mean values ± standard error of the mean were shown in the Table.

MCBF: mean coronary blood flow
DCBF: diastolic coronary blood flow
MABP: mean aortic blood pressure
DABP: diastolic aortic blood pressure

SCBF: systolic coronary blood flow
MABF: mean aortic blood flow
SABP: systolic aortic blood pressure
HR: heart rate
W: cardiac work

7. Heart rate

No significant changes in heart rate were observed.

8. Cardiac work

Dipyridamole increased cardiac work, with the peak effect, $115.6 \pm 5.5\%$ ($p < 0.02$), being reached at three minutes after the injection. All dogs showed an increase in cardiac work with the peak effect ranging from 110.1% to 149.3% being reached within three minutes in six dogs and more than six minutes in four dogs after the injection.

Carbochromene

1. Mean coronary blood flow

Carbochromene caused an initial increase in mean coronary blood flow later than three minutes after the injection. The increase in flow lasted for more than 20 minutes and reached to the peak effect, $120.2 \pm 8.9\%$ ($p < 0.05$) of the control level at ten minutes after the injection. Eight of ten dogs showed an increase in mean coronary blood flow with the peak effect ranging from 114.9% to 196.2% being reached at 15 seconds in

one dog and at six to twenty minutes in seven dogs after the injection. Two dogs showed no increase in mean coronary blood flow.

2. Phasic coronary blood flow

Eight of ten dogs showed an increase in systolic coronary blood flow with the peak effect ranging from 110.1% to 207.1% of the control level being reached later than six minutes in six dogs and within one minute in two dogs after the injection. Carbochromene increased diastolic coronary blood flow with the peak effect, $129.4 \pm 11.8\%$ ($p < 0.05$), being reached at six minutes after the injection. Nine of ten dogs showed an increase in diastolic coronary blood flow with the peak effect ranging from 107.0% to 207.8% being reached later than six minutes in seven dogs and within one minute in two dogs after the injection.

3. Mean aortic blood flow

Carbochromene caused an initial decrease in mean aortic blood flow within 30 seconds and a second decrease at six minutes after the injection, with the peak effect, $88.5 \pm 2.6\%$ ($p < 0.005$), being reached at 30 seconds after the injection.

4. Stroke aortic blood flow

Fig. 3. Effect of intracoronary administration of papaverine hydrochloride 0.05 mg/kg, iproveratril 0.005 mg/kg, dipyridamole 0.02 mg/kg and carbochromene 0.05 mg/kg on mean coronary blood flow (MCBF), mean aortic blood flow (MABF), mean aortic blood pressure (MABP) and cardiac work.

A significant decrease in stroke blood flow was observed at first within 30 seconds transiently and once more at three to six minutes after the injection, with the peak effect, $88.0 \pm 2.6\%$ ($p < 0.05$), being reached at 15 seconds after the injection.

5. Mean aortic blood pressure

Carbochromene caused a brief decrease in mean aortic blood flow with the peak effect, $94.4 \pm 2.2\%$ ($p < 0.05$), being reached at 30 seconds after the injection. Mean aortic blood pressure returned to the control level at one minute after the injection.

6. Phasic aortic blood pressure

No significant changes were observed in both systolic and diastolic aortic blood pressure.

7. Heart rate

No significant changes in heart rate were observed.

8. Cardiac work

Carbochromene decreased cardiac work in six of ten dogs, with the peak effect ranging from 64.9% to 95.0% and increased cardiac work in two dogs with the peak effect ranging from 107.1% to 111.1% of the control level and produced no changes in two dogs.

DISCUSSION

Papaverine

In 1913 PAL first suggested the intravenous use of papaverine to treat anginal syndrome and in 1922 he observed beneficial results in patients after the injection of papaverine intravenously. LINDER and KATZ (1951)², MACHT (1915)³, ESSEX et al. (1940)⁴, WEGRIA et al. (1940)⁵, ECKENHOFF and HAFKENSCHIEL (1947)⁶ and DÖRNER and WICK (1955)⁷ observed a coronary vasodilating effect of papaverine in animal experiments. ELECK and KATZ (1942)⁸ showed that papaverine was useful clinically in coronary insufficiency and myocardial infarction. However, it was observed in many clinical studies that papaverine is of limited, little or no value (EVANS and HOYLE⁹ 1933; WHITE¹⁰ 1944; GRAY and co-workers¹¹ 1945; GOLD¹² 1956; KATZ and co-workers¹³ 1946), and recently LUEBS and BING¹⁴ (1966) observed that papaverine, a smooth muscle relaxant, does not alter myocardial blood flow significantly in individuals with or without coronary artery disease, and suggested that the relief of anginal pain produced by papaverine may be sought in increase in collateral flow or on diminution in cardiac contractility, leading to a diminished myocardial oxygen demand. But

almost all these investigators used intravenous administration of papaverine. Therefore, the results included systemic effect of papaverine. It is the purpose of the present study to observe direct action of papaverine on coronary arteries without systemic effect by administration of the drug directly into coronary artery. It was observed by this method that the intracoronary administration increased coronary blood flow, especially during diastole and decreased aortic blood pressure. Cardiac work and cardiac output showed a decreasing tendency. These results suggest that papaverine has a negative inotropic action on heart and relaxing action on smooth muscle which results in dramatic increase in diastolic coronary blood flow. A negative inotropic action on heart of papaverine may decrease myocardial oxygen demand and the increase in coronary flow may increase the myocardial oxygen supply. These effects of papaverine on heart show its beneficial clinical applicability.

Iproveratril

Iproveratril which was synthesized by DENGEL was shown to increase coronary blood flow and to act as a beta adrenergic blocking substance in animal experiments (HAAS and HARTFELDER¹⁵ 1962; HAAS¹⁶ 1964). Iproveratril also was found to increase the coronary flow after intravenous administration in man without coronary artery disease (LUEBS and BING¹⁴ 1966). Clinical effect on angina pectoris has been observed (TSCHURDEWAGB and KLEPZIG¹⁷ 1963; KNOCH, SCHLEPPER and WITZLEB¹⁸ 1962). A slight fall in systemic blood pressure and increase in cardiac output after the intravenous injection in animal experiments has been observed (HAAS and HARTFELDER¹⁵ 1962; SCHLEPPER and WITZLEB¹⁹ 1962). The variable results concerning an influence on heart rate with a decrease in the heart rate of the dog with the open chest and increase in rate in unanesthetized animal or anesthetized dog with closed chest have been observed by HAAS and HARTFELDER¹⁵ (1962). SCHLEPPER suggested that the changes in heart rate might be related to the lowered arterial pressure, and might be triggered in a reflex manner by way of the pressure-sensitive zones in the arterial flow area. The intracoronary administration was observed to produce an immediate rise in the blood flow within the injected branch of the artery and this phenomenon suggested a peripheral action of the drug (HAAS and HARTFELDER¹⁵ 1962). In the present study, the intracoronary administration

in doses of 0.005 mg/kg caused a definite increase in flow both during systole and diastole. The difference between the phasic flow patterns after the intracoronary administration of iproveratril and those of papaverine may suggest that iproveratril, besides the direct dilating effect on coronary vessels as observed by the administration of papaverine, may increase the coronary flow by other factors which cannot be interpreted on the basis of the present study but may relate with its beta blocking action. Moreover the intracoronary administration decreased aortic blood flow, aortic blood pressure and cardiac work, so that iproveratril has a negative inotropic action on heart. This results might be due to the decrease in cardiac contractility which was observed by HAAS and HÄRTFELDER¹⁵ in the experiments with the Langendorff heart of the rabbit and papillary muscle of the cat. A negative inotropic action on heart, increasing effect on coronary flow and beta blocking action of this drug might have therapeutic action on coronary insufficiency of hyperdynamic type.

Dipyridamole

KADATZ²⁰ showed that dipyridamole, one of the derivatives of prymido-(5, 4)-pyrimidine series, increased coronary blood flow significantly. Since that time, numerous experiments were performed on normal anesthetized animals and all these studies showed the ability of dipyridamole to improve coronary circulation (GRABNER,²¹ 1959: HOCKERTS,²² 1959: BRETSCHNEIDER,²³ 1959: KADATZ and BEISENHERZ,²⁴ 1965: WEST,²⁵ 1962: BETZ,²⁶ 1961: STENICKAR,²⁷ 1961). In most of these experimental studies, the drug was administered intravenously and showed an effect on peripheral circulation to decrease blood pressure in various grade. Consistent results were not obtained by various workers on the effect of the drug on cardiac output, heart rate and cardiac work. The results observed in man were also variable (SPITZBARTH,²⁸ 1959: JUNEMANN,²⁹ 1959: HOCHREIN,³⁰ 1962: LOZANA,³¹ 1966). To evaluate the clinical usefulness of the drug we tried to study the direct action of the drug on coronary artery and heart itself by the direct administration of the drug into coronary artery. An increase in coronary flow by intracoronary administration was shown by KADATZ²⁰ and WEST,²⁵ with no effect on heart rate or blood pressure in doses below 100 µg/kg. But in the present study the doses of 0.02 mg/kg of dipyridamole caused a significant in-

crease in cardiac output, cardiac work and coronary flow and no effect on blood pressure and heart rate. HOCHREIN³⁰ and BOUSVAROUS³² also showed an increase in cardiac work in man. From the results obtained by these experiments, the present author concluded that dipyridamole is beneficial in the case of coronary insufficiency with potential or manifest myocardial insufficiency.

Carbochromene

RITTER and BEYERLE³³ synthesized cabichromene, one of the derivatives of 2-oxo-(1,2-chromene) series and NITZ (1963),³³ LOCHNER (1963),³⁴ and BRETSCHNEIDER (1963)³⁵ observed that the drug caused a prominent and long lasting increase in coronary flow in anesthetized dogs with open or closed thorax. LUEBS and BING (1966)¹⁴ and RUDOLPH (1967)³⁶ observed that in man. The effect on coronary flow and systemic circulation after the intravenous administration in various doses were studied in many works. A small, insignificant, or a transient decrease in blood pressure were observed (LOCHNER,³⁴ BING,¹⁴ RUDOLPH,³⁶ BRETSCHNEIDER,³⁵ NITZ³³). LOCHNER³⁴ and RUDOLPH³⁶ observed an increase in cardiac output in dogs and in man. NITZ³³ and LOCHNER³⁴ observed an increase in heart rate in dogs. LOCHNER³⁴ showed no changes in cardiac work. NITZ³³ proved a decrease in heart rate and a slight increase in cardiac contractility with no increase in coronary flow in experiments with Langendorff heart of guinea pig. The intracoronary administration was discussed by NITZ³³ and LOCHNER,³⁴ and biphasic increase in coronary flow was observed in dogs without no changes in systemic circulation. However, in the present study the intracoronary administration decreased cardiac output, aortic blood pressure and cardiac work, and increased coronary flow but caused no changes in heart rate. This results suggest that carbochromene has a negative inotropic action on heart. From the above results, the present author concluded that carbochromene is a long acting coronary dilator with a negative inotropic effect on cardiac activity.

SUMMARY

Studies on the effects of papaverine, iproveratril, dipyridamole and carbochromene on coronary and systemic circulation after intracoronary administration in small doses were made in anesthetized dogs with electromagnetic flow-

meters. The doses were so small that the same doses caused no changes in both coronary and systemic circulation when given intravenously. All these drugs increased coronary flow, whereas the flow showed the different patterns for each drug. While papaverine increased coronary flow almost only during diastole, iproveratril, dipyridamole and carbochromene increased the flow both during systole and diastole. All these coronary vasodilators except dipyridamole decreased mean aortic blood pressure only in short initial period and thereafter the control level was sustained. Iproveratril and carbochromene decreased mean aortic blood flow significantly. After the administration of papaverine mean aortic blood flow showed a decreasing tendency. But after the administration of dipyridamole mean aortic blood flow showed a statistically significant increase. While iproveratril decreased cardiac work, dipyridamole increased it. After the administration of papaverine and carbochromene cardiac work showed a decreasing tendency, but it was not significant statistically. From the above results, the present author concluded that each of these four so called coronary dilators has its characteristic action not only on coronary but also on systemic circulation. Therefore careful analysis of the circulatory dynamics on patients should be made, in order to obtain most beneficial effect of each drug on clinical cases.

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REFERENCES

- IRIUCHIJIMA, J.: Ryuryosokuteiho *Seitai no Kagaku* 17: 137, 1966. (in Japanese).
- LINDER, E. & KATZ, L. N.: Further observation of the action of drugs on the caliber of coronary vessels. Papaverine hydrochloride, digitalis derivatives, aminophyllin, caffeine, glucose, calcium gluconate and metrazol *J. Pharmacol. & Exper. Therap.* 72: 306, 1941.
- MACHT, D. I.: Action of the opium alkaloids, *J. A. M. A.* 44: 1489, 1915.
- ESSEX, H. E., WEGRIA, R., G. E., HERRICK, J. F., & MANN, F. C.: The effect of certain drugs on the coronary blood flow of the trained dog. *Am. Heart J.* 19: 554, 1940.
- ESSEX, H. E., WEGRIA, R., HERRICK, J. F., & MANN, F. C.: *Am. Heart J.* 19: 554, 1940.
- WEGRIA, R., ESSEX, H. E., HERRICK, J. F., & MANN, F. C.: The simultaneous action of certain drugs on the blood pressure and on the flow in the right and left coronary arteries. *Am. Heart J.* 20: 557, 1940.
- ECKENHOFF, J. E. & HAFKENSCHIEL, J. H.: The effect of nikethamide on coronary blood flow and cardiac oxygen metabolism. *J. Pharmacol.* 9: 362, 1947.
- DORNER, J. & WICK, E.: Vergleichende Untersuchungen zur Wirksamkeit gebräuchlicher coronarerweiternder Pharmaka bei narkotisierten und wachen Hunden *Arzneimittel-Forsch.* 10: 631, 1959.
- ELEK, S. R. & KATZ, L. N.: Some clinical uses of papaverine in heart disease *J. A. M. A.* 120: 434, 1942.
- EVANS, W. & HOYLE, C.: The comparative value of drugs used in the continuous treatment of angina pectoris *Quart. J. Med.* 2: 311, 1933.
- WHITE, P. D.: Seven common and important problems in the management of heart diseases and disorders. *M. Clin. North America* 28: 1129, 1944.
- GRAY, W., RISEMAN, J. E. F., & STEARNS, S.: Papaverine in the treatment of coronary artery disease *New England J. Med.* 232: 389, 1945.
- GOLD, H.: Treatment of coronary artery disease *Am. J. Med.* 1: 539, 1946.
- SIMON, A. J., DOLGIN, M., SOLWAY, A. J. L., HIRSCHMANN, J., & KATZ, L. N.: A re-evaluation of papaverine in the treatment of angina pectoris. *J. Lab. Clin. Med.* 34: 992, 1949.
- LUEBS, E. D., COHEN, A., ZALESKI, E. J., & BING, R. J.: Effect of nitroglycerin, Intensain, Isoptin and papaverine on coronary blood flow in man. *Am. J. Card.* 17: 535, Apr. 1966.
- HAAS, H. & HÄRTFELDER, G.: α -Isopropyl- α -(N-methyl-N-homoveratryl)- γ -amino-propyl]-3, 4-dimethoxyphenylacetoneitril, eine Substanz mit coronargefässerweiternden Eigenschaften. *Arzneimittel Forsch.* 12: 549, 1962.
- HAAS, H.: Zur Wirkungsmechanismus des α -Isopropyl- α -(N-methyl-N-homoveratryl)- γ -amino-propyl]-3, 4-dimethoxyphenylacetoneitrils, einer Substanz mit coronargefässerweiternden Eigenschaften. *Arzneimittel Forsch.* 14: 461, 1964.
- TSCHIRDEWAHN, B. & KLEPZIG, H.: Clinical studies on the effect of Isoptin and Isoptin-S in patients with coronary insufficiency. *Deutsch Med. Wchschr.* 88: 1702, 1963.
- KNOCH, G., SCHLEPPER, M., & WITZELB: Isoptin a clinical study using normal subjects and patients with coronary disease. *Med. Klin.* 58: 1485, 1963.
- SCHLEPPER, M. & WITZELB, E.: Tierexperimentelle Untersuchungen über die Veränderungen von Coronardurchblutung und Sauerstoffverbrauch des Herzens nach α -Isopropyl- α -(N-methyl-N-homoveratryl)- γ -amino-propyl]-3, 4-dimethoxyphenylacetoneitril. *Arzneimittel Forsch.* 12: 559, 1962.
- KADATZ, R.: Die Pharmakologischen Eigenschaften der neuen coronarweiternden Substanz 2, 6-Bis (diaethanolamino)-4, 8-dipiperidino-pyrimido(5, 4-d)pyrimidin. *Arzneimittel Forsch.* 9: 39, 1959.
- GRABNER, G., KAINDLE, F., & KRAUPP, O.: Die Wirkung von 2,6-Bis (diaethanolamino)-4,8-di-

- piperidino-pyrimido (5,4-d)-pyrimidin auf Herz-tätigkeit und Coronarkreislauf narkotisierter Hunde. *Arzneimittel Forsch.* 9: 45, 1959.
22. HOCKERTS, T. & BÖGELMANN, G.: Untersuchungen über die Wirkung von 2,6-Bis(diaethanolamino)-4,8-dipiperidino-pyrimido (5,4-d)-pyrimidin auf Herz und Kreislauf. *Arzneimittel Forsch.* 9: 47, 1959.
 23. BRETSCHNEIDER, H. J., FRANK, A., BERNARD, U., KOCHSIEK, K., & SCHELER, F.: Die Wirkung eines Pyrimidopyrimidin-Derivates auf die Sauerstoff-versorgung des Herzmuskels. *Arzneimittel Forsch.* 9: 49, 1959.
 24. KADATZ, R. & BEISENHERZ, G.: Absorption and activity of 2,6-bis-(diethanolamino)-4,8-dipiperidino-pyrimido-(5,4-d)-pyrimidine (RA8) following enteric administration. *Arch. Int. Pharmacodyn.* 158: 389, 1965.
 25. WEST, J. W., BELLET, S., MANZOLI, U. C., & MÜLLER, O. F.: Effects of persantin (RA8), a new coronary vasodilator, on coronary blood flow and cardiac dynamics in the dogs. *Circul. Res.* 10: 35, 1962.
 26. BETZ, E., BRAASCH, D., & HENSEL, H.: Die Wirkung von 2,6-Bis-(diaethanolamino)-4,8-dipiperidino-pyrimido-(5,4-d)-pyrimidin auf die Durchblutung von Myocard, Gehirn, Niere, Leber, Haut und Muskulatur. *Arzneimittel Forsch.* 11: 333, 1961.
 27. SETNIKAR, I., MURMANN, W., & RAVASI, M. T.: The coronary vasodilator activity of morpholinoethyl-3-methyl-flavone-8-carboxylate in comparison with that of other coronary vasodilators. *Arch. Int. Pharmacodyn.* CXXXI: 187, 1961.
 28. SPITZBARTH, H.: Kreislaufanalytische und klinische Studien über 2,6-Bis-(diaethanolamino)-4,8-dipiperidino-pyrimido-(5,4-d)-pyrimidin. *Arzneimittel Forsch.* 9: 59, 1959.
 29. JÜNEMANN, P.: Persantin, ein neuer Wirkstoff zur Behandlung der Koronarisuffizienz. *Med. Woch.* 8: 340, 1959.
 30. HOCHREIN, H., SCHNEIDER, K. W., & SELL, R.: Über die Wirkung von 2,6-Bis-(diaethanolamino)-4,8-dipiperidino-pyrimido-(5,4-d)-pyrimidin auf das suffiziente und insuffiziente Herz. *Naunyn-Schmiedeberg's Arch. exp. Path. u. Pharmacol.* 243: 119, 1962.
 31. LÓZADA, B. B. & LAGUENS, R. P.: Hypoxia and the Heart, Ultrastructure with Special Reference to the Protective Action of the Coronary Drug Persantin. *Cardiologia Supplementum* 49: 33, 1966.
 32. BOUSVAROS, G. A., CAMPBELL, J. E., & MCGREGOR, M.: Hemodynamic effects of dipyridamole at rest and during exercise in healthy subjects. *Brit. Heart J.* 28: 331, 1966.
 33. NITZ, R. E., & PÖTZSCH, E.: 3-(beta-Diäthylamino-äthyl)-4-methyl-7-carbäthoxy-methoxy-2-oxo-(1,2-chromen), ein Präparat mit spezifischer und lang anhaltender coronargefässerweiternder Wirkung. *Arzneimittel Forsch.* 13: 243, 1963.
 34. LOCHNER, W. & HIRCHE, H.: Untersuchungen mit 3-(beta-Diäthylamino-äthyl)-4-methyl-7-carbäthoxy-methoxy-2-oxo-(1,2-chromen), einer neuen coronargefässerweiternder Substanz. *Arzneimittel Forsch.* 13: 251, 1961.
 35. BRETSCHNEIDER, H. J., EBERLEIN, H. J., KABUS, H. M., NELLE, G., & REICHMANN, W.: Die Wirkungen von 3-(beta-Diäthylamino-äthyl)-4-methyl-7-carbäthoxy-methoxy-2-oxo-(1,2-chromen), einer selektiv coronarerweiternden Substanz, auf Kreislauf, Atmung und Stoffwechsel. *Arzneimittel Forsch.* 13: 255, 1963.
 36. RUDOLPH, W., MEIXNER, L., & KÜNZIG, H. J.: Pharmakodynamisch Beeinflussung von Coronardurchblutung und Stoffwechsel des menschlichen Herzens. Untersuchungen mit 3-(beta-Diäthylamino-äthyl)-4-methyl-7-carbäthoxy-2-oxo-(1,2-chromen)-hydrochloride. *Klinische Wochenschrift*, 45Jg. Heft 7: 333, 1967.