The Circulatory Effects of Roniacol
A Physiologic Study in Normal Man

By G. S. Roback, M.D., M.S., and A. C. Ivy, Ph.D., M.D.

The vasodilatory effects of nicotinic alcohol tartrate (Roniacol) were tested on 12 normal adult males, utilizing digital venous occlusion plethysmography, brachial and digital artery oscillimetry and flicker photometry. Orally administered Roniacol in single doses up to 200 mg. has no significant effect on the auscultatory blood pressure, pulse rate, or peripheral arterial circulation of normal individuals.

There are numerous pathologic conditions having as a common factor arterial insufficiency. These are mainly due to partial or complete reduction in arterial or arteriolar luminal size. This decrease is usually due to organic changes in the vessels, abnormal increase in the sympathetic vascular tone, or a combination of the two.

Various methods have been used in an attempt to increase the arterial blood supply. Locally acting agents and agents that act by the decrease of sympathetic vascular tone have been tried in an attempt to increase the functional vessel size or to increase the collateral circulation by maximal vasodilatation.

Temporary subjective improvement of peripheral arterial insufficiency has frequently been associated with the use of a new drug or type of treatment. The typical clinical course, however, is improvement for only a short period of time; either the basic pathologic processes progress, or the psychologic amelioration disappears, and the patient returns to the former status, or is frequently worse.

In order to determine objectively the effects of various drugs or treatments on the changes in peripheral arterial circulation in the human, various methods have been used. The most common have been: (1) variations in skin temperature, (2) exercise tolerance, (3) venous occlusion plethysmography, and (4) oscillometric volume fluctuations of the major or smaller vessels.

Skin temperature changes, being a measure of the skin circulation only, give only a suggested interpretation of the actual circulation in the deeper structures. Normal ranges of skin temperature have been demonstrated in individuals with markedly impaired muscular circulation.

Exercise tolerance, although frequently an excellent index of muscular anoxia in the lower extremities, is too greatly related to the psychologic situation to serve as more than a clinical test for individual responses. It can not be considered reliable for the purpose of investigation of the physiologic effects of vasodilator drugs or new types of treatment unless continued over long periods of time. Many initial reports of effective vasodilator drugs have proved disappointing after prolonged trial where too much significance has been placed on the initial subjective improvements.

Venous occlusion plethysmography and oscillimetry have proved to be reliable means of measuring peripheral circulatory changes.

The flicker fusion threshold has been previously shown to be a reliable and sensitive indicator of the depressing action of anoxia and to reflect the generalized vascular response to vasodilators by alteration in the flicker fusion threshold. In the normal individual, vasodilation has been shown to produce a depression of the flicker fusion threshold by congestion and relative anoxia of the visual apparatus. In the vasospastic individual there is an increase of the flicker fusion threshold by removing the spasm and thus increasing the blood supply.

Digital venous occlusion plethysmography, brachial and digital artery oscillimetry, and flicker photometry were utilized in this study.

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The recording apparatus is used to measure absolute blood inflow volume in the finger by replacing the blood pressure cuff and diaphragm with a glass cylinder placed on the finger and sealed proximally with a rubber diaphragm, while the opposite end is attached by means of rubber tubing directly with the measuring pipet containing the alcohol droplet. Sudden venous occlusion at 60 mm. Hg pressure on the wrist converts the apparatus into a venous occlusion plethysmograph.

The flicker fusion thresholds were determined with the Krasno-Ivy Flicker Photometer. Control levels of the flicker fusion threshold were obtained by seating the subject 5 feet from the flicker photometer in an evenly lighted room and while the subject concentrated on the flicker photometer light, reducing the flickering light from about 2900 flashes per minute until the subject reported "flicker." The procedure is repeated until approximately the same rate occurs three times consecutively. The same procedure is used after the administration of the test drugs.

Methods. Twelve normal white men, varying in age from 20 to 60 years, were used in all tests. For each determination the individuals were rested for 30 minutes before the control readings were taken. Room temperatures varied between 20 and 23 C. All the determinations were made with the subjects in the sitting position.

Each individual was tested twice with the placebos of lactose, and with 50, 100, and 200 mg. of Roniacol. Each test was done on a different day, but only twice weekly to prevent adaption to the drug. The drugs were prepared in identical tablets and taken orally. Oscillometric tracings from the right arm, pulse rates, and auscultatory blood pressures, were taken from each individual as controls, and repeated every 30 minutes for three hours after oral administration of the tablets.

The tests were repeated with identical drugs and doses, each again on different days, twice weekly. Oscillometric tracings were taken from the third finger right hand. Simultaneous flicker fusion thresholds were determined. Determinations of both were taken before the drugs were administered, and every 30 minutes thereafter for three hours.

The procedure was again repeated with the identical drugs and doses. Digital venous occlusion plethysmographic volume changes were recorded utilizing the Johnson Recording Oscillometer.

Results

General Effects of Roniacol

The symptomatic effects of Roniacol taken orally in the postabsorptive state are similar to those previously reported. In this study the typical response began in anywhere from 5 to 30 minutes, although usually in 10 to 15
minutes, and lasted from 10 to 60 minutes. The onset usually began with a warm, prickling or tingling sensation, starting on the face and spreading to the forehead, ears, back of the neck, upper chest (especially anteriorly), usually progressing to the forearms and hands, occasionally to the legs and feet and rarely to the torso. Occasionally these sensations became burning and extremely unpleasant. A visible flush usually followed the onset of the maximal
circulatory effects, but occasionally preceded or occurred simultaneously. The pattern of the flush was usually similar to the paresthesia. The flush usually lasted longer than the paresthesia.

Slight stomach ache, nausea, and headache occurred rarely. The extent of both the symptomatic effects and the visible flush were directly related to the dosage, usually none being present with 50 mg. Roniacol and almost always to greater degrees with 200 mg. Roniacol.

Circulatory Effects of Roniacol

Results of all tests are summarized in table 1, and all statistical comparisons of significance in table 2.

(a) Brachial Arterial Oscillometry. After oral administration of 50, 100, and 200 mg. of Roniacol, there were no significant changes of the average blood flows for the test period of three hours when compared with the pre-Roniacol blood flow control values ($p > 0.5$), or when compared to the normal physiological variations after taking placebos ($p > 0.5$). The average rates of blood flow for the three-hour test period after oral administration of the placebo, 50, 100, and 200 mg. Roniacol are shown in figure 1.

There was no significant variation in the auscultatory systolic or diastolic pressures after oral administration of 50, 100, and 200 mg. Roniacol when measured 30 to 60 minutes after administration and when compared either with the placebo values, or with their own pre-Roniacol control blood pressure values.

![Table 1: Circulatory Effects of Roniacol](http://circ.ahajournals.org/)

For three-hour test period

<table>
<thead>
<tr>
<th>Measure</th>
<th>Placebo</th>
<th>Roniacol 50 mg.</th>
<th>Roniacol 100 mg.</th>
<th>Roniacol 200 mg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Rate of Brachial Blood Flow†</td>
<td>1937.2 ± 93.2</td>
<td>1925.7 ± 84.3</td>
<td>1978.9 ± 74.2</td>
<td>1962.4 ± 64.0</td>
</tr>
<tr>
<td>Maximal Change of Brachial Blood Flow†</td>
<td>+250.1 ± 108.2</td>
<td>+142.6 ± 154.9</td>
<td>-15.2 ± 167.3</td>
<td>-24.9 ± 170.0</td>
</tr>
<tr>
<td>Average Rate of Digital Blood Flow†</td>
<td>200.2 ± 20.2</td>
<td>202.6 ± 17.7</td>
<td>189.7 ± 15.7</td>
<td>194.9 ± 25.9</td>
</tr>
<tr>
<td>Maximal Change of Digital Blood Flow†</td>
<td>-29.8 ± 29.7</td>
<td>-49.5 ± 29.3</td>
<td>+17.1 ± 23.3</td>
<td>-49.5 ± 36.6</td>
</tr>
<tr>
<td>Average Pulse Rate Per Minute</td>
<td>61.6 ± 2.4</td>
<td>60.4 ± 2.7</td>
<td>58.6 ± 2.4</td>
<td>61.2 ± 2.6</td>
</tr>
<tr>
<td>Maximal Change in Pulse Rate Per Minute</td>
<td>1.9 ± 3.0</td>
<td>0.8 ± 2.7</td>
<td>0.5 ± 2.9</td>
<td>4.2 ± 3.1</td>
</tr>
<tr>
<td>Average Systolic Pressure in mm. Hg</td>
<td>115.8 ± 9.5</td>
<td>115.1 ± 11.7</td>
<td>110.1 ± 8.0</td>
<td>113.7 ± 7.1</td>
</tr>
<tr>
<td>Average Diastolic Pressure in mm. Hg</td>
<td>69.6 ± 7.0</td>
<td>67.3 ± 7.6</td>
<td>66.0 ± 6.0</td>
<td>66.5 ± 7.2</td>
</tr>
<tr>
<td>Average Maximal Change in Systolic Pressure</td>
<td>-1.1 ± 1.8</td>
<td>-0.7 ± 1.8</td>
<td>1.5 ± 1.4</td>
<td>0.9 ± 1.2</td>
</tr>
<tr>
<td>Average Maximal Change in Diastolic Pressure</td>
<td>0.9 ± 1.9</td>
<td>0.9 ± 0.7</td>
<td>1.5 ± 1.6</td>
<td>1.3 ± 1.8</td>
</tr>
<tr>
<td>Average Digital Blood Flow by Venous Occlusion Plethysmography</td>
<td>3.6 ± 1.3</td>
<td>3.5 ± 1.6</td>
<td>3.7 ± 1.6</td>
<td>3.4 ± 1.8</td>
</tr>
<tr>
<td>Maximal Flicker Fusion Threshold Change</td>
<td>29.0 ± 11.4</td>
<td>26.7 ± 16.5</td>
<td>30.0 ± 33.2</td>
<td>28.3 ± 25.6</td>
</tr>
</tbody>
</table>

* All values represent averages of 12 normal male subjects.
† Measured in oscillometric units.
(p > 0.5). The average systolic and diastolic blood pressures for the 12 subjects showed only slight average variation (fig. 2).

There was no significant difference between the normal physiologic variations in pulse rate with placebo and the pulse rates after oral administration of 50, 100, and 200 mg Roniacol (p > 0.5). The average pulse rates for the 12 subjects showed very small average variations during the three hours (fig. 3). The average maximal pulse rate change from the pre-Roniacol levels was 0.75 ± 2.7 beats per minute after 50 mg Roniacol, 0.5 ± 2.9 beats per minute after 100 mg Roniacol, and 4.2 ± 3.1 beats per minute after 200 mg Roniacol, compared with the 1.9 ± 3.0 beats per minute after the placebo.

(b) Digital Oscillometry. Average blood flow

![Fig. 1. Effects of Roniacol on brachial arterial blood flow. In all figures, individual points on the graph represent the average of 12 normal male subjects. The vertical lines represent the standard errors of the group means.](image1)

![Fig. 2. Effect of Roniacol on auscultatory systolic and diastolic pressure. See also legend to figure 1.](image2)

![Fig. 3. Effects of Roniacol on pulse rate. See also legend to figure 1.](image3)
difference between the physiologic variation in placebo values during the three hours and the maximal individual fluctuations of the circulatory flow after oral administration of 50, 100, and 200 mg. of Roniacol (p > 0.5). The average rates of digital blood flow for the three-hour test period after administration of placebo, 50, 100, and 200 mg. Roniacol are shown in figure 4.

(c) Digital Venous Occlusion Plethysmography. There was no significant variation in the average blood flow for the three-hour duration of the test after 50, 100, and 200 mg. Roniacol when compared with the placebo values or the pre-Roniacol blood flow levels (p > 0.5).

(d) Flicker Photometry. There was no significant variation in the average maximal flicker fusion threshold change for the three-hour duration of the test after administration of 50, 100, and 200 mg. Roniacol, when compared to the pre-Roniacol control values or the placebo values (p > 0.5).

**FIG. 4.** Effects of Roniacol on digital blood flow. See also legend to figure 1.

**DISCUSSION**

The rate of blood flow in the hand and foot is changed readily by vasoconstrictor stimuli, although the circulation in the forearm and leg is, for the most part, unaffected by stimuli which do not have a cardiovascular effect and enhanced by those which appear to increase cardiac output. As Roniacol produces no significant change in blood pressure, pulse rate or the systolic ejection expansion of the brachial artery, it consequently appears to have no significant effect on cardiac output.

Roniacol has no significant effect on digital blood flow as measured both in oscilometric units, and directly by venous occlusion plethysmography.

As the volume pulse is a sensitive indicator of the vasomotor activity which is of insufficient degree to show itself on blood pressure changes, lack of significant alteration of the volume pulse following oral administration of 50, 100, and 200 mg. of Roniacol indicates that it has no significant effect on the sympathetic vasomotor tone in the upper extremity. As the lower extremity normally has even a higher degree of sympathetic tone than the upper extremity even less effect would be expected on the lower extremity.

The lack of significant change of the flicker fusion threshold indicates that Roniacol has no significant vascular effects on the visual apparatus. With vasodilation there would have been marked depression of the threshold.

It is unlikely that any significant transient effects occurred between determinations, as most of the 30-minute determinations were made during the period of both maximal symptoms and visual flush.

The presence of flush without measurable changes in circulation, as determined by the tests employed in this study, probably indicates that the clinical effects of Roniacol are due to dilatation of the skin capillaries. This might account for some of the favorable results reported with chronic trench foot and with gangrenous skin. The failure to demonstrate circulatory changes despite the visible flush may be due to several factors, such as (1) insufficient sensitivity of the tests for recording the effects of flushing, or (2) concomitant vasoconstriction in other vessels in the same limb, thus producing no change in the total blood flow. These studies were performed using single doses of Roniacol on normal men and do not necessarily indicate the action of the drug when given continuously in the treatment of disease.
SUMMARY AND CONCLUSIONS

Orally administered Roniacol in single doses up to 200 mg. has no significant effect on the auscultatory blood pressure, pulse rate, or circulation of normal individuals as measured by: (1) brachial arterial and digital oscillometry, (2) digital venous occlusion plethysmography, and (3) flicker photometry.

REFERENCES

9 Pharmacological properties as stated by the manufacturer, Hoffmann-LaRoche, Inc., Roche Park, Nutley, New Jersey.
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