The Effect of Priscoline on Peripheral Blood Flow in Normal Subjects and Patients with Peripheral Vascular Disorders

By Theodore B. Van Itallie, M.D., and Charles W. Clarke, Jr., M.D.

Using the venous occlusion plethysmograph the authors have studied the peripheral circulation of normal subjects and persons with peripheral vascular disease. It is demonstrated that the vasodilating agent Priscoline (2-benzyl-4,5-imidazoline hydrochloride) frequently increases peripheral blood flow to a degree comparable to that produced by either sympathectomy or indirect body heating. In addition, the combined use of plethysmography and a vasodilating procedure is shown to be of value in the diagnosis of peripheral vascular disorders.

In a recent review of clinical plethysmography, Goetz states that immersion of an extremity for 30 minutes in a tank of water kept at 45° C., with the subject covered by blankets to prevent loss of body heat, is still the method of choice for relaxing central vasomotor tone. Previously, he had affirmed that this particular technic (adapted from Gibbon and Landis) was ordinarily comparable in its effects to spinal anesthesia and paravertebral block. From the study of a large series of cases, Goetz found that by body heating he was able to distinguish between the vasospastic and the organic components of peripheral arterial disease, and to estimate the extent of each. In the presence of an arterial block, he was able to measure the degree of collateral circulation by the venous occlusion method. By use of plethysmography in conjunction with the body-heating procedure, he was able to predict and evaluate the effects of lumbar sympathectomy.

On the basis of the work of Goetz and his associates, it appeared that their method of body heating might prove to be a useful yardstick against which to measure the effect of certain vasodilating drugs. Accordingly, an experiment was devised whereby the effect of Priscoline (2-benzyl-4,5-imidazoline hydrochloride), a widely used vasodilating drug, could be compared to the effect of body heating on the peripheral blood flow in normal individuals and in patients suffering from various degrees of peripheral arterial insufficiency.

The pharmacology of Priscoline has been reviewed by a number of authors. Its pharmacologic effects are manifold. Its effect on cardiac output is variable. In larger doses, it acts as an adrenergic blocking agent; in the smaller commonly used doses, it is said to be an effective local vasodilator, particularly in the skin of the extremities.

Procedure

Five normal individuals and 23 patients with complaints suggesting peripheral arterial insufficiency were studied. Each subject visited the laboratory on at least two occasions, separated by an interval of a day or more. In no instance was the subject permitted to smoke, to drink liquor, tea or coffee, or to consume a heavy meal within the 12-hour period preceding the visits.

Upon arrival, the subject was given a hospital garment to wear. He was then asked to lie upon a bed which was kept at a fixed height throughout the investigation. The trunk was elevated at an angle of 40 degrees and the knees were slightly raised. An attempt was made to prevent drafts and sudden disturbing noises.

Skin temperatures were measured at previously marked points on the trunk, arms and hands, legs and feet, by means of a McKesson Dermator Thermocouple. Oscillometric readings were taken at the wrists and ankles, and in some instances at the calves and thighs, with a Collins Sphygmo-Oscilometer. The blood pressure and oral temperature were recorded by clinical methods.

Plastic plethysmograph cups were then placed...
upon a toe (usually the great toe) of each foot. In subjects who gave no clinical evidence suggesting an appreciable difference in blood flow in the two lower extremities, one of the cups was attached to the index finger of the left hand. The material used to produce an airtight seal between the cup and the skin without jeopardizing venous drainage was Cambridge Plethysmograph Jelly, a plastic mixture of printer's roller compound and glue.

The subject was kept comfortable at bed rest for a period of 45 to 90 minutes. Then, by use of an air reservoir, blood pressure cuffs placed at the ankles or at the ankle and wrist were rapidly inflated to a pressure level of 42 to 46 mm. Hg. The pulse volumes prior to venous occlusion and the blood flow on venous occlusion were recorded from both parts simultaneously on a plethysmokymograph.

The plethysmokymograph used in this study was constructed on the basis of a principle described in detail by Goetz in 1940. It consists of two horizontal 1 cc. volumetric pipets of identical bore mounted side by side on an optical bench. In each pipet is a small column of alcohol. The plethysmograph cups attached to the digits are connected with the pipets by means of thick-walled capillary rubber tubing. In the airtight system, in which the air content is at a minimum, the alcohol columns in the pipets are activated by changes in volume of the enclosed digits. The pulsating columns cast moving shadows in the optical field which are projected to the photographic paper in a photokymograph. In this instance, the photokymograph is an electrocardiograph camera. A clock timer permits the accurate measurement of paper speed, and a pneumograph attachment makes possible the recording of the respiratory excursions. Since the pipets are already calibrated, the calibration is optically projected to the photographic paper and recorded along with the shadows produced by the pulsating mensurces.

The mounting of the various lenses and the pipets on an optical bench makes it possible to alter the size of the image as desired. Changes in volume of 0.001 cc. are readily distinguished in the completed plethysmogram. The recording of digital pulsations and rate of congestion on venous occlusion in two parts simultaneously permits an exact comparison of the vascular status in two extremities. An example of this may be found in figure 1 C. The tracings in C are taken from the two great toes of a patient (G. L.) with thromboangiitis obliterans involving both lower extremities. No pulsations are visible from the left side, suggesting complete occlusion of a major vessel in that extremity. The rate of increase of digital volume following venous occlusion is presumed in this instance to be a measure of the collateral circulation. The difference between the two sides is readily appreciated.

The blood flow measurements taken after completion of the rest period were ordinarily repeated at least twice. If found consistent, they were regarded as the "resting levels." When the resting levels for blood flow and pulse volume had been recorded, 50 mg. of Priscoline was administered to the subject intramuscularly. Pulse volumes and blood flow were recorded 5, 10, 20 and 30 minutes after the administration of the drug. Thirty-five minutes

![Fig. 1. Representative Plethysmograms. (Venous occlusion at arrow. White horizontal lines indicate changes in volume of 0.01 cc. Ordinates equal 3 seconds. From the rate of increase of digital volume after venous occlusion (slope of curve) the values for blood flow can be calculated. From the amplitude of pulsations, pulse volume is calculated. Details in text. A. Normal subject at rest (first left toe and second left finger). B. Same subject ten minutes after intramuscular injection of 50 mg. of Priscoline. C. Subject with thromboangiitis obliterans involving both lower extremities (first left toe and first right toe). Tracing recorded 20 minutes after indirect body heating. Note complete absence of pulsations on the left.](http://circ.ahajournals.org/doi/10.1161/01.RES.32.4.821)
filling it with water from a pipet. The finger volume
was measured by observing the amount of water it
displaced from a graduated cylinder.

In order to standardize the results, it was neces-
sary to correct for variations in digital volume. This
was done by correcting the digital volumes to a
mean of 15 cc. The corrected pulse volume and rates
of blood flow* were calculated by use of two formu-
las:

\[
pulse \text{ volume (corrected)} = \frac{pulse \text{ volume (recorded) \times 15}}{\text{digital volume in cc.}}
\]

\[
r = \frac{i \times 100 \times 60}{v}
\]

where \( r \) is the rate of blood flow in cc. per minute
per 100 cc. of tissue; \( k \) is a constant to correct for
the site of the occluding cuff (it is 3 at the wrist8-9
and ankle); \( i \) is the increase in digital volume per
second in cc.; \( v \) is the digital volume in cc.

On the second visit, similar observations were
made with regard to resting values for blood flow
and pulse volume. The skin temperatures, oscillo-
metric readings, blood pressure and oral temperature
were also recorded as before. Then the subject’s right
arm was immersed to a point 4 to 6 inches above
the elbow in water kept at 40-47 C. The subject was
covered with a woolen blanket to prevent dissipation
of heat.

Blood flow and pulse volume were measured 10,
20 and 30 minutes after immersion of the arm.
Fifteen of the subjects received 50 mg. of Priscoline
35 minutes after the start of body heating, and pulse
volume and blood flow were measured, 5, 10 and 20
minutes thereafter. Except for the use of the heating
technic instead of Priscoline, the conditions of the
two experimental periods were kept as nearly similar
as possible.

**RESULTS**

For the purpose of evaluating the results
clinically, the subjects were divided into four
groups: normal individuals; patients with vaso-
spastic disease; patients with organic disease;
sympathectomized patients.

Normal subjects, in this investigation, were
volunteers below the age of 30, without com-
plaints or symptoms referable to the circulatory
system, and in whom there was no clinical
evidence of peripheral vascular disease.

The group with vasospastic disease included
those patients who gave evidence of peripheral
arterial insufficiency, but in whom body heating
could produce pulse volume and blood flow
values well in excess of those found under
similar conditions in the group with organic
disease. This group had resting values which
tended to be considerably lower than normal
and which, in the absence of a successful vaso-
dilating procedure, could well have been in-
terpreted as evidence of organic occlusive dis-
ease. They described symptoms such as cold
extremities, nocturnal leg pains, and intermit-
tent claudication. These patients especially
displayed marked improvement on oral Prisco-
line (25 to 50 mg. four times a day). This group
included 2 men and 2 women. One subject
(G. L.) had had a unilateral sympathectomy.
Their ages ranged from 29 to 51.

The group with organic disease was made up
of patients who had unmistakable clinical evi-
dence of peripheral arterial insufficiency and
who, during plethysmography, displayed im-
paired digital blood flow and pulse volume
after body heating. There were 15 subjects in
the organic disease series. This group was the
largest and also the oldest studied. The aver-
age age of its members was 63 years. They
ranged in age from 40 to 86. There were 11
men and 4 women.

The remaining group consisted of 3 indi-
viduals who had undergone unilateral lumbar
sympathectomy for the relief of symptoms of
arterial insufficiency.

The essential data,* including skin tempera-
ture readings, with respect to the 5 normal vol-
unteer subjects and the 23 patients studied
are in table 1.

Prior to the administration of Priscoline, the
average resting blood flow of the 5 normal
persons was found to be 12.6 cc. (per minute
per 100 cc. of tissue). The group of patients
with vasospastic disease had a resting blood
flow which averaged 2.4 cc., illustrating the

* Approximate blood flow values (after indirect
body heating): normal, 45-100 cc./min./100 cc. tissue;
borderline, 35-45 cc./min./100 cc. tissue; patho-
logic, <35 cc./min./100 cc. tissue.

* Data derived from oral temperature and blood
pressure studies and the oscillometric readings and
skin temperature determinations were analyzed.
However, the complete findings are not presented in
detail in this paper because of limitations in space.
They will be discussed in a separate communication.
markedly impaired flow which can be found in this type of disorder. The average resting blood flow in the group with organic disease was 11.5 cc. The averages for pulse volume at rest in the three groups were respectively 0.006 cc., 0.0018 cc. and 0.0025 cc. Following the administration of Priscoline, the averages for maximal blood flow were as follows: normal group, 56.6 cc.; vasospastic disease group, 25.8 cc.; organic disease group, 22.9 cc. Thus, in the normal group, blood flow increased approximately fivefold; for the patients with vasospastic disease the increase was approximately tenfold. In the group with organic disease, the blood flow was only doubled. The averages for pulse volume in the three groups were calculated to be 0.0178 cc., 0.0144 cc. and 0.0034 cc. respectively. This represented a threefold increase in the normal group, an eightfold increase in the vasospastic group, and less than a twofold increase in the group with organic disease.

Average resting values for blood flow in the three groups prior to body heating were: normal group, 29.4 cc.; vasospastic disease group, 5.8 cc.; and organic disease group, 12.3 cc. After body heating these averages increased to 79.2 cc., 49.8 cc. and 21.1 cc. respectively. The increases exhibited were thus approximately threefold for normal patients, ninefold for patients with vasospastic disease, and, again, less than twofold for patients with organic disease.

The average values for resting pulse volume prior to heating were: normal group, 0.009 cc.; vasospastic group, 0.0056 cc., and organic group, 0.0014 cc. These values increased to 0.017 cc., 0.019 cc. and 0.003 cc. respectively, after heating. Increases, therefore, were approximately twofold in the group of normal patients, threefold among those with vasospastic disease, and twofold in the group of patients with organic disease.

After indirect body heating followed by the administration of Priscoline, the averages for blood flow among the various groups studied were as follows: normal group, 48 cc., vasospastic group 75.3 cc., and organic group, 25 cc. Using the average resting values found prior to body heating (29.4 cc., 5.8 cc., and 12.3 cc.) the increases proved to be less than twofold in the one normal subject studied,* approximately thirteenfold for patients with vasospastic disorders, and twofold for those with organic disorders.

Average pulse volumes after heat followed by Priscoline administration were 0.011 cc., 0.021 cc. and 0.0048 cc. for normal subjects, the vasospastic disease group and the organic disease group respectively. Using the resting values obtained prior to body heating (0.009 cc., 0.0056 cc., 0.0014 cc.) as a base, the increases were fourfold in the group with vasospastic disease and threefold in the group with organic peripheral vascular disease. The one "normal" subject studied in this manner is not representative of normal subjects (see earlier footnote).

In order to emphasize their distinguishing characteristics, the averages derived from each group are shown together graphically in figure 2.

Under separate consideration is the group of patients studied before and after sympathectomy. Prior to operation, these subjects showed an average resting blood flow of 15 cc. which rose to 18 cc. after Priscoline. The pulse volume remained at 0.001 cc. After sympathectomy the average resting blood flow was 24 cc., increasing to 31 cc. after Priscoline. Following the administration of Priscoline, the average pulse volume increased from 0.003 cc. to 0.008 cc. among postsympathectomy patients.

The average resting blood flow prior to body heating in patients before operation was 18 cc. After heating, the average blood flow was 25 cc., and after heat plus Priscoline it increased to 30 cc. Pulse volumes remained at 0.000 cc. during these tests.

After sympathectomy, the average resting blood flow was 25 cc. before heating, 23 cc. after heating and 24 cc. after heating plus

* Poor pulse volume and blood flow increases noted here are based on study of a single patient in the normal group. Subsequent studies have shown this to be in error, as most normal persons will respond with greatly increased (four- or sixfold) blood flow and pulse volume when heat and Priscoline are administered together.
### Table 1—Data Obtained by Plethysmographic and Skin Temperature Studies of Normal Persons, Patients with Vasospastic and Organic Peripheral Vascular Diseases and Certain Patients before and after Sympathectomy. The Instruments and Techniques Used are Described in the Text.

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Average: 11.5/.0025, 22.9/00345, 12.3/.0014, 21.1/.003, 25/.0048

† Blood flow is measured in cc./min./100 cc. of tissue.
‡ Pulse volume is measured in cc.
* Blood flow decreased to this level.
The instruments and technic used are described in the text.
### Table 1—Continued

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† Blood flow is measured in cc/min./100 cc of tissue.
‡ Pulse volume is measured in cc.
* Blood flow decreased to this level.

The instruments and technic used are described in the text.
Priscoline. The average postoperative pulse volume before heating was 0.005 cc., after heat 0.006 cc. and after heat followed by Priscoline 0.005 cc.

The averages derived from the pre- and post-sympathectomy groups also appear in figure 2.

No serious toxic effects were observed following the intramuscular administration of Priscoline* to the 28 patients studied, with one exception. This occurred in an 83 year old woman with arteriosclerotic peripheral vascular disease, who fainted as she changed from the supine to a standing position. A concomitant fall in blood pressure could not be measured. Formication and piloerection were reported by 12 patients, a feeling of warmth occurred in 9, flushing in 6, chilly sensations in 5, palpitation and tachycardia in 4 and diaphoresis and nausea in 2 cases.

COMMENT

In brief, the lowest resting values are found among patients with vasospastic diseases, yet these same individuals exhibit the greatest increase in blood flow after body heating and/or Priscoline. In contrast, postsympathectomy patients, being already more or less in full vasodilatation, show the least increase in blood flow after heat or Priscoline, and nearly the highest resting values. Also it is seen that while the average patient with organic peripheral vascular disease displays a value for resting blood flow below that found in a normal person, the presence of permanent changes in the arteries and arterioles is best demonstrated by their inability to dilate in response to Priscoline or heat and thereby produce increases in blood flow to the degree observed in normal persons. It is also seen that body heating and Priscoline are roughly comparable in their effects on blood flow.

It is well to state that the Goetz modification

* All patients received 50 mg. with the exception of 2 of small stature who received 37 mg.

**Fig. 2. Averages of results obtained by plethysmographic study of the four groups examined (normal, vasospastic, organic, pre- and postsympathectomy). Poor blood flow shown above in normal group after administration of heat plus Priscoline is not in agreement with more recently recorded results (unpublished).**
of the Gibbon and Landis procedure for ablating sympathetic tone, although useful, is not invariably effective. Goetz, in his writings, has pointed out several qualifications. First, there are certain rare individuals whose sympathetic tone simply cannot be relaxed by the procedure of body heating. Such individuals, says Goetz, respond well to the direct application of heat. Second, patients suffering vascular impairment of the immersed extremity will have a poor return to the hypothalamus of heated blood. Accordingly, vasorelaxation will be delayed, diminished, or absent, depending on the heat gradient influencing the hypothalamus.

In spite of these qualifications, it appears that the diagnostic use of body heating by the indirect method has satisfactorily stood the test of clinical application and may be regarded as a useful standard against which the effect of Priscoline and other vasodilating drugs can be measured. Body heating by the indirect method is a practical and safe procedure, and therefore well adapted to investigations involving studies on patients.

An examination of the resting values for each group makes it plain that little of diagnostic value is to be gained from a study of resting values alone. However, in unpublished studies done in this laboratory it was shown that in normal subjects, Priscoline had an effect on resting blood flow and pulse volume in the toes that was about three times as great as the effect on the resting values in the fingers at the same time. It was further found that the average resting blood flow and pulse volume values in the digits of the lower extremity in this group was approximately one-third that found in the digits of the upper extremity. This finding was consistent with what is already known about the arterial and arteriolar tone in the lower extremities, namely, that the tone there considerably exceeds that found in the fingers. This has been regarded by some authors as an adaptation on the part of the circulation to the increased arterial pressure and flow produced in the legs by the upright posture of the human body. In any case, this normally increased tone in the lower extremities should not be confused with "spasm."

The fact, then, that a greater response is elicited in the toes by Priscoline than in the fingers, is hardly a basis for believing that the vasculature of the skin of the toes is unusually responsive to the drug in a pharmacologic sense. The more feasible and, indeed, obvious explanation is that the toes' vessels are more constricted at the outset and therefore are capable of a wider range of dilatation.

In some instances, Priscoline was able to produce a rather marked increase in blood flow over resting values when body heating did not. This was true even if the resting values were similar. The administration of Priscoline to patients already subjected to prolonged body heating produced variable results. In certain individuals with severe organic peripheral vascular disease and in the sympathectomized group, blood flow actually diminished after body heating, yet, in the majority of cases, Priscoline appeared to have an additive effect upon that produced by heating.

**Summary and Conclusions**

The effect of a vasodilating agent, Priscoline, was studied on four groups of subjects: normal individuals; patients with peripheral vasospastic disease; patients with organic disease of the peripheral arteries and patients before and after sympathectomy.

Values for peripheral blood flow and digital pulse volume were determined by means of a plethysmokymograph, utilizing the venous occlusion technic before and after vasodilatation produced by body heating and intramuscular Priscoline.

From the resulting data, the following conclusions may be drawn:

1. Priscoline produced significant increases in blood flow and pulse volume in normal subjects and certain patients.

2. Owing to the considerable variations in resting blood flow exhibited by normal subjects and patients, opinions regarding an agent or a procedure based on its effects on resting flow alone, should be guarded.

3. The use of indirect body heating is a practical and safe method for producing vasodilatation in the skin of the extremities. The "maximal flow" brought about by indirect heating is thought to be a reproducible standard of
reference against which the effect of Priscoline and other agents can be measured. The limitations of indirect heating as an effective vasodilating agent do not detract appreciably from its clinical usefulness.

4. The use of Priscoline in conjunction with the plethysmokymograph is found to be a convenient hospital procedure for the preliminary appraisal of peripheral circulatory status. At the same time it is helpful in predicting the probable therapeutic value of the drug for a given patient.

5. Digital plethysmography is a valuable adjunct to the study of peripheral arterial disease and the effects of various agents upon peripheral circulation.

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THEODORE B. VAN ITALLIE and CHARLES W. CLARKE, JR.

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