Direct Arterial Study of the Blood Pressure Response to Cold of Normotensive Subjects and Patients with Essential Hypertension before and during Treatment with Various Antihypertensive Drugs

By John H. Windesheim, M.D., Grace M. Roth, Ph.D. and Edgar A. Hines, Jr., M.D.

The cold pressor test was performed three times at 15-minute intervals on 65 normotensive subjects and on 60 patients with essential hypertension both before and during treatment with antihypertensive drugs. The arterial pressure was recorded directly from the radial artery. On the basis of differences in the cold pressor response among individuals in the control group, the criteria for normal reaction and for hyperreaction were modified. The cold pressor response in the patients with essential hypertension was markedly depressed by the ganglionic blocking agents, but was not affected by various combinations of hydralazine, proateratrine and reserpine.

It has long been realized that variations in blood pressure occur throughout the day in both normal and hypertensive persons. The latter group, however, show more marked fluctuations of blood pressure than normal individuals in response to stimuli of equal intensity. Hines and Brown demonstrated the phenomenon of vascular hyperreactivity by the cold pressor test. They arbitrarily considered a rise of blood pressure of more than 20 mm. Hg systolic and 15 mm. diastolic in response to cold to be abnormal, and placed their subjects into three groups according to the response of the blood pressure to cold. The first group consisted of individuals with usually normal blood pressures and a rise of less than 20/15 mm. Hg in response to cold. These subjects were called "normal reactors." The second group had normal blood pressures, but their blood pressures rose excessively during the cold pressor test and they were called "normal hyperreactors." The third group consisted of patients with essential hypertension.

In 1940, Hines reported results of cold pressor tests on 1,015 persons with normal blood pressure and on 841 patients with essential hypertension. There were 859 normal reactors, and their mean rise of blood pressure in response to cold was 12.4/10.1 mm. Hg. One hundred fifty-six persons fell into the "normal hyperreactor group" with a mean increase of blood pressure of 31.2/27.5 mm. during the cold pressor test. The 841 patients with essential hypertension had a mean rise of blood pressure of 46.6/30.9 mm. in response to the cold pressor test. Hines postulated that the normal hyperreactors are in a "prehypertensive" phase of essential hypertension, and are likely to have the disease later. In a six-year follow-up of his original normal subjects, he found that none of the normal reactors had essential hypertension, whereas 38 per cent of the normal hyperreactors had developed this disease.

Since the first description of the cold pressor test, many investigators have reported their results, but relatively few have used Hines and Brown's exact technic. Hardgrove and associates, Ayman and Goldshine, Miller and Burger, and Feldt and Wenstrand

---

From the Mayo Clinic and the Mayo Foundation; the latter is a part of the Graduate School of the University of Minnesota, Rochester, Minn.

Abridgment of thesis submitted by Dr. Windesheim to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine.
utilized Hines and Brown's technic and reported findings in close agreement with those of the latter authors.

The present study was undertaken in order to evaluate the response of blood pressure to cold as determined by an intra-arterial method of recording blood pressure, since this method allows a greater degree of accuracy than the indirect (cuff) method. Our major objectives were (1) to evaluate the consistency of the pressor response to cold when the stimulus was applied repeatedly, (2) to compare the cold pressor responses of control subjects with normal basal blood pressures with the response of patients with essential hypertension and (3) to determine the effect of antihypertensive drugs on the pressor response to cold in the patients with essential hypertension.

METHODS

The control group consisted of 65 volunteers whose blood pressure was known to be normal. There were 30 men and 35 women. The mean age for the group was 26 years and ages ranged from 18 to 62 years. Results on 42 of the controls were taken from a previous study in the same laboratory by Dr. J. O. Godden.7 The 60 patients with essential hypertension were chosen consecutively from those admitted to the hospital for treatment of hypertension. Individuals were excluded if they were found to have renal disease, Cushing's disease or other specific causes of hypertension, if they had been taking antihypertensive drugs or sedatives or if they were severely ill. All were ambulatory hospital patients. Their ages ranged from 35 to 71 years with a mean of 52 years. There were 38 men and 22 women.

The procedure was carried out in the following manner: The subject was allowed to rest in the supine position until the blood pressure became stabilized at its lowest or basal level. This period varied from 15 to 60 minutes. The blood pressure of most control subjects attained basal levels within 15 minutes, whereas at least 30 minutes were required for most of the patients with essential hypertension. The room temperature ranged from 73 to 76 F. and all extraneous noise was excluded.

A 20-gauge needle was inserted into the right radial artery through the skin which had been anesthetized with procaine hydrochloride. The indwelling needle was connected through polyethylene tubing to a three-way stopcock. This in turn was connected to a Statham strain-gauge manometer (15 P.S.I.) and the direct arterial pressure was recorded on a Sanborn multichannel recorder. Heparin was flushed through the stopcock periodically to insure patency. The site of puncture and the manometer were adjusted to the level of the midchest at the third intercostal space. The inner diameter of the arterial needle was 0.3 mm., and this was the smallest diameter of any part of the system. The dynamic response of the arterial pressure system, as measured on the pistophone,8 showed that it was flat to 12 cycles per second, and the natural frequency of the system was 40 cycles per second. Respiratory excursion was recorded simultaneously on the Sanborn recorder by means of a face mask connected to another strain-gauge manometer and the electrocardiogram was also recorded simultaneously.

When the direct arterial pressure became stabilized at basal level, the first cold pressor test was performed. The exact technic of Hines and Brown was employed: The left hand was immersed in water at 4 to 6 C. to well above the level of the wrist for exactly one minute. This procedure was repeated twice more at intervals of 15 minutes. Thus three cold pressor tests were performed on all subjects whenever possible, but due to severe discomfort or technical difficulty we recorded only one or two in a few subjects.

The paper was run at a speed of 1 mm. per second between the cold pressor tests, but 30 seconds before immersing the hand in ice water, the speed was increased to either 5 or 25 mm. per second to allow a greater degree of accuracy in analysis. Thirty seconds after the cold pressor test was over, the speed was again returned to 1 mm. per second.

We analyzed the cold pressor response as follows: The 30 pulse waves immediately before the hand was immersed in ice water were used to determine the basal blood pressure before the cold pressor test. The maximal systolic and diastolic blood pressures were found by measuring the highest single pulse beat during or after the cold pressor test. This was done separately for the systolic and the diastolic pressure, since often the maximum for one did not occur in the same pulse wave as that for the other. Since there is some objection to comparing maximal pressure in a single beat with a mean basal pressure, we analyzed 10 records by measuring mean systolic and diastolic pressure in consecutive 10-second intervals for 90 seconds after immersion of the hand in ice water. It was noted that the maximal pressure occurred at the same time, and was only slightly less (1 to 3 mm. Hg systolic and diastolic) than by taking a single wave as the maximal blood pressure. For convenience, therefore, we continued using the latter measurement. Since it was almost impossible to determine accurately the time of return to basal blood pressure, the half maximal time was used as a measure of the rapidity of return to normal blood pressure. This was recorded by finding the first pulse wave after the maximal pressure that showed a blood pressure halfway between the basal and maximal pressures. This also was measured separately for
systolic and diastolic pressures, since they rarely occurred in the same pulse cycle.

The procedure was performed twice on the patients with essential hypertension in order to evaluate the effect of drugs on the cold pressor response. The first test was done the day after admission to the hospital, before treatment was started, and the second at the time of dismissal from the hospital.

**RESULTS**

**Consistency of the Cold Pressor Response.**

The results of the three cold pressor tests, performed at intervals of 15 minutes, were compared. The results in the control group are shown in table 1. It is readily apparent that the basal and maximal diastolic pressures, as well as the increase in diastolic pressure in response to cold, were very constant, whereas the systolic pressures showed a slight, but statistically insignificant, variation. The time to reach maximal pressure and to return to half maximal pressure is also remarkably consistent.

The degree of hypertension was classed as 1 to 4 according to the Keith-Wagener classification of essential hypertension. Comparison of the results of the three cold pressor tests before and also during treatment of patients with hypertension of each group revealed no statistically significant differences. We, therefore, could compare cold pressor tests 1, 2 and 3 for the total hypertensive group of 60 patients before and during treatment (table 1). The result of comparison was very similar to that of the control group: The diastolic pressures were more constant than the systolic pressures but there were no statistically significant changes from test to test. The results of the three cold pressor tests, therefore, could be averaged and in the discussion from this point on we will consider only the mean of the three

<table>
<thead>
<tr>
<th>Blood Pressure</th>
<th>Cold Pressor Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. 1</td>
</tr>
<tr>
<td></td>
<td>Systolic</td>
</tr>
<tr>
<td>Basal blood pressure, mm. Hg</td>
<td>115.80</td>
</tr>
<tr>
<td>Response to cold</td>
<td>±1.93*</td>
</tr>
<tr>
<td>Maximal pressure, mm. Hg</td>
<td>140.85</td>
</tr>
<tr>
<td>Rise, mm. Hg</td>
<td>±2.48</td>
</tr>
<tr>
<td>Time to maximal pressure, sec.</td>
<td>±1.53</td>
</tr>
<tr>
<td>Time to half maximal pressure, sec.</td>
<td>±1.83</td>
</tr>
<tr>
<td>65 Control subjects</td>
<td>60 hypertensive patients before treatment</td>
</tr>
<tr>
<td>Basal blood pressure, mm. Hg</td>
<td>±2.44*</td>
</tr>
<tr>
<td>Response to cold</td>
<td>241.47</td>
</tr>
<tr>
<td>Maximal pressure, mm. Hg</td>
<td>±5.14</td>
</tr>
<tr>
<td>Rise, mm. Hg</td>
<td>±20.23</td>
</tr>
<tr>
<td>Time to maximal pressure, sec.</td>
<td>±1.53</td>
</tr>
<tr>
<td>Time to half maximal pressure, sec.</td>
<td>±1.53</td>
</tr>
</tbody>
</table>

* Standard error of mean.
cold pressor tests of the control and hypertensive groups.

Responses of the Control Group to Cold Pressor Test. The findings in the control group of 65 subjects on whom a total of 182 cold pressor tests were performed are shown in table 2 and the figure. The average blood pressure response to cold for the group was a rise of 22.7/15.6 mm. Hg but there were marked individual differences in response. We arbitrarily decided to consider the cold pressor response abnormal if the maximal diastolic pressure rose to 85 mm. or more by direct arterial measurement. By this criterion alone, there were 36 individuals whose maximal diastolic pressure did not reach 85 mm. Their mean cold pressor response was 17.2/11.1 mm., and they were considered to be definite "normal reactors." Nineteen subjects had a maximal diastolic pressure of 85 mm. or more in the cold pressor test and they will be referred to as "normal hyperreactors." Their average basal pressure was significantly higher than that of the normal reactors, and the average response of the blood pressure to cold was 31.4/21.7 mm. Hg. In a third group of 10 subjects, the maximal direct diastolic pressure did not reach 85 mm. Hg but response to the cold stimulus was in the same order as that of the normal hyperreactors (27.0/20.2 mm.). Their basal blood pressure was comparable to that of the normal reactors, and their maximal diastolic pressure was only 77.4 mm.

Responses of Hypertensive Group to Cold

![Table 2](Image)

<table>
<thead>
<tr>
<th>Control Group</th>
<th>Subjects</th>
<th>Cold Pressor Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal reactors</td>
<td>36</td>
<td>102</td>
</tr>
<tr>
<td>Normal reactors</td>
<td>10</td>
<td>26</td>
</tr>
<tr>
<td>Normal hyperreactors</td>
<td>19</td>
<td>54</td>
</tr>
</tbody>
</table>

* Standard error of mean.

![Graph](Image)

**Fig. 1**. The maximal response of the systolic and diastolic blood pressures of 65 control subjects and 60 patients with essential hypertension before treatment to the cold stimulus.

Pressor Test. The 60 patients with essential hypertension before beginning treatment had a mean basal blood pressure of 204.0/100.9 mm. Hg with a cold pressor rise of 37.9/25.8 mm. (table 3 and figure). A division into hypertension groups 1 to 4 made on the basis of funduscopic changes, revealed that the basal and maximal blood pressures gradually rose from group 1 to 4. The pressor response to cold was most marked in patients with group 2 hypertension (45.7/28.1 mm.) and next greatest among those with group 3 hyperten-
sion. Patients with groups 1 and 4 hypertension demonstrated responses which were almost equal. Six of the 21 patients with essential hypertension, whose diastolic pressures rose 20 mm. or less in response to cold, had group 1 or 2 hypertension, five had group 3 and 10 group 4 hypertension.

During treatment, the same 60 patients had an average increase of blood pressure in response to cold of 34.0/20.0 mm. Hg. The average basal blood pressure which had been markedly decreased was 173.6/78.8 mm. and the average maximal pressure was 207.6/98.8 mm. Hg. This group will be discussed further later in this paper.

The time from immersion of the hand to maximal blood pressure was approximately equal in the control group and among the hypertensive patients before and during treatment, whereas the time of return to half the maximal blood pressure shows some variation. The tables demonstrate that the half maximal time is directly dependent on the blood pressure increase in response to cold. In general, subjects with the greatest blood pressure rise also had the longest half maximal times, and vice versa.

Effect of Antihypertensive Drugs on the Blood Pressure Response to Cold. The patients received various combinations of agents, and at the time of repetition of the procedure had been under treatment with the drugs at least one week, and most had been receiving treatment two to three weeks or more. Therapeutic results were considered adequate to allow the patients' dismissal from the hospital. The effect of the various drugs and combinations of drugs on the basal blood pressure and the maximal response to cold are given in table 4. The table has been arranged according to the height of the pretreatment basal diastolic blood pressure.

Eleven patients received a combination of protoveratrine and reserpine (Serpasil), which decreased the basal pressures from an average of 186.2/91.8 to 163.7/75.3 mm. without any effect on the cold pressor response. A similar result was observed in five patients receiving a combination of hydralazine and reserpine.

Thirteen patients received hydralazine hydrochloride (Apresoline), protoveratrine and reserpine. Their blood pressure was affected favorably by this combination, with an average decrease of 25.7/20.7 mm. during treatment, but there was little change in the cold pressor response during treatment. The response of the systolic blood pressure to cold was actually greater during treatment than before, but that of the diastolic pressure was slightly less.

Eleven patients, with an average basal blood pressure of 208.5/103.2 mm. before treatment, were treated with hexamethonium and reserpine. The mean basal blood pressure was decreased 27.4/19.6 mm. by these drugs.
and the response to cold was somewhat decreased from 36.2/25.8 mm. before treatment to 29.7/19.5 mm. during treatment.

Only four patients were treated with pentapyrroldinium (M. & B. 2050) since only a limited amount was available at the time this study was conducted. This drug produced an average decrease of 26.3/19.7 mm. in the basal blood pressure. Before treatment, the rise in blood pressure in response to cold was 34.4/22.8 mm. whereas during treatment it was only 16.8/11.9 mm.

Hexamethonium, hydralazine hydrochloride and reserpine were given to four patients and also proved to be effective in decreasing the response of the blood pressure to cold, as well as causing a marked decrease, 58.0/38.3 mm. Hg in basal pressure.

The final group of six patients shown in table 4 was treated with the combination of hexamethonium and hydralazine hydrochloride. Again the basal blood pressure was markedly reduced by treatment from an average pretreatment level of 222.1/117.3 to 170.6/82.0 mm. on dismissal. During treatment the pressor response to cold was only 14.3/8.4 mm. whereas before treatment was begun it had been 24.8/20.1 mm.

**Pulse Rates of Normal and Hypertensive Groups During Cold Pressor Test.** The pulse rates in the control and hypertensive groups are shown in table 5. The rates were taken from the records made at the time of measurement of the direct arterial blood pressure. The "random" pulse was checked five minutes before immersion of the hand in water. The
pulse rate immediately prior to immersion and the pulse at the time of maximal diastolic pressure are also recorded in table 5. In all three groups, a slight, but statistically insignificant, increase in pulse rate occurred between the taking of the random pulse and the pulse prior to the cold pressor test. The pulse rates of the control group did not change appreciably during the cold pressor test while those of the hypertensive patients rose approximately 6 beats per minute during this period. This was noted both before and during treatment. Treatment caused a decrease of the pulse rate of 5 to 6 beats per minute.

**DISCUSSION**

The Method. The intra-arterial method of recording blood pressure allowed us to evaluate the rise in arterial pressure in response to the cold stimulus with greater accuracy. Whereas the indirect (cuff) method measures the blood pressure during one heart beat only, the continuous direct registration of arterial blood pressure allowed us to measure the response at any point on the record, during immersion of the hand in water and until the blood pressure returned to basal levels. The procedure is relatively simple, and we encountered no complications.

The Cold Pressor Test. The patients were all questioned as to the amount of pain noted during each of the three cold pressor tests. Nearly all experienced less discomfort during the second and third than during the first, yet the pressor response did not change from test to test. Although pain is a factor in the cold pressor response, there was no correlation between the severity of the pain and the blood pressure response to cold in this study.

The set of three cold pressor tests was repeated at intervals varying from 1 to 5 months on eight persons in the control group. Each one had almost exactly the same cold pressor response during both sets of tests. Although this group is small, it certainly seems that the response of the blood pressure to cold, especially that of the diastolic pressure, as measured by the direct method is constant for each person, whether the time between tests is 15 minutes or several months, provided the test is carried out by exactly the same method and in the same environment.

Significance of Excessive Reactions in Control Group. The application of cold caused some rise in blood pressure in all of the control subjects, but the amount varied markedly. The final significance of excessive reactions in the control subjects will be known only after follow-up for a number of years in order to note the development of essential hypertension, but certain suppositions are presented herein. We would expect essential hypertension to develop in few, if any, of the 36 (55.4 per cent) control subjects who were normal reactors, having a maximal diastolic pressure of less than 85 mm.

The incidence of essential hypertension among the 19 hyperreactors should be high in the future. The basal blood pressure for this subgroup was significantly higher than that of the other two control subgroups. Although there is no clear explanation for this phenomenon, it is possible that due to the marked vascular reactivity, basal levels were not attained in this group before the cold pressor test was begun. However, this is unlikely, since special attention was paid to the basal blood pressure, and the study was not done.
until at least two to three cuff readings were at the same level after at least 15 minutes of rest. A second explanation is that mild sub-clinical essential hypertension may already be developing in some of the normal hyper-reactors, thereby raising the basal blood pressure of the group. There must be a period at the onset of essential hypertension during which vasoconstriction is so mild that the measurements of blood pressure by the indirect method do not attain the diastolic level of 90 mm., which is the arbitrary upper limit of normal, although the disease is already present. Although none of the control subjects had a basal diastolic pressure by cuff reading greater than 87 mm. Hg, a significant number approximated this figure and all were hyper-reactors.

The third control group, consisting of the 10 control subjects who showed a marked rise in blood pressure in response to the cold stimulus, but did not attain a maximal diastolic blood pressure (ceiling) of 85 mm. Hg by the direct method, will probably not have essential hypertension in the future. Although their blood pressures reacted more markedly to cold than those of the normal reactors, their mean maximal diastolic pressure was well within normal limits.

Since the cold pressor test is designed to measure peripheral vasoconstriction, the change in diastolic pressure should be the measuring stick of abnormality, for it is the indicator of peripheral resistance. Because of this, as well as the fact that the response of the systolic blood pressure to cold varies much more than the diastolic response, we have placed much more emphasis on the increase in diastolic pressure and the maximal diastolic pressure. In our opinion the criteria for abnormality of the cold pressor response should be not only an increase of 15 mm. Hg or more in diastolic blood pressure, but also a maximal diastolic blood pressure of 85 mm. or more by the direct arterial method (90 mm. or more by the indirect method). If both the rise in blood pressure and “ceiling” blood pressure are taken into account, fewer persons will be found to be vascular hyperreactors to cold, but they can definitely be considered to have abnormal vascular lability (the so-called prehypertensive phase of essential hypertension). If we now combine the two groups of “normal reactors,” that is, those persons who either did not have an increase in diastolic blood pressure of 15 mm. or more in response to cold and those who had an increase in diastolic blood pressure of more than 15 mm., but did not have a maximal diastolic blood pressure of 85 mm. Hg by direct arterial measurement, we find that 46 (70.8 per cent) of the 65 control subjects were in the normal reactor group and 19 (29.2 per cent) can be considered to be normal hyper-reactors.

Unfortunately, only seven of our control subjects were 40 years old or more, with a range of 41 to 62 and a mean age of 50 years. Five (71.4 per cent) of these persons were normal reactors, and two (28.6 per cent) were normal hyperreactors. No definite conclusions can be drawn from such a small group but it should be pointed out that the percentage of hyperreactors in regard to the diastolic blood pressure response is the same in the younger and older control subjects in this study. This does not support Russek and Zohman’s theory that vascular hyperreaction is a normal occurrence in persons in the older age group.

Effect of Severity of Hypertension on Pressor Response to Cold. The reason for the smaller increase in blood pressure to the cold stimulus in persons with hypertension of group 1 before treatment than in those in group 2 is not clear. The progressively smaller response of blood pressure to cold before treatment from groups 2 to 4 is undoubtedly due to the fact that as the severity of hypertension increases, the peripheral vessels have become persistently narrowed and cannot constrict much more when the cold stimulus is applied.

The Ganglionic Blocking Drugs. In evaluating the effect of the antihypertensive agents on the cold pressor response of the hypertensive patients, it should be noted that the patients with the more severe hypertension received the ganglionic blocking agents, hexamethonium and pentapyrrolidinium. The combinations of protoveratrine and reserpine, and hydralazine hydrochloride and reserpine did not change the blood pressure response to cold in any way in
an interval of one to three weeks between tests. This again shows the consistency of the cold pressor test when repeated at varying intervals of time. The combination of hydralazine hydrochloride, protoveratrine and reserpine caused little change in the cold pressor response, although the diastolic response was slightly less during treatment.

Although the cold pressor response was not completely blocked in any patient, the ganglionic blocking agents definitely diminished the response of blood pressure to cold. It seems that when hydralazine is combined with the hexamethonium ion, the combination not only lowers the basal pressure but also the pressor response to cold, although it is possible that this depression is entirely due to hexamethonium. The depression of the cold pressor response by the ganglionic blocking agents demonstrates that the efferent pathway of the cold pressor response is neurogenic and via the sympathetic nervous system. This finding is in agreement with those of other investigators.

The diminution of the pressor response to cold by the ganglionic blocking agents is of significant clinical importance. The hypertensive patient, during his normal daytime activities, has a blood pressure closely approximating that of the maximal blood pressure during the cold pressor test. His blood pressure decreases to basal levels only when he is at rest in the supine position. The ganglionic blocking agents cause a decrease of the basal blood pressure and also depress the pressor response to cold and therefore the maximal pressure during the cold pressor test. This suggests that the patient’s blood pressure during the average day’s activity is less than it would be if antihypertensive agents which do not depress the cold pressor response were used in treatment of the hypertension. This is well shown in table 4. The patients treated with hexamethonium and hydralazine, for example, had an average maximal blood pressure of 246.9/137.4 mm. whereas during treatment it was only 184.8/90.4 mm. They had the most severe hypertension of any group in our study, as shown by the basal and maximal pressures before treatment. The maximal pressure of the patients in response to the cold stimulus during treatment with protoveratrine and reserpine (the mildest hypertensive patients in this study) was 212.5/102.6 mm. Although the resting pressure during treatment was somewhat lower than that of the patients treated with hexamethonium and hydralazine, the maximal pressure after the cold stimulus was significantly higher.

In general, findings are the same for the other groups shown in table 4; that is, the patients with severe essential hypertension treated with hexamethonium or pentapyrrolidinium had maximal pressures in response to the cold stimulus during treatment lower than or almost equal to those of the patients with milder hypertension treated with medications which did not decrease the cold pressor response. Also, table 4 shows that during treatment with the ganglionic blocking agents the maximal blood pressure in response to the cold stimulus was lower than, or equal to, the pretreatment basal pressures, whereas in the group receiving the other combination of drugs the maximal pressure approximated the pretreatment basal blood pressure or was much higher than the pretreatment basal pressure. This observation again shows the advantage of the ganglionic blocking agents in lowering blood pressure over other antihypertensive drugs.

Ideal Time to Determine Maximal Response to Cold Pressor Test. The results obtained in our measurements of the time to reach maximal blood pressure show that when the cold pressor test is done clinically by the indirect method, the blood pressure reading most likely to give the true maximal blood pressure should be made between 50 and 60 seconds after immersion of the hand in the ice water. In this study the maximal blood pressure very rarely occurred less than 50 seconds after the hand was immersed in the cold water.

Pulse Rate. The minimal rise in pulse rate during the cold pressor tests in this study is in agreement with observations of others. The increase is most likely to be secondary to the painful cold stimulus. A rise in pulse rate might be expected to occur immediately before immersion of the hand in ice water, while the technician is stirring the ice and removing it.
from the container. At this time, the patient realizes that the cold stimulus is about to be applied, and some anxiety with a secondary increase in pulse rate may be expected. The fact that the pulse rate did not change between the time of the “random” pulse reading and the readings immediately before the cold pressor test suggests that there is practically no psychic factor involved in the cold pressor response.

Summary

Three cold pressor tests were performed at intervals of 15 minutes between each test on 65 normotensive and 60 hypertensive persons and the study was repeated on some of the control subjects in from 1 to 5 months and all of the hypertensive patients in about three weeks. In this study, the blood pressure was measured by the direct arterial method. The cold pressor test so performed proved a reliable index of vasoconstrictor reactivity, both of normotensive and hypertensive persons. Repetition of the test at short and long intervals yielded consistently constant responses of blood pressure for each person. The response did not seem to change with age, although only a small number of patients of older age were included in the control group.

The time between immersion of the hand in ice water and the maximal blood pressure was between 50 and 60 seconds in most of the control subjects and patients with essential hypertension. Therefore, the indirect reading most likely to give the true maximal blood pressure should be made at this time.

The cold pressor response was considered abnormal (1) if the increase in the diastolic blood pressure in response to cold was 15 mm. Hg or more and (2) if the maximal diastolic blood pressure (“ceiling” blood pressure) was 85 mm. Hg or more by the direct arterial method of recording blood pressure (90 mm. Hg or more if measured by the indirect method). Subjects with normal basal blood pressure whose diastolic blood pressure rose more than 15 mm., but whose maximal diastolic pressure was less than 85 mm. by direct measurement, were included in the normal reactor group. With these criteria, 46 (70.8 per cent) of the 65 control subjects were considered to be “normal reactors” and 19 (29.2 per cent) “normal hypertensive.”

The 60 patients with essential hypertension were studied before treatment was begun and while under treatment of the hypertension in order to evaluate the effect of various antihypertensive drugs on the cold pressor response. The response of their blood pressures to cold before treatment was uniformly greater than that of the control subjects except among those with the most severe hypertension. It is likely that the vessels of the latter could not constrict more under the added stimulus of cold, since they were already maximally constricted.

The ganglionic blocking agents, hexamethonium and pentapyrrolidinium, markedly depressed the cold pressor response and this observation appeared to be clinically significant. Hydralazine hydrochloride in combination with hexamethonium possibly aided in the depression of the pressor response to cold. Protoperatrine, reserpine and hydralazine in various combinations had no effect on the cold pressor response.

That the load placed on the heart by activity during treatment was greater in the less severely hypertensive patients than in those with severe hypertension is suggested by the fact that the severely hypertensive patients, who were treated with ganglionic blocking agents, had reduction of basal pressure and cold pressor response, and hence lower maximal pressure during activity, than did the milder hypertensive patients, who were treated with the other drugs. Thus, the ganglionic blocking agents would appear to have a clinical advantage over the other agents.

Summario in Interlingua

Le reaction del tension sanguinee a stimulation per frigido esseva registrare tres vices a intervallos de 15 minutas in 65 subjectos normotensive e in 60 patientes con hypertension essential tanto ante como etiam durante le tractamento con drogas antihypertensive. Le tension arterial esseva registrare directemente ab le arteria radial. Super le base de differentias in le responsas del individuos in le gruppo de controlo, le criterios de normo- e hyperreactivitate esseva modificate. In le patientes con
hypertension essential, agentes ganglioblocante produceva un marcate reduction del responsa a stimulation per frigido, sed varie combinationes de hydralazina, protoveratrina, e reserpina habeva nulle tal effecto.

REFERENCES

2. —: The significance of vascular hyperreaction as measured by the cold-pressor test. Am. Heart J. 19: 408, 1940.
7. GODDEN, J. O.: Unpublished data.
Direct Arterial Study of the Blood Pressure Response to Cold of Normotensive Subjects and Patients with Essential Hypertension before and during Treatment with Various Antihypertensive Drugs

JOHN H. WINDESHEIM, GRACE M. ROTH and EDGAR A. HINES, JR.

Circulation. 1955;11:878-888
doi: 10.1161/01.CIR.11.6.878

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1955 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/11/6/878

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/