EFFECT OF PITRESSIN IN CIRCULATORY COLLAPSE INDUCED BY SODIUM NITRITE

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Pitressin is frequently used in the treatment of circulatory collapse. Evaluation of its usefulness has been hindered by the difficulty of interpreting symptoms and of obtaining circulatory measurements in critically ill patients. Previous studies on normal subjects in the upright position (1) (2) have demonstrated that sodium nitrite produces a type of collapse, often ending in syncope, which is similar in its circulatory manifestations to certain types of clinical shock. The symptoms of this collapse are accompanied by a fall in arterial pressure and by a decrease in pulse pressure. There is an increase in arteriolar tone, but a decrease in venous tone. The blood flow in the hand, as indicated by plethysmographic studies, shows no marked changes during the early stage of collapse because of compensatory changes; later, however, there is a progressive fall in blood flow, which frequently drops to zero as syncope develops. The syncope is the result of progressive cerebral anoxia which develops when the venous return to the heart and the cardiac output are decreased because of the blood pooled in the veins of the dependent portions of the body. This type of collapse, which could be produced under controlled conditions, was ideal for study of the action of pitressin. Similar studies on the effect of epinephrin have previously been reported (3).

METHODS

The subjects rested on a tilting table in the horizontal position for at least 30 minutes after all apparatus had been adjusted and before any observations were made. The heart rate was counted by arterial palpation or by precordial auscultation. Arterial pressure was determined in the arm at heart level by the auscultatory method, using a mercury manometer. The blood flow in the hand was measured by Freeman's modification (4) of the plethysmographic method of Hewlett and Van Zwaluwenburg (5). The increases in hand volume caused by raising the venous pressure from the resting level to 20, 30 and 40 mm. Hg were used to indicate the venous tone or venous distensibility calculated as cubic centimeters per liter of hand, according to the method described by Capps (6). The water bath in which the right hand was immersed was maintained at 32° or at 37° C. The vessels of the left hand were dilated by keeping the temperature of the water bath at from 43° to 45° C. The venous tone in the hand at 43° C. was not computed, since in some subjects the measurement has been found to be unsatisfactory at temperatures above 40° C.

The experiments consisted of the following procedures carried out on the same subject. After repeated control measurements had been obtained, observations were made on different days on the effects of (*1*) elevation of the subject to the upright position (75 degrees) for 30 minutes, followed by return to the horizontal position; (*2*) intramuscular administration of 0.5 or 1.0 cc. of pitressin, followed in 10 to 18 minutes by elevation to the upright position for 30 minutes if collapse did not occur, and return to the horizontal position; (*3*) oral administration of 0.12 or 0.18 gram (2 or 3 grains) of sodium nitrite to the subject in the horizontal position, followed in 25 minutes by elevation to the upright position; (*4*) administration in the horizontal position of the same dose of sodium nitrite and, in 15 minutes, the same dose of pitressin, followed in 10 minutes by elevation of the subject to the upright position. The subject was urged to remain motionless while in the upright position. At the height of the collapse, which was associated with syncope, the subject was promptly returned to the horizontal position and observations were continued for at least 30 minutes. Studies on the effect of pitressin (7) and of sodium nitrite (1) (2) in the horizontal position have been reported.

Six normal young adults served as subjects. Four of them had a complete series of experiments, as outlined above. After the injecton of pitressin, 2 subjects developed syncope when they were tilted to 75 degrees; therefore they were not given sodium nitrite.

RESULTS

The effect of the intramuscular administration of 1 cc. of pitressin followed by tilting of the subjects to the upright position was studied in 6 subjects. Four subjects stood without difficulty; 2, however, fainted. Figure 1 shows the usual circulatory adjustments which occurred in the group of subjects who stood without difficulty. In subjects in the horizontal position pitressin produced ab-

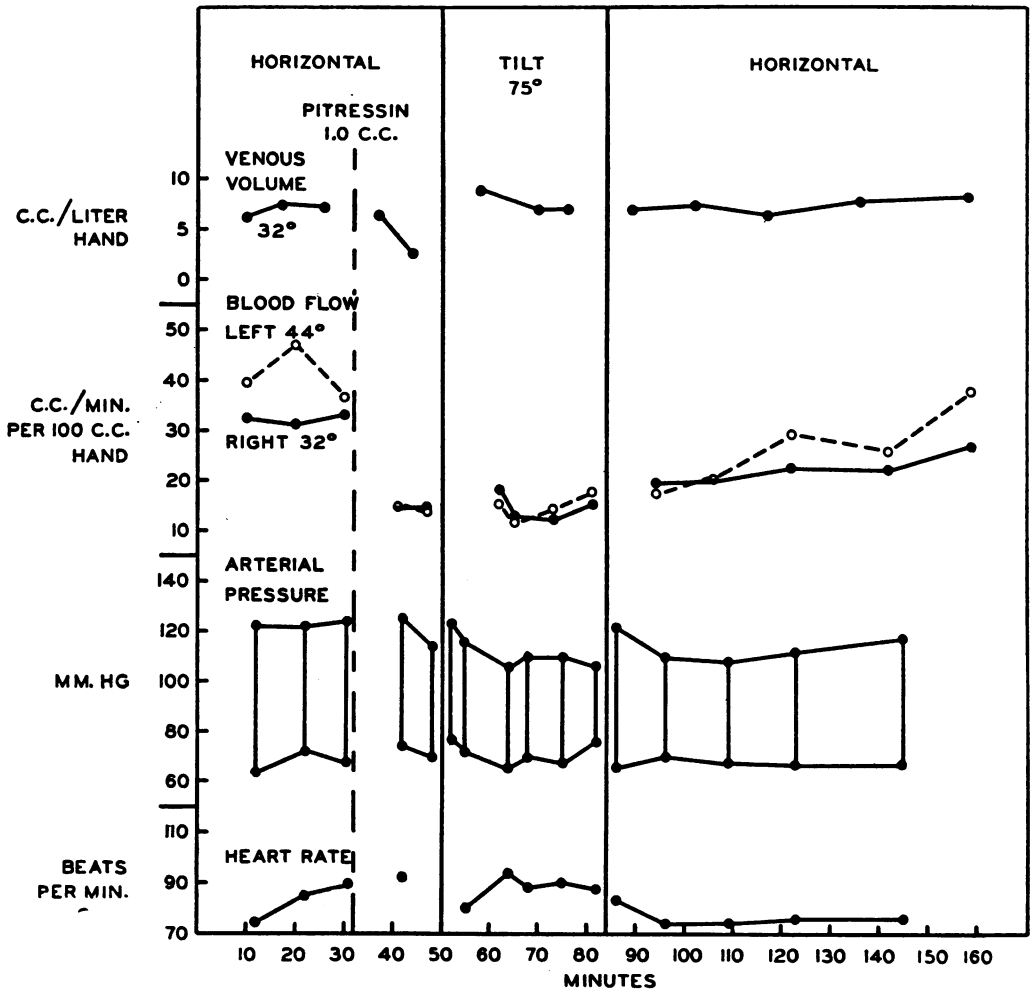

FIG. 1. THE EFFECT IN A NORMAL MALE SUBJECT, E. S., AGE 29, OF 1 CC. OF PITRESSIN INTRAMUSCULARLY FOLLOWED IN 18 MINUTES BY TILTING TO 75 DEGREES

dominal cramps, ashen pallor and a marked decrease in blood flow in the hand, both at 32° and at 44° C. The venous tone in the hand showed no consistent change. Pitressin had no constant effect on the heart rate and blood pressure. The most common findings were a slight elevation of the diastolic pressure, a slight fall in the systolic pressure and an unaltered heart rate. When the subject was raised to the upright position no significant changes in the heart rate or arterial pressure occurred. The systolic pressure was frequently lowered and the pulse pressure slightly narrowed. The blood flow in both hands remained very low. No new symptoms developed. The abdominal cramps, however, were usually relieved when the subject was placed in the upright position. At the end of 30 minutes the subject was returned to the horizontal position. In the next hour the blood flow in the hands gradually returned to normal.

The combination of the intramuscular injection of pitressin and of tilting the subject to an angle of 75 degrees produced syncope in 2 normal young adults, in 1 within 7 minutes after tilting, in the other within 2 minutes. These subjects had previously stood motionless for periods of 30 minutes without syncope. Figure 2 shows the reactions of a normal 26-year-old male, L. R., to tilting to 75 degrees 12 minutes after 1 cc. of pitressin was administered intramuscularly. Without any medication this subject had previously stood for 30 minutes with slight fullness in the epigastrium,

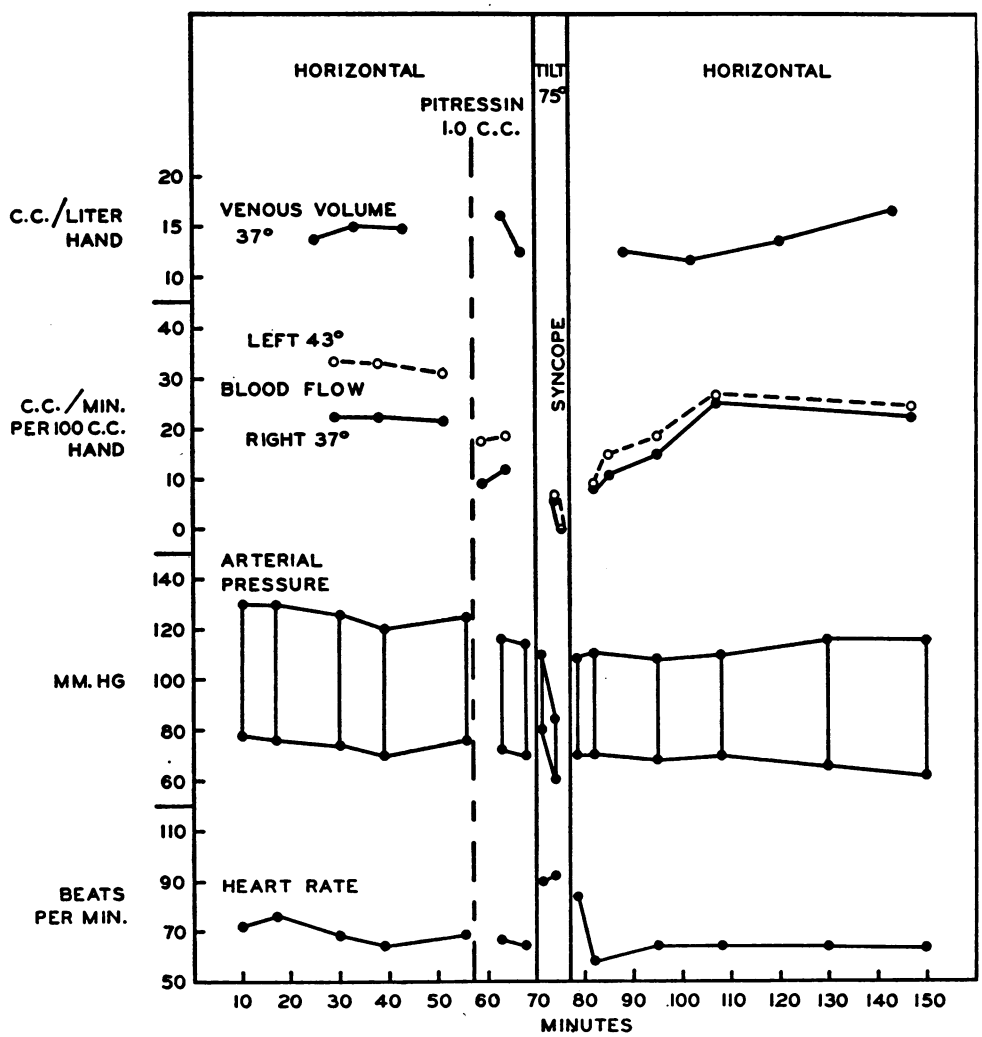

FIG. 2. COLLAPSE ENDING IN SYNCOPE INDUCED IN A NORMAL MALE SUBJECT, L. R., AGE 26, BY 1 CC. OF PITRESSIN INTRAMUSCULARLY FOLLOWED IN 13 MINUTES BY TILTING TO AN ANGLE OF 75 DEGREES ABOVE THE HORIZONTAL

pallor and sweating, but with normal circulatory adjustments; namely, a moderate drop in systolic and pulse pressures, a slight increase in pulse rate and venous tone, and a moderate diminution in blood flow to both the warm and cool hands. These mild symptoms disappeared immediately when the subject assumed the horizontal position. The administration of pitressin to the subject in the horizontal position produced marked pallor and a slight drop in blood pressure. The blood flow in both hands was decreased by 50 per cent. After the subject was tilted to 75 degrees, ashen pallor, weakness, nausea and dilated pupils developed; in 7 minutes syncope occurred. During the period of collapse there was a marked fall in systolic pressure and a lesser fall in diastolic pressure, resulting in a great decrease in pulse pressure. The pulse rate reached 90 per minute and at the time of syncope the blood flow in both hands had fallen to zero. When the subject was returned to the horizontal position the symptoms rapidly disappeared, though the blood flow to the hands remained well below control levels for the next 30 minutes.

In 2 normal subjects collapse, ending in syncope, occurred as the result of tilting to 75 degrees after the ingestion of 0.18 gram (3 grains) of sodium nitrite. In one of these subjects syncope occurred 14 minutes after tilting, but, when pitressin was

administered after the sodium nitrite, syncope occurred as soon as 6 minutes after tilting. In the other subject the circulatory collapse induced by sodium nitrite and tilting ended in syncope within 6 minutes but, when in addition ½ cc. of pitressin was given, although syncope did not occur for 23 minutes, the blood flow and narrow pulse pressure indicated that circulatory collapse and syncope were imminent throughout this period. In 1 person collapse was not induced by tilting the subject to the upright position after the ingestion of 0.24 gram (4 grains) of sodium nitrite or after the injection of 1 cc. of pitressin. When the same subject was given 0.18 gram (3 grains) of sodium nitrite followed by the injection of 1 cc. of pitressin, profound collapse ending in syncope occurred 10 minutes after the subject was tilted to the upright position (Figure 3).

Most of the subjects volunteered the information that the hand at 43° to 45° C. felt hotter after the administration of pitressin than before. This feeling of increased heat occurred when the blood flow in the hand was markedly diminished. At temperatures of from 43° to 45° C. the skin in contact with the water is presumably cooled by the rapid flow of blood at body temperature. When the blood flow is decreased by pitressin, this cooling mechanism is less effective and the hand feels

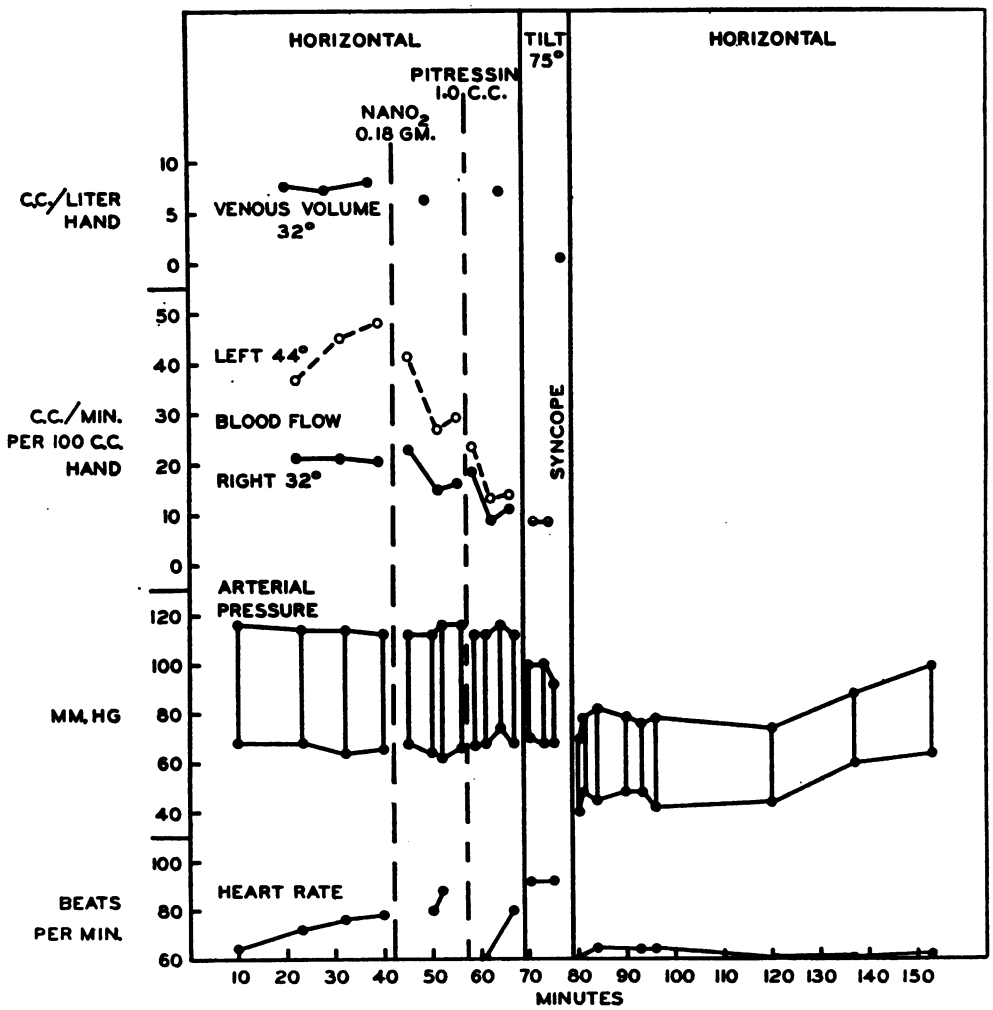

FIG. 3. COLLAPSE ENDING IN SYNCOPE INDUCED IN A NORMAL MALE SUBJECT, E. S., AGE 29, BY 0.18 GRAM OF SODIUM NITRITE FOLLOWED IN 15 MINUTES BY 1 CC. OF PITRESSIN INTRAMUSCULARLY AND IN 12 MINUTES BY TILTING TO 75 DEGREES

hotter. In 1 case, following the administration of pitressin, the skin was blistered when the water bath was maintained at 45° C., although the same temperature was well tolerated when no drug had been given. For this reason the temperature was not raised above 43° C. in the remainder of the pitressin experiments.

Circulatory changes in normal subjects following the oral administration of sodium nitrite with subsequent tilting to the upright position have been reported previously by Weiss, Wilkins and Haynes (1) (2). When further observations were made on a larger group of persons it was found that in the upright position sodium nitrite produced collapse and syncope in about 50 per cent of normal subjects. As yet there are no known criteria which indicate how a given person will react. The physical strength of the individual has no relation to the tendency to collapse induced by sodium nitrite. Increasing the dose of sodium nitrite above 0.18 gram (3 grains) usually had little effect on subjects in whom a smaller dose did not produce collapse.

DISCUSSION

Previous studies (1) (2) on sodium nitrite have shown that a drug which produces no subjective and few objective circulatory changes in the horizontal position may have dramatic effect on a subject who is standing motionless. The action of a drug on the venous side of the circulation is easily overlooked unless this effect is enhanced by posture.

The action of pitressin was studied in subjects in both horizontal and upright positions in order to evaluate more fully its effect on the peripheral circulation. Pitressin in the horizontal position did not produce any significant change in venous tone. On being tilted to the upright position, however, 2 of the subjects fainted, indicating that pitressin alone probably brings about pooling of the blood in some manner. It is not possible to state whether this is the result of a direct decrease in venous tone, which is too small to be detected by the plethysmographic method, or whether it is the result of some other action of pitressin.

Previous studies on the mechanism of the collapse produced by the oral administration of sodium nitrite in the upright position have indicated that the ideal drug for preventing this type of collapse should have primarily a venospastic effect sufficient to increase the venous return to the heart. It should not produce arteriolar constriction and thereby further reduce blood flow in the tissues. Observations on pitressin in the horizontal position show that it does not fulfill these requirements, because the only constant effects demonstrated are (*1*) marked peripheral vasoconstriction in the skin, resulting in pallor and in a greatly reduced blood flow in the hands; (*2*) marked abdominal discomfort and cramps. No constant change in venous tone in the hand is noted. In some persons there is an increase and in others a decrease of moderate to small magnitude. Pitressin has no consistent effect on the pulse or blood pressure in normal subjects. The most common finding is a slight elevation of the diastolic and a slight fall in the systolic pressure.

This investigation of the collapse ending in syncope produced by placing the subject in the upright position again emphasizes the remarkable sensitivity of the peripheral vascular bed. The healthy heart is not easily damaged and its function remains fairly constant even in the presence of noxious stimuli. The peripheral circulation, on the other hand, frequently gives way after apparently only slight exposure to noxious agents. The sensitivity of the peripheral vascular system to certain drugs varies greatly in the same subject from day to day. Thus, in our experience, circulatory collapse can easily be induced in a person who has been working intensively and losing sleep, although the same procedure may produce no signs or symptoms of collapse when he is rested. Likewise the sensitivity of the peripheral vascular system to drugs and to other agents varies greatly in different subjects. Comparable differences in the response of the circulation of various persons to infectious diseases, operative procedures and trauma under apparently identical circumstances have long been noted clinically, but the reasons for these differences have not yet been determined.

Care must be taken in applying the results and conclusions obtained from an experimental study of this type directly to clinical cases where many factors may be operative in the production of shock, and where the state of the peripheral circulation may vary from arteriolar constriction to arteriolar dilatation (8) (9) (10). The studies

here reported, however, indicate that pitressin would not have a favorable action, and, indeed, it may well be harmful, in the very common type of collapse associated with cold, ashen gray skin, with small, thready, rapid pulse, with decreased venous return to the heart and with arteriolar constriction, as manifested by a fairly well-maintained diastolic pressure, low pulse pressure and decreased blood flow in the tissues.

SUMMARY AND CONCLUSIONS

1. Pitressin in man was ineffective in experimental collapse induced by sodium nitrite and tilting because it did not cause an increase in venous tone, and because the arteriolar constriction produced by the drug tended further to reduce tissue blood flow.

2. The intramuscular injection of 1 cc. of pitressin with subsequent tilting of the subject to the upright position produced collapse ending in syncope in 2 of the 6 normal subjects tested.

3. In 2 subjects in whom collapse was induced in the upright position by the administration of sodium nitrite, pitressin did not prevent the development of collapse and in 1 of these it hastened it. In 1 subject, in whom neither sodium nitrite nor pitressin in the upright position produced collapse, sodium nitrite followed by pitressin induced profound collapse ending in syncope. In still another subject neither sodium nitrite nor pitressin, singly or combined, produced syncope.

4. Pitressin, given in doses of 0.5 or 1 cc. to normal subjects in the horizontal position, produced abdominal cramps, ashen pallor and a marked decrease in blood flow both in the hand at 32° and that at 43° C. It produced no change in venous tone in the hand, heart rate or arterial pressure.

5. Pitressin slowed the blood flow in the hand to such a degree that water at a temperature of from 43° to 45° C. felt distinctly uncomfortable, and in 1 case caused the skin to be blistered at 45° C.

6. Sodium nitrite produced circulatory collapse and syncope in the upright position in about 50 per cent of a large group of subjects tested. No criteria have been developed to predict the postural response of any given person to the administration of sodium nitrite.

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