KIDNEY FUNCTION AND CIRCULATORY COLLAPSE. POST-SYNCOPAL OLIGURIA[1]

By CLAUS BRUN, E. O. E. KNUDSEN and FLEMMING RAASCHOU

(From the Third Department of the Kommunehospital, Copenhagen. Physician-in-Chief: Poul Iversen, M.D.)

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In the course of investigations on renal function in the passive erect posture maintained on a tilt-table, we observed a number of unintentional cases of circulatory collapse. We noted that syncope was followed immediately by a reduction in urine flow which, in relation to the quantity of liquid ingested and the foregoing diuresis, was very pronounced. We have called this phenomenon "post-syncopal oliguria."

The literature reveals that similar forms of oliguria have been observed before, but without having attracted particular attention. Chasis, Ranges, Goldring and Smith (1) induced orthostatic hypotension by the ingestion of sodium nitrite, and they observed protracted oliguria which continued even after the subject had been placed in the horizontal position. Marked and abrupt reduction in urine flow in experiments utilizing the tilt-table are also recorded by Smith (2, 3). In neither case, however, is the mechanism of the oliguria discussed.

PASSIVE ERECT POSTURE

Our experiments have been concerned with the passive erect posture, in which the hydrostatic changes in the circulation which normally occur in the erect posture are especially accentuated. We have obtained this passive erect posture by placing the individual on a tilt-table, where he is supported by sitting on the saddle so that the lower extremities hang down motionless and without support. By this means the muscle pump of the lower extremities is removed from action. Passive erect posture where the tilting board forms an angle of 60° with the horizontal, and with the head upwards, is designated as + 60°.

[1] This investigation was performed with the support of Miss P. A. Brandt's Bequest.

CIRCULATORY CHANGES IN THE PASSIVE ERECT POSTURE

As a consequence of accumulation of blood in the lower parts of the body, the hydrostatic pressure in the peripheral veins below the heart increases, and with it the total cross-section of the venous system. Capillary pressure rises and blood accumulates in the tissues as edema. Central venous pressure is reduced, resulting in a decreased filling of the heart and decreased stroke volume. Through excitation of the pressor receptors the pulse is accelerated, and vasoconstriction occurs in certain parts of the body. The systolic blood pressure usually remains fairly constant, whereas the diastolic blood pressure rises as a consequence of arterial constriction, so that the pulse pressure is decreased. Our observations on blood pressure changes are in agreement with those illustrated by Smith (2, 3). This posture is tolerated by normal subjects for periods varying from minutes to about 2 hours, depending on as yet undefined physiological conditions. Sooner or later the blood pressure begins to fall, and in the course of a few minutes may drop to unmeasureably low values. This is accompanied by the common subjective and objective symptoms of syncope and terminates in the loss of consciousness, which is quickly restored when the individual is brought into the horizontal posture.

EXPERIMENTAL PROCEDURES

The individuals studied here were healthy undergraduates who received 100 ml. of water every 10 minutes throughout the experiment. A few of our experiments were carried out without water.

Glomerular filtration was measured by the inulin clearance, and renal plasma flow by the diodrast clearance. Hemoconcentration was followed by determination of the hemoglobin concentration, the cell volume and the viscosity of the blood. Occasional determinations of plasma protein concentration were also made.

The water-loaded person (or in some cases subjects without a water load) was placed on the tilt-table in the passive erect posture. Blood pressure was observed every ½ minute. When the intended degree of circulatory collapse was reached the subject was returned to the horizontal position. Normal circulation was reestablished immediately, as judged from pulse rate and blood pressure, and subjective feelings disappeared at once. Immediately after recovery the subject rose from the table and voided, which is important as it was necessary to separate the urine produced during the collapse period from that produced after syncope. The renal clearance of the brief collapse period is therefore included in the last clearance period in the passive erect posture. In the majority of experiments we employed a catheter *à demeure* with bladder lavage.

EXPERIMENTAL RESULTS

In all, we have made 16 series of tilting experiments including circulatory collapse, and all 16 experiments have given concordant results.

In our first experiment we observed that after a brief fall in blood pressure, there occurred a period of protracted, apparently complete, anuria. As this observation was unexpected, the subject was catheterized 40 minutes after syncope, and it was found that the bladder was completely empty, although throughout the experiment he had drunk 200 ml. of water every 10 minutes.

Figure 1 shows the diuresis curve from a typical experiment with post-syncopal oliguria. Immediately after syncope the urine flow fell to relatively low values, where it remained for about 65 minutes, thereafter rising again to the initial value. Post-syncopal oliguria lasts from 15 to about 90 minutes after syncope.

In most of our experiments the values of the blood pressure during syncope could not be observed owing to the velocity with which the blood pressure fell. Notwithstanding the inadequacy of the data, there seems to be a rough proportionality between the extent of blood pressure reduction and the duration of the period of oliguria. This supposition is supported by the following experiment. After ingesting the usual amount of water, a subject was tilted 4 times, each time with an interval in the horizontal position. The tilting angle

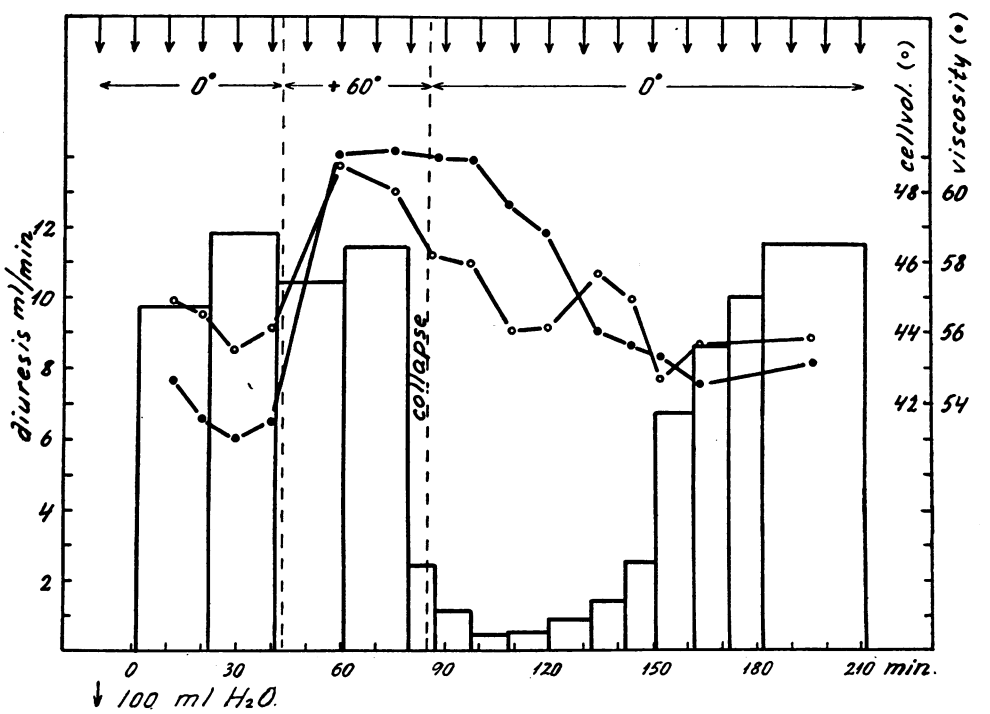

FIG. 1. EXPERIMENT SHOWING OLIGURIA AND HEMOCONCENTRATION AFTER A BRIEF SYNCOPE

0°: The individual in the horizontal posture. + 60°: The individual in the passive, erect posture, head upwards; the tilting board forms an angle of 60° with the horizontal plane. Columns: Urine flow (ml. per min.). Open circles: Blood cell volume (per cent); closed circles: Viscosity of the blood (seconds); arrows: Water, 100 ml. every 10 mins.

and the duration of tilting were gradually increased, by which means it was possible to induce progressively increasing reductions of the blood pressure. A steadily increasing and more protracted reduction in urine flow was observed when the individual was returned to the horizontal position.

In water loaded individuals the urine flow drops from 5 ml. per minute, or better, to 0.3 to 1 ml. per minute after syncope. This same urine flow is reached after syncope in subjects who have received no water load (Figure 2).

The specific gravity of urine during post-syncopal oliguria rises from low values to 1.020 to 1.025.

The inulin U/P ratio rises during oliguria to about 120, whereas in the control periods when the urine flow is at a rate of about 10 ml. per minute, the inulin U/P ratio has a value of about 12.

The subjective condition of the subject is greatly improved or essentially normal immediately after being returned to the horizontal position. It should be noted, however, that for the first 10 or 20 minutes after collapse there may be some pallor, due no doubt to capillary constriction in the skin.

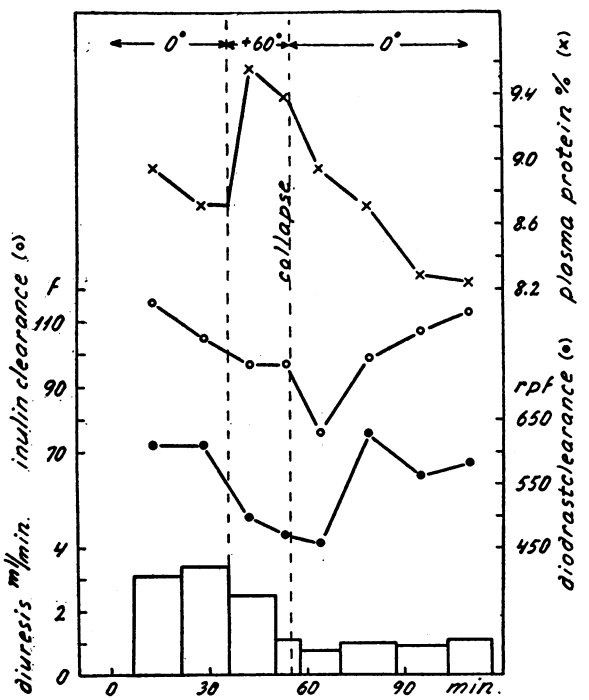

FIG. 2. EXPERIMENT SHOWING THE INULIN AND DIODRAST CLEARANCE IN THE PASSIVE ERECT POSTURE AND AFTER A BRIEF COLLAPSE

Crosses: Plasma protein (per cent); open circles: Inulin clearance (ml. per min.); closed circles: Diodrast clearance (ml. per min.).

Pulse rate and blood pressure return rapidly to normal after the subject is restored to the horizontal position.

The hemoconcentration which occurs in the passive erect posture (Figure 1) is replaced by a gradual dilution of the blood when the subject is returned to the horizontal position, the control values being reached in about 40 minutes.

Figure 2 shows the inulin clearance or glomerular filtration rate during a syncopal experiment. In this subject the bladder was catheterized and emptied with lavage. Immediately following syncope the filtration rate was reduced to about 70 per cent of its control value, whereafter it returned to the normal.

The diodrast clearance, or effective renal plasma flow, is also shown in Figure 2. The renal plasma flow was also reduced to about 75 per cent of its control value after syncope, returning later to its initial value. Our observations on the renal plasma flow and glomerular filtration rate are in agreement with other recorded data (2, 3).

Thus during the period of post-syncopal oliguria the subject feels quite well and the blood pressure, pulse, filtration rate and renal plasma flow are normal, while the hemoconcentration which appeared during the first phase of the oliguria is corrected. Having regard to these facts and to the high U/P ratio of inulin and the high specific gravity of urine, we infer that the mechanism governing the oliguria consists of a greatly increased reabsorption of water in the renal tubules. It may be supposed that this increased reabsorption of water occurs in consequence of an increased secretion of the antidiuretic hormone from the posterior lobe of the pituitary gland. Indeed, post-syncopal oliguria lasting 90 minutes is comparable with the effects of 3 to 4 i.u. of Insipidin (A.B.).[2]

DEMONSTRATION OF THE SECRETION OF THE ANTIDIURETIC HORMONE DURING POST-SYNCOPAL OLIGURIA

We have endeavored by various means to demonstrate the secretion of antidiuretic hormone dur-

[2] Insipidin A.B. (Alfred Benzon, Copenhagen). 1 ml. equals 20 i.u.

ing post-syncopal oliguria. First we tried to show that the effect on diuresis is of a humoral nature by transfusing blood from newly collapsed subjects. Next we tested the chloride output in the urine after collapse, since the antidiuretic hormone is supposed to influence the excretion of chloride by the kidney. Finally we induced collapse in 2 patients suffering from diabetes insipidus in order to find out if the post-syncopal oliguria is reduced in intensity or duration.

TRANSFUSION EXPERIMENTS

Blood transfusion from subjects with post-syncopal oliguria

The donors were normal subjects who had been loaded with 100 ml. of water every 10 minutes for a period; they were made to collapse on the tilt-table and in the course of 5 minutes after collapse, venesection was performed and 200 to 450 ml. of blood were withdrawn, coagulation being prevented by adding 15 mgm. of heparin to each 500 ml. of blood. The blood was transfused as quickly as possible (in the course of 5 to 10 minutes) to another subject who was in the horizontal position and in the state of constant diuresis. The blood pressure was followed during venesection and transfusion.

Figure 3 shows the diuresis curve of the recipient in 1 of these transfusion experiments. Prior to transfusion, the diuresis was fairly constant at about 14 ml. per minute. Two hundred ml. of blood were transfused from the subject who had just had a severe collapse, and in conjunction with which there was post-syncopal oliguria for 65 minutes. In the period immediately after the transfusion the recipient's urine flow fell to 2.9 ml. per minute, remaining at a reduced rate for about 45 minutes. During and after transfusion the recipient's blood pressure was unaffected. Table I gives the results of 3 experiments of this kind.

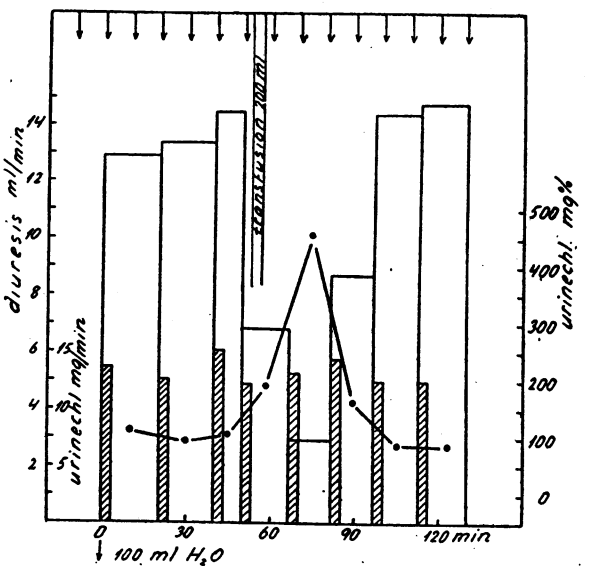

FIG. 3. DIURESIS AFTER TRANSFUSION OF 200 ML. BLOOD FROM A SUBJECT WITH POST-SYNCOPAL OLIGURIA

Closed circles: Urine chloride concentration (mgm. per cent); hatched columns: Chloride output in urine (mgm. per min.); plain columns: Urine flow (ml. per min.).

Control transfusion experiments

A total of 5 transfusion experiments were made using 2 recipients who were water loaded in the horizontal position in the usual manner. When the diuresis had become constant, venesection and transfusion of heparinized blood (275 to 450 ml.) were performed.

It will be seen from Table II that in none of the 5 experiments did the donors show a decreased urine flow after venesection. In 4 out of 5 experiments there was no significant decrease in

TABLE I

Experiments with transfusion of blood

Donor			Recipient		
Blood pressure fall	Duration of oliguria (<2 ml. per min.)	Symptoms	Transfused volume of blood	Duration of oliguria	Fall of diuresis
	min.		*ml.*	*min.*	*ml. per min.*
132/92 to 80/62	90	Pallor, dizziness, deep inspirations, dimness of vision	400	30	11.3 to 4.5
112/75 to (0)?	38	Dimness of vision, oppression, no pulse	450	37	13.2 to 4.3
122/75 to ?	65	Complete collapse	200	47	14.5 to 2.9

TABLE II

Control experiments

Recipient				Donor		
Diuresis			Transfused volume of blood	Diuresis		
Before	During transfusion	After		Before	During venesection	After
ml. per min.	*ml. per min.*	*ml. per min.*	*ml.*	*ml. per min.*	*ml. per min.*	*ml. per min.*
12.2	10.8	11.5	450	13.1	11.3	10.7
16.3	17.0	17.5	300	15.6	13.6	16.0
10.4	8.4	7.7 to 10.2	300	14.5	15.0	16.7
16.5 to 19.5	20.5	19.5	175	13.6	6.3	16.8
14.3	5.8	7.3 to 12.1	300	14.4	17.3	13.0

urine flow in the recipients. In 1 experiment there was a moderate decrease in urine flow, from 14.3 to 5.8 ml. per minute, but it should be noted that because of poor veins the transfusion technique was not very successful, 3 painful punctures having to be made. The other experiments were unexceptional, technically.

These experiments show that a considerable reduction in urine flow can be brought about by transfusing blood from subjects who have just suffered syncope, whereas the transfusion of blood from control subjects had no such effect. The decrease in urine flow in the recipients is less and much shorter than the post-syncopal oliguria produced in the donors, but this is to be expected since only $\frac{1}{10}$ to $\frac{1}{20}$ of the blood volume is transfused.

We believe that the above evidence shows that the oliguria observed after circulatory collapse is caused by an antidiuretic substance in the blood, a substance that can be transferred by blood transfusion.

Urine chloride after administration of the antidiuretic hormone

Starling and Verney (4) experimenting with heart-lung-kidney preparations, showed that the addition of the posterior pituitary hormone to the blood brought about a greatly increased concentration of chloride, and that the absolute excretion of chloride per minute in the urine was increased (see also Shannon, 1942). Smith and MacKay (5) observed the same effects on man.

We have examined the plasma chloride concentration and the chloride concentration and the chloride ouput in the urine in a normal subject after the intramuscular injection of 5 i.u. of Insipidin (A.B.) with the usual water load (100 ml. every 10 minutes). The chloride concentration in the urine during the ensuing oliguria rose considerably, whereas the per minute output fell. The urine chloride concentration remained considerably (about 40 per cent) above the plasma concentration as long as the oliguria lasted. The fall in chloride output observed by us is apparently contradictory to Smith and MacKay's observations, but one explanation may be that our subjects were in a state of pronounced negative chloride balance.

Urine and plasma chloride in post-syncopal oliguria

Figure 4 shows that the chloride concentration of the urine increases considerably during post-syncopal oliguria, reaching the value of 570 mgm. per cent, much higher than the plasma concentration. On the other hand, the chloride output does not rise: in fact, it has rather a tendency to fall. Two similar experiments gave this same result.

Urine and plasma chloride in oliguria transmitted by transfusion

Figure 3 shows the urine chloride concentration and the chloride output of a recipient during the

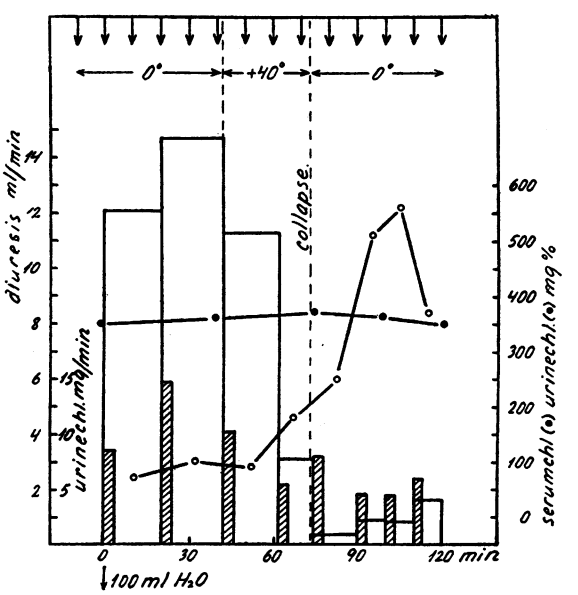

FIG. 4. DIURESIS AFTER CIRCULATORY COLLAPSE

Open circles: Urine chloride concentration (mgm. per cent); closed circles: Plasma chloride concentration (mgm. per cent); hatched columns: Chloride output in urine (mgm. per min.).

oliguria transmitted by blood transfusion. Here we find the same phenomenon, namely, a marked increase in urine chloride concentration, this value exceeding the blood chloride concentration. The chloride output, however, remains almost constant.

Although in our experiments the chloride output has not increased during post-syncopal oliguria, we consider that our results constitute circumstantial evidence in support of our hypothesis. We attach importance to the fact that the chloride output after the infusion of Insipidin and during post-syncopal oliguria behaves in the same manner under our experimental conditions. The fact that we found no increased chloride output in either circumstance may, as already stated, be due to the fact that our subjects were in a state of negative chloride balance owing to the heavy water load.

Circulatory collapse in patients with diabetes insipidus

Two young, otherwise healthy men with diabetes insipidus were employed as experimental subjects. Both subjects reacted positively to posterior pituitary extract, and their 24-hour urine output when not receiving extract was 6 to 14 liters respectively.

Both subjects reacted in the same manner after syncope. They showed a decreased urine flow of the same order of magnitude as shown by normal persons, and the inulin U/P ratio rose just as high (to 120). On the other hand, the duration of oliguria in both subjects was about 20 minutes, a much shorter period than is observed in corresponding experiments on normal subjects (60 to 90 minutes). The blood pressure fell as in normal subjects; likewise, the clinical condition during collapse was comparable with that of the completely collapsed normal subjects, and they recovered just as quickly as the normals after return to the horizontal.

It should be noted that diabetes insipidus was slight in one of our subjects and only moderately severe in the other, and hence we would not expect to find any excessive deviation in behavior from the normal. Nevertheless, we believe that the shorter duration of the oliguria in the subjects with diabetes insipidus must be attributed to their inability to produce antidiuretic hormone in the same quantities as normals do in the same situation.

Summarizing the results of the 3 series of experiments, none of which taken separately can be said to constitute absolute proof of the correctness of the theory, but all of which point in the same direction, we believe that we have produced evidence that post-syncopal oliguria is caused by an increased secretion of the antidiuretic hormone. Nothing can be concluded from our experiments as to the nature of the releasing mechanism operating on pituitary secretion. The effective stimulus might be either cerebral anoxia, caused by the fall of blood pressure, or a reflex effect on the pituitary gland mediated through the pressor receptors.

Finally, some brief reference may be made to what we imagine may be the effect on the organism of this pituitary regulation of diuresis as demonstrated in the case of circulatory collapse.

In the passive erect posture the circulating blood volume is reduced sometimes to catastrophically low values, the result being syncope. Regulation of the diuresis may possibly contribute towards reestablishing the normal blood diuresis, but quite quantitatively it can scarcely be of much importance when the diuresis is of the usual volume.

The regulation may perhaps be regarded merely as an *accompanying phenomenon* to another pituitary regulation, first and foremost a regulation of the tone of the capillaries, which would be appropriate in a situation such as that described. It should be mentioned in this connection that the subjects were always rather pale for some time after the syncope, a sign of capillary contraction in the skin.

It may be presumed that the hormonal regulation of diuresis may be contributory to the oliguria observed in cases where there is circulatory insufficiency, for example, hemorrhage, fall of blood pressure and shock as in lumbar anesthesia, shock caused by burns, cardiac insufficiency, diabetic coma, etc.

SUMMARY

Brief circulatory collapse brought about in water-loaded subjects by means of a tilt-table is followed by a protracted period of oliguria (post-syncopal oliguria). The degree and duration of

the oliguria seem to depend upon the degree of circulatory collapse.

Since the rate of glomerular filtration is rapidly restored to normal after the syncopal period, the oliguria may be attributed to an increased reabsorption of water by the renal tubules.

It is suggested that post-syncopal oliguria is due to an increased secretion of the antidiuretic, posterior pituitary hormone. This hypothesis is supported by the following experiments:

1. The transfusion of blood from subjects who had just collapsed with post-syncopal oliguria into water-loaded subjects caused a distinct decrease in urine flow in the latter.

2. The increased chloride concentration of the urine and the rate of chloride excretion during post-syncopal oliguria corresponds to the changes observed after administration of posterior pituitary extract.

3. Circulatory collapse in 2 patients with moderate diabetes insipidus was followed by post-syncopal oliguria, which was of considerably shorter duration than in normal persons.

The initiating mechanism of post-syncopal oliguria and its possible clinical relations to other forms of oliguria are discussed.

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