

THE LOSS OF FLUID AND PROTEIN FROM THE BLOOD DURING A SYSTEMIC RISE OF VENOUS PRESSURE PRODUCED BY REPEATED VALSALVA MANEUVERS IN MAN¹

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It is well known that protein-poor fluid moves from the vascular to the extravascular space during venous congestion of the forearm or lower extremity (1-5) and during a more generalized increase of venous pressure such as is induced by quiet standing (6, 7) or by pressure breathing (8, 9). No quantitative comparison has been made, however, between local and generalized congestion as to the quantity and duration of capillary filtration per unit increase of venous pressure.

Our interest in the role played by generalized capillary filtration in the pathophysiology of congestive heart failure and in postpartum hemoconcentration (10) stimulated the following experiments in which venous pressure was increased by repeated performance of Valsalva maneuvers for half-hour periods by healthy subjects. Fluid losses were calculated from changes in venous hematocrit. It will be shown *a*) that in the first 10 minutes the unit rate of filtration is about the same for generalized as for local congestion, but *b*) that the rate subsequently falls off much more abruptly when the filtration area and the early fluid loss are larger than when only the forearm is involved.

PROCEDURE, METHODS AND CALCULATIONS

The venous pressure manometer consisted of glass tubing (inside diameter, 3 mm.) attached to a scale with zero 10 cm. above the table top. The rubber tubing between manometer and vein was interrupted by a T-tube leading from a calibrated 120 ml. reservoir. The entire system was filled with heparinized saline. Manipulation of reservoir level and connecting pinchcocks permitted rapid adjustment of the fluid column in the manometer to match the fluctuations of venous pressure and prevented regurgitation of blood or unnecessary infusion of saline during and after Valsalva maneuvers.

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The subjects were healthy² men and women under the age of 45. They came directly to the laboratory in the morning, usually without breakfast, and reclined for at least 45 minutes to allow stabilization of postural changes in fluid distribution before observations were begun. An indwelling 18 gauge needle was then placed in the antecubital vein of each arm. One was used for measurements of pressure and injection of dye, and the other for sampling. To keep it patent, the latter was connected to a 20 ml. syringe containing heparinized 0.9 per cent saline so that minimal amounts of blood and saline could be exchanged (0.1 to 0.2 ml.). Before collection of any sample, 3 ml. of blood was discarded.

The subjects rested for another 10 to 30 minutes while three or four blood samples were collected and three or four readings of venous pressure were recorded, and in one experiment on each subject plasma volume was determined with T-1824. A series of Valsalva maneuvers was then performed. Readings of venous pressure were called out by an observer, while the subject, lying on his back with legs flexed, attempted to raise the pressure as high as possible by tensing his abdomen and making respiratory efforts against his closed glottis. Efforts lasted 20 out of every 30 seconds. Each fifth minute was devoted to rest and collection of blood samples (see Figure 1). The manometer was read every five seconds. Observations continued during 30 minutes of recovery. The volumes of saline delivered and of blood withdrawn were recorded.

Samples were collected in oiled syringes to minimize hemolysis. Three ml. of each sample was transferred to a tube containing the appropriate amount of Wintrobe's anticoagulant mixture; the remainder was allowed to clot. Wintrobe hematocrit tubes were filled in duplicate immediately after the procedure, covered with a drop of mineral oil, and centrifuged for 30 minutes at 3,000 rpm. The buffy coat was included in the estimated height of the cell column, and no correction was applied for trapped plasma. Serum proteins were estimated by the falling drop method of Kagan (11); falling times were determined in triplicate. Optical densities of

² A. McL. had had amputations of one leg at the ankle and the other at the junction of the middle and lower third of the foreleg.

the serum were determined with an Evelyn microcolorimeter.

The venous pressure readings taken during the 60 minutes of effort and recovery were plotted on coordinate paper, and the average of the resting readings was drawn as the baseline. The mean increase or decrease of pressure from resting level was then determined by planimetry for each five minute period.

The average value for the three resting samples was used as the "initial" value for both hematocrit and serum protein concentration. Initial plasma volume, when measured, was calculated from the average of the optical densities of samples taken 10 and 15 minutes after injecting the dye. Initial whole blood and red cell volumes were calculated from this value and the initial hematocrit. In experiments where plasma volume was not measured, plasma and whole blood volumes were calculated from the initial hematocrit and the red cell volume as determined in the companion experiment on the same subject.

For each successive sampling period, the initial values were corrected for the losses of cells, plasma and total circulating protein caused by sampling, using the hematocrit and protein values of the preceding sample. In this way "predicted" values for hematocrit and protein concentrations were obtained for comparison with the observed values for the same period. A second set of predicted values was estimated on the assumption that the plasma volume had been expanded by the exact amount

of the infused saline. The formulas introduced by Landis, Jonas, Angevine and Erb (2) were used to calculate the apparent changes of plasma volume, of total circulating protein and of the protein content of the capillary filtrate. Details of the calculations and an analysis of the reliability of the results appear in the Appendix.

Because the volumes of saline infused during the Valsalva experiments were relatively large in relation to the observed filtration volumes, 10 experiments were performed in which comparable volumes of saline were infused, but Valsalva maneuvers omitted. Each healthy subject rested for at least 45 minutes, after which two or three samples were taken at 5 minute intervals from an 18 gauge needle kept open with a very slow drip of saline. Saline was then infused at an approximately constant rate for 30 minutes to achieve totals of 150 to 210 ml. A 5 ml. sample was taken every five minutes after 3 ml. of blood had been discarded. The hematocrit of each sample was determined in duplicate.

RESULTS

1. Antecubital venous pressure

Figure 1 shows two examples of the curves obtained by plotting manometer readings during Valsalva maneuvers and during rest.

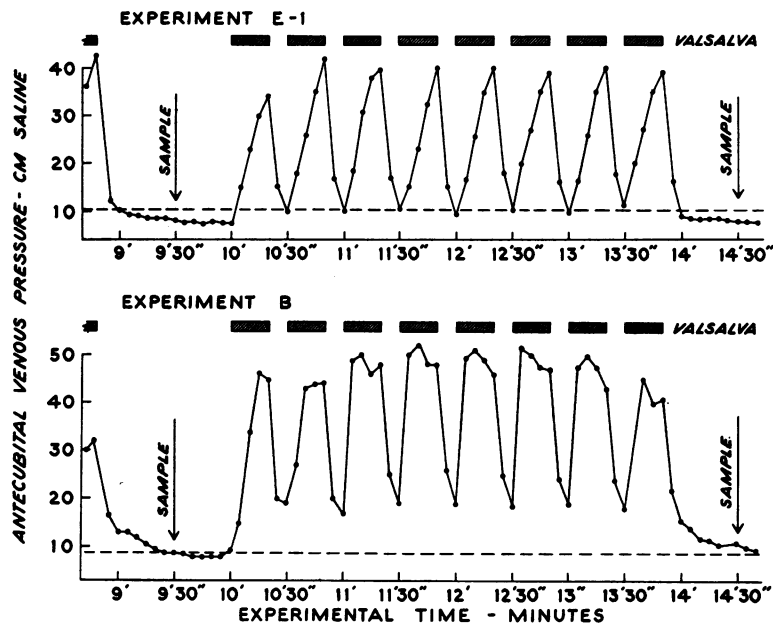


FIG. 1. TWO EXAMPLES OF VENOUS PRESSURE CURVES OBTAINED BY PLOTTING SALINE MANOMETER READINGS DURING VALSALVA MANEUVERS AND DURING REST

Manometer zero 10 cm. above the skin of the back. Dotted lines show average pressures during initial rest period.

TABLE I
Summary of Valsalva experiments

Expt. no.	Date 1947	Subject	Sex	Weight	Plasma volume	Volume of saline added	Volume of blood samples	Maximum venous pressure*
				<i>Kg.</i>	<i>ml.</i>	<i>ml.</i>	<i>ml.</i>	<i>cm. saline</i>
A-1	11/29	J. H.	M			210	7	46
A-2	12/9	J. H.	M	80.0	3,360	155	15	41
B	12/16	F. L.	M	72.8	3,460	130	15	42
C	12/2	J. S.	M	76.5	3,197	170	15	45
D-1	11/25	A. McL.	M			142	7	32
D-2	12/11	A. McL.	M	56.6	2,970	120	15	30
E-1	11/28	E. B.	F			160	7	28
E-2	12/18	E. B.	F	60.0	3,100	135	15	28
F-1	12/4	B. F.	F			100	7	27
F-2	12/30	B. F.	F	58.5	2,505	120	15	23

* Average of the maxima reached during Valsalva maneuvers minus the mean resting pressure.

near the original baseline. Table I shows the average peak pressures attained. Some subjects achieved more effective increases of pressure than others, but performance was fairly uniform in each experiment. Average increases of between

10.4 and 20.8 cm. H₂O were sustained during the half-hour periods of Valsalva maneuvers (see Table III and Figure 2). Venous pressure always remained below the initial resting level during the entire 30 minutes of recovery.

TABLE II
Effects of small saline infusions on the plasma volume during rest

Subject	Sex	Weight	Time	Hematocrit		Volume of saline infused	Apparent excess (+) or deficit (-) of plasma
				Predicted	Observed		
H. R.	M	Kg. 70	min. 10 30	% 48.1 46.7	% 47.6 46.9	ml. 60 180	(% of infused volume) + 78 - 10
R. W.	M	82	10 30	41.9 39.9	42.1 41.0	60 180	- 41 - 77
S. H.	M	65	10 30	48.9 47.3	48.2 47.1	60 180	+ 97 + 10
P. H.	M	81	10 30	47.2 46.1	45.9 46.4	60 180	+210 - 17
D. Z.	M	73	10 30	47.8 46.5	47.7 47.2	70 210	+ 7 - 31
J. K.	M	87	10 30	40.3 39.0	40.3 40.2	70 210	0 - 58
E. B.	F	66	10 30	42.6 41.4	43.3 42.6	75 200	- 87 - 58
M. D.	F	54	10 30	38.4 37.2	39.1 38.5	50 150	-129 - 93
M. S.	F	47	10 30	41.4 40.1	41.0 40.5	50 150	+ 39 - 22
M. J.	F	62	10 30	40.3 39.3	40.9 40.5	60 180	- 71 - 70
						Average at 10 minutes	+ 10.3 (S.D. = 95)
						Average at 30 minutes	- 44 (S.D. = 33)

2. Experiments in which no Valsalva maneuvers were performed

The amounts of saline infused, 2.2 to 3.2 ml. per Kg. of body weight, were similar in magnitude to those used in the Valsalva experiments. The "predicted" hematocrits shown in Table II represent the average resting values corrected for sampling losses and for the infused saline. Thus, the calculated excesses or deficits represent differences between the apparent changes in plasma volume and the expected changes if all the saline had remained intravascular. The results were extremely variable. At the time of the 10 minute sample more fluid appeared to have been added to the plasma than had been injected in the majority of experiments. At 30 minutes, after infusion of 150 to 210 ml., evidence in all but one experiment indicated that some portion of the fluid had left the blood. The average loss of 44 per cent was derived from values ranging between a loss of 93 per cent of and a gain of 10 per cent over the injected volume.

3. Hemoconcentration during the period of Valsalva efforts as calculated from hematocrit

Because the fate of the saline introduced during the experiments could not be determined exactly (see above), calculations were made in two ways:

a) without consideration for the saline, and b) assuming that plasma volume was expanded progressively by the saline. Values corrected for saline will henceforth be labeled "cs" and uncorrected values "ucs." When correction was made for saline, the predicted hematocrit was always lower and the apparent filtration volume greater than when the saline was left out of consideration. Figure 2 shows the results of two experiments in which the increments of venous pressure were about the same. It shows the similarity between curves obtained by plotting ucs and cs values. In every experiment the fluid loss as calculated from hematocrits was rapid at first, became progressively slower, and ceased after 10 to 20 minutes. In six experiments fluid was regained during the latter part of the period of increased venous pressure (see Experiment A-2, Figure 2).

In general, the largest subjects and those who maintained the highest increments of venous pressure filtered the most fluid. The three heaviest subjects, A, B and C, maintained venous pressures 17 to 22 cm. above resting. During the first nine and a half minutes their fluid losses were 333 to 501 ml. (5.6 to 8.1 per cent of initial blood volume cs). The two females, E and F, maintained venous pressures only 9 to 13 cm. above resting and lost only 3.1 to 3.9 per cent of blood volume (see Table III).

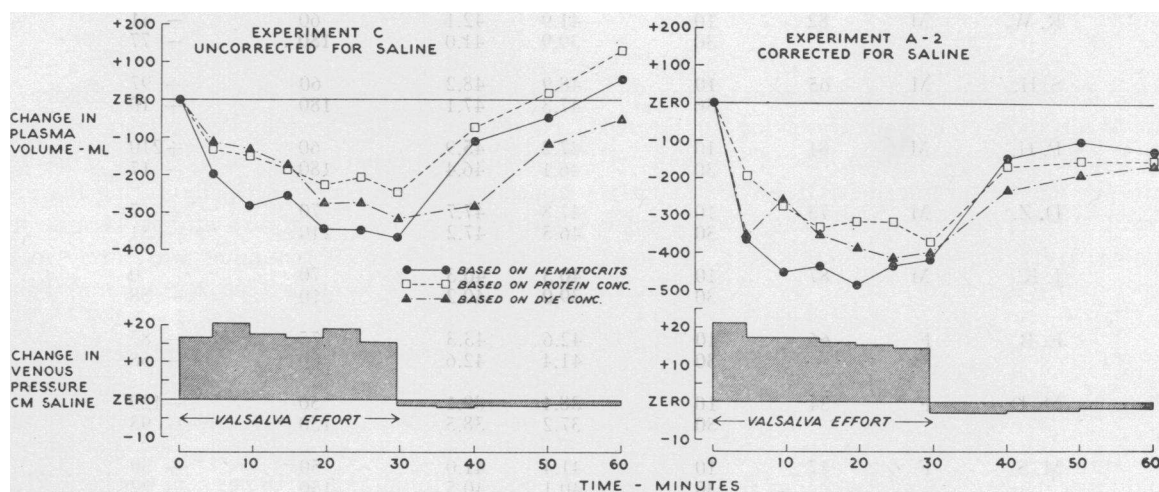


FIG. 2. SUMMARY OF TWO EXPERIMENTS

Below are the average changes of venous pressure during Valsalva efforts and during recovery, as determined by planimetry of pressure curves for each five minutes. Apparent changes in plasma volume, as calculated from hematocrits, serum proteins and optical densities, appear above. Values for optical density have been calculated as though dye were leaving the blood continuously at a rate of 10 per cent per hour.

TABLE III
Results at 9½ and 29½ minutes in Valsalva experiments

Expt. no.	Time	Increase in venous pressure*	Hematocrit			Serum protein conc.			Volume filtered‡		Blood volume lost§		Unit rate of filtration§		Change in total circulating protein
			Observed	Predicted		Observed	Predicted		cs	ucs	cs	ucs	cs	ucs	
	min.	cm. saline	%	%		Gm. %	Gm. %		ml.		%		ml./min./cm./Kg.		Gm.
A-1	9½	19.1	49.85	47.04	47.61	6.322	5.851	5.989	333	262	5.7	4.5	0.023	0.018	- 6.5
	29½	20.1	49.75	45.95	47.62	6.391	5.603	5.989	460	250	7.8	4.3	0.010	0.005	- 5.8
A-2	9½	19.2	48.50	44.93	45.31	6.305	5.796	5.886	454	402	7.4	6.6	0.033	0.028	-11.4
	29½	16.9	47.35	44.17	45.35	6.343	5.660	5.882	417	262	6.8	4.3	0.010	0.006	- 2.9
B	9½	20.8	47.45	43.60	43.91	6.567	5.938	6.010	501	459	8.1	7.4	0.035	0.032	-11.0
	29½	20.8	48.30	42.96	43.88	6.764	5.785	6.005	687	556	11.1	9.0	0.015	0.012	-11.2
C	9½	18.6	49.30	46.54	46.98	5.861	5.544	5.642	339	282	5.6	4.7	0.025	0.021	- 9.6
	29½	17.5	50.05	45.68	46.99	6.130	5.351	5.643	534	363	8.8	6.0	0.014	0.009	- 6.9
D-1	9½	13.4	47.60	44.82	45.22	6.754	6.049	6.150	304	258	5.9	5.0	0.042	0.036	- 0.3
	29½	13.8	48.40	44.02	45.24	6.716	5.851	6.147	477	335	9.2	6.5	0.021	0.015	- 6.5
D-2	9½	11.4	46.15	43.80	44.14	6.531	6.361	6.447	270	230	5.1	4.3	0.045	0.038	-12.5
	29½	11.6	47.70	43.03	44.02	6.900	6.188	6.442	523	403	9.9	7.6	0.027	0.022	-14.4
E-1	9½	14.1	39.45	37.93	38.36	6.070	5.898	6.006	186	132	3.9	2.8	0.023	0.016	- 6.2
	29½	11.3	38.90	37.06	38.33	6.014	5.690	6.005	228	70	4.8	1.5	0.011	0.003	- 3.8
E-2	9½	12.7	38.15	36.54	36.87	6.230	5.966	6.051	208	164	4.2	3.3	0.029	0.023	- 4.7
	29½	10.8	37.25	35.77	36.75	6.007	5.799	6.050	197	65	4.0	1.3	0.010	0.003	- 5.2
F-1	9½	9.3	43.65	42.02	42.36	6.911	6.221	6.309	152	120	3.8	2.9	0.030	0.023	+ 5.8
	29½	10.7	43.70	41.33	42.36	6.818	6.052	6.313	223	123	5.4	3.0	0.012	0.007	+ 3.3
F-2	9½	12.2	41.70	40.28	40.67	6.446	6.180	6.280	130	104	3.1	2.5	0.019	0.015	- 1.7
	29½	10.4	41.33	39.44	40.58	6.470	5.986	6.278	194	75	4.6	1.8	0.011	0.004	- 0.1
Mean at 9½ min.													0.031	0.025	
S.D.													0.008	0.008	
Mean at 29½ min.													0.014	0.009	
S.D.													0.005	0.006	

* Cumulative average increase above resting.

† Values corrected for infused saline.

‡ Values uncorrected for infused saline.

§ Calculated from hematocrits.

|| cs and ucs values are the same.

For the first nine and a half minutes the unit rate of filtration (URF), representing ml. filtered per Kg. body weight per cm. rise of venous pressure per minute, averaged 0.031 cs (0.025 ucs). The URF for 29½ minutes was always much smaller, averaging 0.014 cs (0.009 ucs). In most experiments the ratio of URF for 29½ minutes to URF for 9½ minutes was about 1:2 cs (1:3 ucs).

4. Serum proteins and optical density

During the period of Valsalva maneuvers, the fluid loss calculated from the change in serum protein concentration was always less than that calculated from hematocrits. This relationship became reversed, or at least the values approximated each other, during recovery. Examples of these

directional changes are illustrated in Figure 2. There was a calculated loss of total circulating protein in all experiments except F-1. This loss appeared to have occurred chiefly during the first part of the period of Valsalva efforts, because the calculated loss at 29½ minutes was rarely more than that at 9½ minutes (see last column, Table III).

The observed changes in optical density provide only qualitative information because rates of disappearance of T-1824 during rest were not established. If it is assumed that the dye left the blood at an initial rate of 10 per cent per hour (12) and that the rate was unchanged during the procedure, the results are as shown in Figure 2. In the early part of the experiment the apparent volume filtered approximated that calculated from

the protein data, whereas toward the end of the half-hour of Valsalva efforts, it lay close to the volume calculated from the hematocrits. During the recovery period, however, the curve representing volume changes based on optical density fell below the hematocrit and protein curves, indicating that the rate of dye loss was slower during recovery than during the period of efforts.

DISCUSSION

1. Possible influence of factors other than fluid loss from the blood on venous hematocrit

Some of the limitations of calculating changes in plasma volume from hematocrits are shown by the results of the experiments with infusions of saline but without performance of Valsalva maneuvers. The differences sought between initial and observed values were necessarily so small that they could have been affected materially by spontaneous changes in the venous hematocrit. In 7 of the 10 experiments the blood samples taken before beginning the infusion showed evidence of the so-called "spontaneous hemodilution" which has been described repeatedly and which has been variously attributed to a gain of plasma volume or a rise of the body: venous hematocrit ratio (12-15). Thus, in six experiments the hematocrit of the last pre-infusion sample was 0.1 to 0.6 per cent³ lower than that of the first, and in one (S. H., Table II), the fall amounted to 1.2 per cent. This was the experiment in which plasma volume appeared to have expanded even more than could be accounted for by the infusion, even at the time of the 30 minute sample. It seems probable, therefore, that the variability of the results of these experiments was caused chiefly by individual differences in the degree and persistence of spontaneous hematocrit changes following the initial venipuncture. In 8 of the 10 Valsalva experiments the hematocrit fell 0.2 to 0.7 per cent during the initial rest period. However, the minor fluctuations characteristic of the resting state probably did not continue during the Valsalva efforts when major circulatory derangements and rapid capillary filtration were in effect.

The addition of saline to the circulation had little influence on the results during the early part of the Valsalva experiments when the filtered vol-

umes were large and infused volumes small. By the end of 30 minutes the influence of the saline was relatively more important, particularly in those experiments where the volumes of filtrate were small. The results of the infusion experiments where no Valsalva maneuvers were performed show that the "true" values probably were about midway between the results calculated as though all the saline remained intravascular (cs) and as though all of it had left the blood (ucs).

Three factors must be considered which might conceivably have caused systematic errors in estimating fluid movements from changes in the venous hematocrit under the conditions of these experiments. 1. Cell-rich blood might have been transferred from some reservoir into the general circulation during the Valsalva efforts. There is no evidence to support this suspicion. Although about 200 ml. of blood can apparently be expressed from the lungs by a five second maximum Valsalva effort (16), this represents a redistribution of whole blood rather than a transfusion of cells because the hematocrit of the pulmonary circuit is about the same as that of the body as a whole (17) and the quantity of blood involved is only a small fraction of total blood volume. Finnerty, Buchholz and Guillaudeu (18) recently reviewed and contributed to the evidence against the presence, in healthy men, of storage areas which are capable of contributing cell-rich blood to the circulation. 2. Theoretically, the reduced rate of blood flow in small vessels during a Valsalva maneuver would tend to lower the body: large vessel hematocrit ratio. Although this ratio tends to be deranged during severe circulatory disturbances (19) and may be reduced in heart failure as much as 2 per cent (20) to 4 per cent (21), our results were probably not affected in this way because the blood samples were taken during intervals of rest and not during Valsalva efforts. 3. Cell volume might have been affected by changes in blood gas contents or pH caused by breath-holding and venous congestion. Landis and associates (2) have summarized this problem as it pertains to the effects of venous congestion. The good agreement which was found between calculated fluid losses based on hemoglobin and on hematocrit values by them (2) and by Henry, Hendrickson, Movitt and Meehan (8) indicates that with severe venous congestion or prolonged pressure breathing, sig-

³ Hematocrit scale divisions.

nificant changes in cell size either do not occur or are reversed during aerobic handling of the blood samples *in vitro*. There is no reason to suppose the error from this source was any greater in our experiments. The samples were collected during intervals of rest, and they were freely exposed to air during transfers and while being mixed with anticoagulant before filling the Wintrobe tubes. Should any of the three sources of error just discussed be in effect, it would make the estimate of fluid loss based on hematocrits appear falsely high. Such systematic errors, at most, could not exceed the observed differences between the fluid losses calculated from hematocrits and those calculated from changes in protein concentrations. They could, however, account for some or all of the apparent loss of protein to the capillary filtrate.

2. Venous pressure and fluid movement during Valsalva maneuvers

The fidelity of the system used here to record venous pressure was probably adequate. Rushmer (22), using optical manometers, found that antecubital venous pressure rises slowly (0.74 mm. Hg per second) and reaches its maximum in 20 seconds during Valsalva maneuvers. Our curves have similar characteristics. Although pressure rises more rapidly in veins lying below the level of the heart than above (22), the changes observed in the antecubital vein when located just below heart level in the recumbent subject, as in our experiments, represent an approximate average for the body.

The average increase of antecubital venous pressure corresponding to a given percentage depletion of blood volume in our experiments was less than one-third of the airway pressure required to produce similar losses in humans (8) and in anesthetized cats (9) subjected to pressure breathing for like periods of time. This illustrates the fact that peripheral venous pressure may rise to only one-third or one-half of airway pressure during Valsalva efforts, the exact relationship apparently depending on the elasticity of the lung, the severity of cardiac tamponade, and the intensity of vasomotor responses (22, 23).

Landis and Gibbon (3), measuring changes in extravascular volume by pressure plethysmograph,

found the URF during 10 minutes of venous congestion of the human forearm to be 0.0033 ml. per cm. of venous pressure per minute per 100 Gm. of tissue. Our values, expressed per 100 Gm. body weight, are similar but slightly smaller (0.0031 cs; 0.0025 ucs). Hamilton, Woodbury and Harper (24) found that effective capillary pressure fails to rise within thorax, abdomen and skull during cough and strain because intravascular and extravascular pressures rise equally. The URF for 9½ minutes of Valsalva efforts becomes 0.0036 cs (0.0029 ucs), in close agreement with the URF for 10 minutes of localized congestion of the forearm (3), if the contents of these protected cavities are taken to represent 15 per cent of body weight and the calculations therefore based on 85 rather than 100 per cent of body weight.

In contrast, the URF for 29½ minutes of Valsalva efforts was only one-third to one-half as great as the URF for 30 minutes of forearm congestion as found in three investigations: 0.0014 cs (0.009 ucs), as contrasted with 0.0023 (1), 0.0028 (3) and 0.0027 (4). It appears that a sustained rise of venous pressure ceases to be effective as a cause of capillary filtration much sooner when large portions of the body are involved than when congestion is localized. Thus, the URF decreased 50 per cent or more between 9½ and 29½ minutes of Valsalva efforts, but only 18 per cent between 10 and 30 minutes of forearm congestion (3).

The hemoconcentration resulting from Valsalva efforts is comparable in degree to that found when venous hypertension of like severity and duration is produced by other means, such as orthostasis (6, 7), thigh cuffs (5) or pressure breathing. The rapid decline of filtration after the first 10 to 20 minutes of extensive congestion has been noted by others (5, 6, 9).

An explanation for the more rapid cessation of filtration during generalized as compared with localized venous hypertension is to be found in the rapid rise of plasma oncotic pressure. Comparison of predicted with observed values (Table III) shows that the protein concentration of the plasma rose in some instances as much as 0.7 Gm. per cent after 9½ minutes and 0.9 Gm. per cent after 29½ minutes of Valsalva efforts. In the case of localized congestion, continued filtration is opposed only by rising tissue pressure, but when con-

gestion is widespread the influence of rising oncotic pressure is added, because relatively large amounts of protein-poor fluid leave the blood early in the course of the experiment and lymphatic return of protein is unimpaired. It seems unnecessary to invoke other explanations for the cessation of filtration after the early loss of 3 to 10 per cent of blood volume even though it is known that the mechanisms for conservation of body water may be set off by this degree of depletion (25, 26). Under the conditions of our experiments the basal rate of urine flow must have been small (27), so that even a 50 per cent reduction of flow (25, 26) could have had little influence on our results.

3. Protein and dye loss

The calculated losses of protein to the capillary filtrate deserve some consideration despite their relative unreliability because similar data are available in the literature for comparison (2, 8). Our results were fairly consistent, particularly in the first six experiments (Table III) where fluid movements were fairly large. This suggests that variations due to random errors in hematocrit and protein values were generally smaller than those in the extreme examples chosen to illustrate the possible range of technical error (see Appendix). Appreciable protein was lost during the Valsalva efforts, so that the calculated content of the filtrate at 29½ minutes was about 1 to 2 Gm. per 100 ml. Henry and co-workers (8) found similar losses during pressure breathing, whereas Landis and his associates found that the filtrate formed during forearm congestion at similar pressures was free of protein (2). Possible explanations for the apparent difference in protein loss during localized compared to more generalized congestion seem to be that *a*) during Valsalva maneuvers or sustained pressure breathing, effective capillary pressure might rise sufficiently in permeable areas such as the liver to cause loss of protein-rich fluid, or *b*) factors other than loss of fluid from the blood might contribute to the rise of hematocrit during the Valsalva maneuvers or pressure breathing, but not in localized congestion. Such factors might include changes in blood gas contents and pH or disturbances in the body: venous hematocrit ratio, as discussed earlier in this report.

Protein appeared to be re-entering the circula-

tion, presumably via the lymphatic system, during recovery and possibly in the latter part of the Valsalva period, as evidenced by the increase in total circulating protein between 9½ and 29½ minutes seen in several experiments. Although Hyman and Goodman (9) found the rate of disappearance of T-1824 from the blood was unaffected by pressure breathing, our data show that dye loss was slightly more rapid during the period of Valsalva efforts than during recovery.

4. Clinical implications

The amounts of fluid leaving the blood during 10 to 30 minutes of repeated "bearing down" efforts are sufficient to account for the rise of hematocrit usually seen during the second stage of obstetric labor (28). Because the loss of fluid caused by venous hypertension is stopped by rising plasma oncotic and tissue pressures, the modest elevation of venous pressure caused by postpartum administration of oxytocic drugs (10) would not be expected to have further effect, except to limit the rate of reabsorption of fluid filtered during labor. However, the same rise of venous pressure after cesarean section not preceded by labor would be expected to cause some hemoconcentration (10).

It would appear from our results that in heart failure, clinical edema could not result from venous hypertension without concomitant renal retention of salt and water, since massive capillary filtration is self-limited. However the results of the Valsalva experiments cannot necessarily be applied quantitatively to the problem of cardiac edema because factors influencing the rate of rise of interstitial and plasma oncotic pressures during capillary filtration may be different in the patient with edema compared to the healthy subject. In the patient the initial volume of fluid filtered per unit rise of central venous pressure might be greater than suggested by our results because the capillary beds of thorax and abdomen would be affected, whereas they were "protected" in the Valsalva experiments. The resultant depletion of plasma volume might call into play the homeostatic mechanisms regulating fluid balance more rapidly. On the other hand, plasma oncotic pressure might not be maintained as well in the cardiac patient as under experimental conditions because

a) protein-rich fluid would probably be filtered in the liver, and b) renal retention of salt and water would tend to dilute the plasma. Local factors to be considered are a) reduced tissue elasticity and b) impaired lymphatic drainage, as found by McMaster (29) in patients with cardiac edema. The former would cause tissue pressure to rise less rapidly and thus enhance filtration. The latter would work in the opposite direction. The possible effects of altered total return of fluid and protein via lymphatics to the blood cannot be estimated.

SUMMARY

1. In 10 experiments on healthy subjects, systemic venous pressure was raised 11 to 21 cm. H₂O for half-hour periods by repeated performance of Valsalva maneuvers. Changes in venous hematocrit, plasma protein and T-1824 concentrations showed that fluid left the blood rapidly during the first 10 to 20 minutes. Filtration stopped or diminished greatly after an initial loss of 3 to 10 per cent of blood volume.

2. During the first 10 minutes the unit rate of filtration was similar to that observed during localized congestion of the forearm, if it is assumed that there was no rise of effective capillary pressure and no filtration within thorax, abdomen or skull. Cessation of filtration was more abrupt than in the locally congested forearm. The extensive loss of protein-poor fluid and more rapid establishment of a new balance of forces across the capillary walls when venous congestion is generalized can account for the difference.

3. The apparent concentration of protein in the filtrate was about the same as that observed in experiments with pressure breathing, but greater than that noted during forearm congestion. Total circulating protein usually failed to decrease further after the modest loss which occurred during the first 10 minutes. The rate of loss of T-1824 from the blood was slightly more rapid during the period of Valsalva efforts than during recovery.

4. It is concluded that the quantity of fluid leaving the blood during 10 minutes of Valsalva efforts is sufficient to account for the hemoconcentration commonly associated with parturition. Because of its self-limited nature, capillary filtration cannot be solely responsible for the production of generalized clinical edema.

APPENDIX

Symbols and equations. The following procedures were used in calculations, where

H = hematocrit

P = plasma protein concentration

Vrbc, Vpl, and Vwb = total volumes of cells, plasma and blood

TP = total circulating protein ($P \times Vpl$)

x_h = volume of fluid lost per 100 ml. of blood, calculated from hematocrits

$\bar{X}_h$ = total volume of fluid lost, calculated from hematocrits

x_p = volume of fluid lost per 100 ml. of plasma, calculated from protein concentrations

$\bar{X}_p$ = total volume of fluid lost, calculated from protein concentrations

$\bar{P}$ = loss of circulating protein

P_x = protein concentration of filtrate.

Subscripts o and p refer to observed and predicted values, respectively.

Equations:

$$1. \quad x_h = 100 - 100 \times \frac{H_p}{H_o}$$

$$2. \quad \bar{X}_h = x_h \times Vwb$$

$$3. \quad x_p = 100 - 100 \times \frac{P_p}{P_o}$$

$$4. \quad \bar{X}_p = x_p \times Vpl$$

$$5. \quad \bar{P} = TP_p - P_o \times (Vpl - \bar{X}_h)$$

$$6. \quad P_x = \frac{\bar{P}}{x_h}$$

Sample calculation. The handling of the data for nine and a half minutes, Experiment A-1 (line 1, Table III) may serve as an example. Vpl and Vwb for this experiment were calculated from the resting hematocrit, using the value for Vrbc which was obtained in the companion experiment on the same subject, A-2, in which plasma volume was measured.

Predicted values for nine and a half minutes were derived and tabulated as follows:

	Initial values	Losses from two preceding samples, and gains from infused saline	Predicted	
			cs	ucs
H (ml. %)	47.60		47.04	47.61
Vrbc (ml.)	2,785	- 7	2,778	2,778
Vpl (ml.)	3,065	- 7	3,127	3,058
Vwb (ml.)	5,850	-14	5,905	5,836
P (Gm./100 ml.)	5.990		5.851	5.989
TP (Gm.)	183.594	- 0.444	183.150	183.150
Saline (ml.)		+70		

Using the values corrected for infused saline (cs), Equations 1 to 6 give the following results:

$$1. \quad x_h = 100 - 100 \times \frac{47.04}{49.85} = 5.64 \text{ ml./100 ml. blood}$$

$$2. \quad \bar{X}_h = 5.64 \times 59.05 = 333.04 \text{ ml.}$$

$$3. \quad x_p = 100 - 100 \times \frac{5.851}{6.322} = 7.46 \text{ ml./100 ml. plasma}$$

4. $\bar{X}_p = 7.46 \times 31.27 = 233.3 \text{ ml.}$
5. $\bar{P} = 183.149 - 6.322 \times (31.27 - 3.33) = 6.5 \text{ Gm.}$
6. $P_x = \frac{6.5}{333} = 1.95 \text{ Gm./100 ml.}$

Accuracy of calculated results. The accuracy of H_p and H_o affects the reliability, not only of x_h and $\bar{X}_h$, but of $\bar{P}$ and P_x . We have found the standard deviation of a single venous hematocrit to be 0.27 ml. per cent. This is based on measurements of three successive samples taken from an indwelling needle at five minute intervals in each of 103 experiments, and includes the effects of spontaneous fluctuations in the venous hematocrit, as well as analytical error when each hematocrit is measured in duplicate. In the experiments reported here, the most extreme error which might be anticipated from random deviations in H may be calculated by adding 0.27 to H_p and subtracting 0.27 from H_o . The values representing the largest and smallest filtration volumes of the series, *i.e.*, 29½ minutes, Experiment B, and 9½ minutes, Experiment F-2 (see Table III), may be used to test the effects of this manipulation. In the instance of the largest filtered volume, the apparent value of $\bar{X}$ is reduced 10 per cent (from 687 to 621 ml.), while $\bar{P}$ and P_x are reduced 35 and 28 per cent, respectively. In the case of the smallest filtration volume, similar manipulation of the data lowers $\bar{X}$ 28 per cent and $\bar{P}$ 94 per cent. (This changes $\bar{P}$ from an apparent loss of 1.7 to a gain of 1.3 Gm.)

If it is assumed that the serum protein concentrations may err by ± 0.16 Gm. per 100 ml. (11), the significance of our calculated values may be tested by adding 0.16 to P_p and subtracting 0.16 from P_o . With the data for 29½ minutes, Experiment B, this substitution makes $\bar{P}$ increase 127 per cent, or from 11 to 25 Gm., while P_x also rises more than 100 per cent (from 1.6 to 3.6 Gm. per 100 ml.).

Henry, Goodman and Meehan (30) found that if the numerical value of the product $(H_o - H_p)(P_o - P_p)$ is about 6, P_x may vary over a range of plus or minus 2 Gm. per 100 ml. due to random errors of determining P and H . As the product becomes progressively smaller, the variability increases. The corresponding products for our data range between 0.3 and 5.3, showing that the degree of hemoconcentration achieved in the experiments was not great enough to permit accurate calculation of P_x .

Thus, values for $\bar{X}_h$ can be relied upon within limits ranging from plus or minus 10 per cent of the largest and plus or minus 30 per cent of the smallest values in our series. $\bar{P}$ and P_x are dependable only in the general range of plus or minus 100 to 200 per cent.

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