

# Transcapillary Refilling After Hemorrhage in Normal Man: \*

## Basal Rates and Volumes; Effect of Norepinephrine

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REPARTITION of the body water, with compensatory refilling of the vascular tree, is an important homeostatic mechanism following hemorrhage. It was recognized in the 19th century and ascribed to an increased flow of lymph from the thoracic duct. Disputing this, Starling,<sup>35</sup> in a series of classic experiments published in 1896, showed that the passage of water across the capillary wall depended on the oncotic pressure exerted by the plasma proteins, as well as on hydrostatic pressure changes.

The physiologic effects of hemorrhage and of shock have been studied extensively since Starling's time. Most of the data have come from animal experiments, and though the processes of hemodilution following

hemorrhage in the dog and in man are analogous, there are important differences that require elucidation. For example, the dog has been found to refill to a maximum level in some instances in an hour or less,<sup>7, 27, 38</sup> and usually to fall short of complete refilling. The response of the human being is more gradual, occupying 36 to 48 hours and usually, in normal man, the subject achieves complete refilling.

Keith<sup>25</sup> reported an experimental human hemorrhage in 1919. He removed 800 ml. of blood from a normal donor and, using a vital red dilutional technic, he demonstrated a 600 ml. expansion of the plasma volume one hour after the bleed. Hemodilution continued until the fourth to sixth day, after which red cell volume started to be restored. This represented the first attempt to quantitate dilution after hemorrhage in man, and coincided more or less with the development of dye dilutional technics for measuring blood and plasma volume. It was soon recognized that accurate determination of the blood volume required simultaneous measurement of the red cell volume and plasma volume directly.<sup>34</sup> Accurate estimates of the red cell volume had to await the availability of radioisotopes and red cell tagging with isotopes of iron and chromium.

Plasma volume changes following experimental human hemorrhage were studied in several clinics in the early 1940's, and with more refined methods, the impressions of earlier studies were confirmed. Ebert, Stead

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and Gibson<sup>11</sup> bled six volunteer patients rapidly, removing 15 to 20 per cent of the blood volume. Five of the six subjects had circulatory collapse manifested by pallor, sweating and hypotension to 50 mm. Hg, or below. Plasma volumes fell with the hemorrhage, then increased gradually, so that at the end of three or four days the plasma expansion had overcompensated for the blood withdrawn.

Another report, published in 1941 by Wallace and Sharpey-Schafer,<sup>37</sup> described venesections performed in 28 convalescent patients. The volumes, again, were large, varying from 700 to 1,150 ml., and rapid, and resulted in moderate to severe hypotension. Using the carbon monoxide method to measure blood volume, these investigators found variable degrees of dilution, with refilling occurring in some individuals as early as three hours and in others as late as 90 hours. Undoubtedly the wide range of dilutional quantities and rates in these patients were related to the blood volume technic used.

Simeone<sup>33</sup> re-emphasized the concept of hemodilution following shocking hemorrhage in wounded soldiers and noted that red cell dilution was greater than protein dilution because of entrance of protein from the tissues into the blood. He tried to demonstrate mobilization of intracellular water by studying levels of plasma magnesium, and found that plasma magnesium increased only after hemorrhages of 25 per cent of blood volume.

The general pattern of plasma expansion has been confirmed by others,<sup>5, 15, 38</sup> studying hemorrhage in volunteer subjects. In preliminary studies in experimental human hemorrhage in this laboratory, and in reviewing the literature, it was apparent that the sum of the available data for the human response to hemorrhage was small, and that more extensive quantitation of the rates and limits of normal was required.

Interest in another aspect of plasma dilution and extracellular water repartition has

been stimulated by reports indicating that intravenously administered norepinephrine causes reduction of the plasma volume in man and in the dog.<sup>21, 32</sup> This effect has been suggested to be responsible for some of the serious limitations to the use of this vasopressor in the treatment of shock.<sup>31</sup> Earlier reports showed a similar effect on plasma volume by epinephrine infusion in dogs.<sup>20</sup> The confirmation of this action of norepinephrine in man, and its effect on transcapillary refilling, were therefore of interest.

### Materials and Methods

Sixteen healthy young men volunteers were studied. They were admitted to the hospital at least two days prior to the experiment. Physical examinations, chest x-rays, and electrocardiograms excluded detectable disease processes.

On the day before the experiment, the red cell volume (RV) and the plasma volume (PV) were measured. On the following morning, the subject was placed on a bed scale, electrocardiographic leads were attached and a polyethylene catheter was placed in an arm vein in such manner that good flow could be obtained with gentle suction on a 20 ml. syringe. The hemorrhages varied in magnitude from 490 to 968 ml., and ranged from 10 to 20 per cent of blood volume. They were carried out in 15 to 20 minutes, samples of the hemorrhage blood being taken at intervals during the bleed for quantitative determination.

In only one instance was the blood pressure lowered significantly. This occurred near the completion of the largest hemorrhage (B. W.), after 868 ml. had been removed. The blood pressure fell from 100/60 to 50/30 for several minutes, and this was associated with a mild bradycardia, and a sensation of vertigo. During the norepinephrine infusions all of the subjects became apprehensive, restless, one said he "felt mad." These reactions ended with the infusions. In most instances the

postepinephrine systolic blood pressure was 10 or 15 mm. Hg lower than it had been before the infusion. This always returned to normal within five hours.

Blood sampling was continued for 72 hours. No tourniquets were used for sampling. Estimations of hematocrit, serum sodium, potassium, chloride, osmolality, creatinine, plasma proteins, 17-hydroxysteroids, and erythropoietin were carried out in various samples in frequency sufficient to provide the desired information for a given experiment. Red cell volumes and plasma volumes were remeasured at 24 or 48 hours after the hemorrhage. In a few instances in which sampling volumes were very large, some of the blood taken for the hemorrhage, and heparinized, was reinfused in measured volumes, none of which exceeded the sampling excess.

The subjects took nothing by mouth from midnight before the hemorrhage until seven to ten hours after the hemorrhage. They were kept fasting for the blood volume measurements, but otherwise were on *ad lib* measured intakes. All urine was collected during the hospitalization period, and analyzed for concentrations of sodium, potassium, chloride, osmolality, creatinine, 17-hydroxysteroids, ketosteroids and erythropoietin.

Two subjects were studied for the effects of sampling without hemorrhage. In six subjects, intravenous infusions of norepinephrine were begun four hours after the start of hemorrhage. Total doses varying from 2.4 to 10.8 mg. were given in 0.0008 per cent solutions in 5.0 per cent glucose in water. The durations varied from two to four hours, and the rate was adjusted to maintain a 40 to 50 mm. Hg elevation of the systolic blood pressure. Red cell and plasma volumes were measured one hour after the norepinephrine was begun, and in one instance (K. D.) were measured one hour before starting norepinephrine. The effects of norepinephrine without hemorrhage were studied in two subjects.

Red cell volumes were measured by dilution of erythrocytes, tagged with Cr<sup>51</sup>, and plasma volumes by the dilution of Evans Blue dye (T1824). In the latter determinations, three-point curves were used to extrapolate to time zero. Hematocrits were spun in Wintrobe tubes, in duplicate, at 2,500 r.p.m. for 55 minutes, then for successive ten-minute periods until two consecutive readings of the height of the red cell column were the same. Plasma and urine concentrations of sodium and potassium were measured with the Baird flame photometer, concentrations of chloride by the Wilson-Ball method,<sup>39</sup> osmolalities with the Fiske osmometer, and creatinine content by the Folin method.<sup>19</sup> Plasma protein concentrations were measured by electrophoresis. Erythropoietin assays were carried out on samples of serum and urine by measuring the effect on the uptake of Fe<sup>59</sup> in polycythemic rats.

**Calculations.** In addition to direct measurement of the plasma volume, and in order to obtain a more frequent assessment of this volume, the large vessel hematocrit (LVH) was used to estimate plasma volume ( $PV_t$ ), taking into account the reduction in red cell volume by sampling. This assumes that in the first 48 hours after hemorrhage no red cells are added to the active circulation from inactive stores,<sup>13</sup> and that increased red cell production due to the hemorrhage has not yet begun. The red cell volume at any point in time could be calculated by subtracting the red cell volume removed in hemorrhage and sampling ( $RV_{H+S}$ ) from the initial red cell volume ( $RV_1$ ). The accuracy of this calculation was confirmed by multiple direct measurements of the red cell volume. The plasma volume at any time is given by the formula:

$$PV_t = \frac{(RV_1 - RV_{H+S})}{(LVH_t)(WBH/LVH)} - (RV_1 - RV_{H+S}).$$

The LVH was corrected for the average ratio of whole body hematocrit (WBH)

to large vessel hematocrit (LVH), obtained for each individual from all the values of this ratio determined for him, and based on the measurements of his RV and PV directly. The ratio is constant over a wide range of physiologic circumstances,<sup>6</sup> and is unaltered by hemorrhage. In our data the ratio is constant with few exceptions.

The formula is a simple statement of the fact that the blood volume at any time is equal to the red cell volume at that time divided by the whole body hematocrit. It was thus possible to calculate the plasma volume as often as the hematocrit was measured and curves could be drawn that approximated the continuous changes of plasma volume. The difference between the *predicted*\* and the *actual* calculated plasma volumes represented the volume of fluid added to, or removed from the circulation, and a continuous record of expansion and contraction of the plasma volume could be obtained.

The validity of these calculations was checked by direct measurement of the plasma volume at several points in each experiment. In most instances these checked well, within the limits of error of the two methods.

### Results

The results of the experiments are summarized in Tables 1 and 2. Only the data concerning transcapillary refilling are included. Other data obtained in these experiments will be reported in detail elsewhere.

*Effect of Hemorrhage on Plasma Volume.* Figure 1 shows the LVH changes in the two subjects who had sampling only. These curves showed gradual dilution accompanying the multiple small hemorrhages,

TRANSCAPILLARY REFILLING AFTER HEMORRHAGE  
EFFECT OF SAMPLING  
CHANGE IN LVH

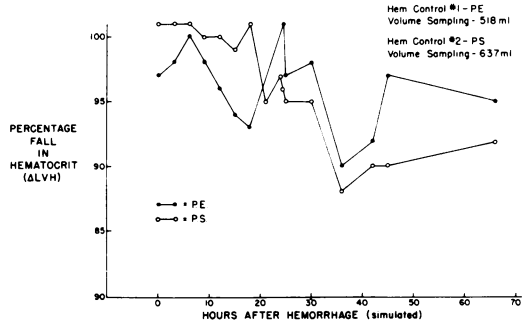


FIG. 1. LVH changes for the control subjects who had sampling only. These are plotted as percentage of prebled hematocrit.

and served to confirm the idea of the sensitivity of the mechanism to small bleeds. They also indicated that calculations of percentage refill had to take into account blood lost in sampling, albeit small.

The LVH changes in the first six subjects who were bled are superimposed in Figure 2. The percentages of hematocrit reduction at 72 hours varied from 13 to 25 and were roughly related to the magnitude of the hemorrhage plus sampling. Individual variations occurred and the relationship was not truly linear.

Figure 3 shows the data plotted for a typical experiment. The lower half of the figure illustrates the curve for *actual* plasma volumes, calculated from changes in LVH. The difference between this curve and the *predicted* curve, drawn in broken line, represents the plasma added due to hemorrhage. Individual hematocrits can be affected in the healthy individual by changes in hydration through the course of the day. These changes are transient and do not affect over-all refilling rates, so that smooth curves have been drawn and refilling rates have been calculated from the curves rather than from the points themselves. The close correlation between the calculated plasma volumes and the plasma volumes measured directly at PV<sub>1</sub> and PV<sub>2</sub> can be seen. These correlations were good in most

\* The term "predicted" is used to refer to the plasma volume which would obtain were no eventuality other than hemorrhage to have occurred; the term "virtual" has been used in other publications<sup>29</sup> to describe the same entity.

TABLE 1

Subject	Vol. of Hemorrhage Plus Sampling, ml.		Prebleed Blood Vol. by Direct Measure, ml.		Blood Vol. 24 Hours Post-bleed, ml.		LVH Pre-bleed, %	LVH 72 Hours, %	Rates of Transcapillary Refilling, ml./hr.			% Re-filling		
	24 Hr.	48 Hr.	RV	PV	RV	PV			0-24 Hr.	24-48 Hr.	0-48 Hr.	24 Hr.	72 Hr.	
J. C.	1,103	1,209	1,220	2,272	2,780	1,689	4,040	46.0	34.3	36.7	14.2	25.5	80	112
D. S.	550	1,182	1,269	2,230	3,343	1,654	4,174	42.9	34.1	35.8	12.5	24.2	73	94
T. G.	500	1,049	1,155	1,914	3,035	1,415	2,990	44.6	34.9	28.3	9.2	18.8	65	82
T. T.	643	751	805	2,355	1,997	1,928	3,459	50.0	43.3	18.8	3.8	11.3	60	66
C. A.	755	909	943	2,124	2,997	1,717	4,175	48.6	37.4	25.8	15.0	20.4	68	103
B. W.	968	1,069	1,085	2,168	2,673	1,712*	3,455*	49.7	38.8	22.1	12.1	17.1	50	82

\* Measured 120 hours after hemorrhage.  
Data for subjects who had hemorrhage alone.

TABLE 2

Subject	Vol. of Hemorrhage Plus Sampling, ml.		Prebleed Blood Vol. by Direct Measure, ml.		Blood Vol. 48 Hours Post-bleed, ml.		LVH Pre-bleed, %	LVH 72 Hours, %	Rates of Transcapillary Refilling, ml./hr.			% Re-filling		
	24 Hr.	48 Hr.	RV	PV	RV	PV			0-24 Hr.	24-48 Hr.	0-48 Hr.	24 Hr.	72 Hr.	
K. D.	450	661	696	1,393	2,353	1,025*	2,530*	43.5	34.1	22.1	11.3	16.7	80	107
W. W.	538	628	648	1,780	2,702	1,403	2,707	44.6	37.8	19.6	7.9	13.8	75	104
J. M.	490	619	660	1,965	2,944	1,592	2,985	47.1	40.3	23.3	3.3	13.3	90	98
W. E.	555	707	729	2,280	3,347	1,882	3,778	45.6	39.1	25.8	5.8	31.6	88	100
J. M.	584	700	722	2,558	3,283	2,164	3,707	48.3	43.6	17.9	2.5	10.2	61	69
W. W.	575	793	801	2,077	3,120	1,651	3,571	44.0	35.2	25.4	15.8	20.6	77	118

\* Measured 24 hours after hemorrhage.  
Data for subjects who had hemorrhage and norepinephrine infusion.

instances. In general, any wide discrepancy was accounted for by an error of injection or sampling technic, an interpretation confirmed by apparent changes in the WBH/LVH ratio. These ratios were constant in most instances, and their occasional inconstancy suggested technical error rather than physiologic change.

A composite picture of transcapillary refilling in these six subjects is seen in Figure 4. The rates of refilling in the first 24 hours varied from 18.8 to 36.7 ml./hr., with an average rate of 27.9 ml./hr. The refilling rates in the second 24 hours were lower. They varied from 3.8 to 15 ml./hr. and averaged 11.1. The over-all 48 hour rates ranged from 11.3 to 25.5 and averaged 19.5 ml./hr. The figures were somewhat lower than those obtained in earlier experiments performed in this laboratory and reported by Moore *et al.*<sup>28</sup> The range of these rates reflects the variation with magnitude of hemorrhage and the attempt of the organism to restore its lost blood volume. The percentages of refilling at 72 hours demonstrate the tendency to

TRANSCAPILLARY REFILLING AFTER HEMORRHAGE

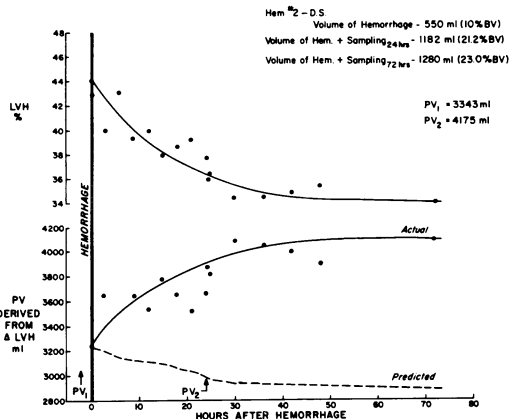


FIG. 3. LVH and plasma volume changes in a typical experiment. The plasma volume curve is derived from LVH at each point (see text). PV<sub>1</sub> and PV<sub>2</sub> are measured directly.

complete refilling, and vary from 66 to 112 per cent with an average of 108 per cent. The smallest percentage of refilling in this group occurred in the individual with the smallest total hemorrhage (T. T.). In the remaining five, the variation between 82 and 112 per cent could not be accounted for by a relationship to initial or total hemorrhage. Healthy individuals vary in their quantitative responses to hemorrhage; limits to the variation are imposed by the general rule of complete refilling, near refilling, or slight overfilling, at 36 to 48 hours.

*Effect of Norepinephrine on Transcapillary Refilling.* The effect of norepinephrine

TRANSCAPILLARY REFILLING IN MAN  
CHANGE IN LVH RELATIVE TO VOLUME LOSS

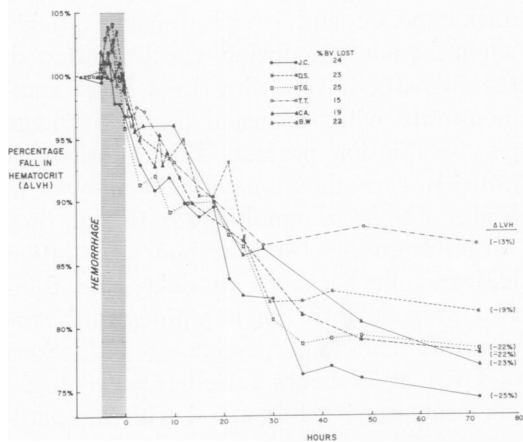


FIG. 2. LVH changes for the six subjects who had hemorrhage alone. The shaded area, representing the period of hemorrhage, is diagrammatic, and does not represent the true duration of each hemorrhage. These durations varied from 15 to 20 minutes.

TRANSCAPILLARY REFILLING AFTER HEMORRHAGE:  
CALCULATED FROM ΔLVH

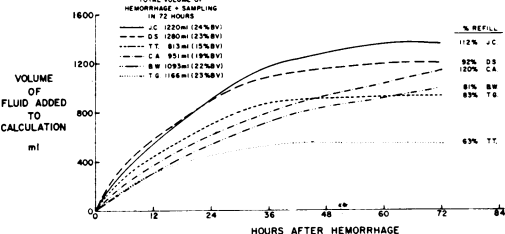


FIG. 4. Transcapillary refilling in the six subjects with hemorrhage alone. These are plasma volumes added to the circulation after hemorrhage, and are derived from LVH.

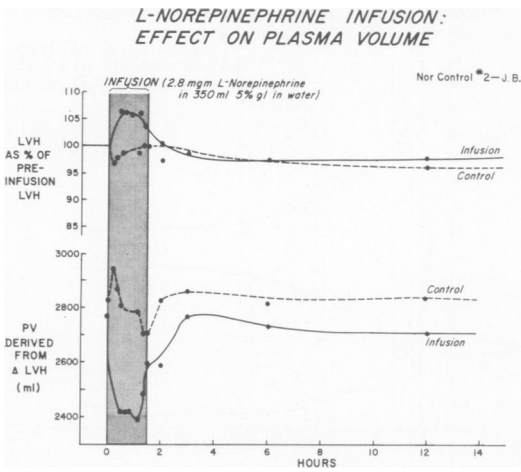


FIG. 5. Effects of norepinephrine alone on LVH and plasma volume, in one of the control subjects. The broken lines represent a study in which only 5.0% glucose in water was infused, at the same rate and with the same sampling as for the norepinephrine infusion.

on the plasma volume was studied in two individuals, not subjected to hemorrhage. Separate experiments in these subjects measured the effects of infusion of 5.0 per cent glucose in water and of sampling. Figure 5 shows these effects graphically. The infusion rates and sampling volumes were the same for the control and norepinephrine experiments and the difference

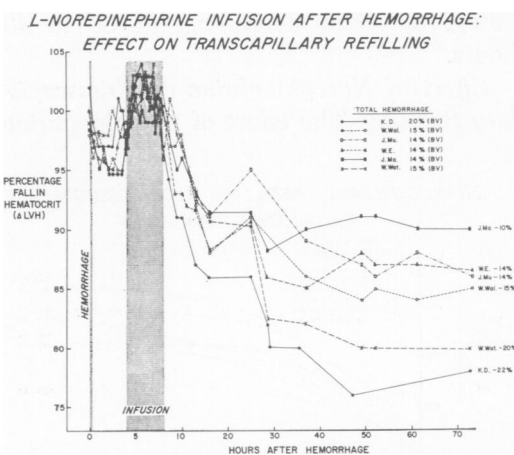


FIG. 6. LVH changes for the six subjects who had norepinephrine infusions after hemorrhage. The duration of infusion is drawn to be four hours for each of the subjects, though these durations varied from two to four hours.

between the two curves was due to the effect of norepinephrine. The LVH increased very quickly after the desired blood pressure elevation was attained, and there were corresponding reductions in plasma volume of 15 per cent (C. M.) and 19 per cent (J. B.). When the norepinephrine was discontinued, the blood pressure returned to normal quickly, and so did the LVH and the plasma volume.

Because of the clear-cut plasma volume reduction in these individuals, and the close time relationship between norepinephrine administration and plasma volume reduction, it was decided to pit the vasopressive substance against the forces of transcapillary refilling.

Figure 6 shows the LVH changes for the six subjects given norepinephrine after hemorrhage. The curves are similar to those for hemorrhage alone, with the exception of the period of the norepinephrine infusion. There was always a hemoconcentration, accompanied by plasma volume reduction, while norepinephrine was being infused. This represented a reversal of the usual homeostatic response, between four and eight hours after hemorrhage, when the rates of transcapillary refilling were greatest. The response was instantaneous and reversed itself quickly when the norepinephrine was discontinued, the hematocrit returning to a level commensurate with the usual posthemorrhage plasma dilution process. The durations of infusions are diagrammatically shown in Figure 6 to be of equal length, though they varied from two to four hours. Duration had no effect except to delay the dilution process until the norepinephrine was stopped. The final percentage reductions of LVH at 72 hours varied from 10 to 22 per cent, varying in general with the magnitude of hemorrhage.

Figure 7 is a chart of the first 16 hours of a characteristic norepinephrine infusion. It shows the falling LVH after hemorrhage, the rise with norepinephrine, and then a

return to hemodilution as the blood pressure returns to the pre-infusion range. Plasma volume expansion over 72 hours, calculated from LVH, is shown for the six subjects in Figure 8. Plasma volume reductions during norepinephrine varied from 220 to 480 ml. or 9.0 to 14 per cent of the pre-infusion plasma volumes. The return to the dilution curve was accompanied by shifts of water into the circulation at rates varying from 100 to 180 ml./hr., a six-fold increase over the usual rates in this rapid phase.

The 24-hour refilling rates were a little lower than in the group with hemorrhage alone. They varied from 17.9 to 25.8 ml./hr. and averaged 21.4 ml./hr. The rates in the second 24 hours averaged 7.8 ml./hr., with a range of 2.5 to 15.8, and the over-all rates for 48 hours varied from 10.2 to 20.6 with an average of 14.6 ml./hr. The percentages of refilling averaged 99, varying from 69 to 118.

**Effects on Plasma Proteins.** Plasma proteins were measured in six subjects, four with norepinephrine and two without. In one individual the concentrations remained unchanged throughout the study, but in the others there was a fall after hemorrhage of 1.4 to 7.2 per cent. Norepinephrine caused a protein concentration which was reversible, and proportional to the hemocentration. After the initial dilution, and excluding the norepinephrine effect, the protein levels remained constant, indicating restoration of protein to the circulation. No consistent changes in the relationship of albumin to globulin were observed.

**Effects on Urine Electrolytes.** Glomerular filtration rates were calculated from endogenous creatinine clearance and no consistent changes were found. The ratio of urinary sodium ion concentration to potassium ion concentration fell consistently with the hemorrhage, and this was unaffected by norepinephrine. Figures 9 and 10 show these changes graphically and are representative of the group. The duration of the

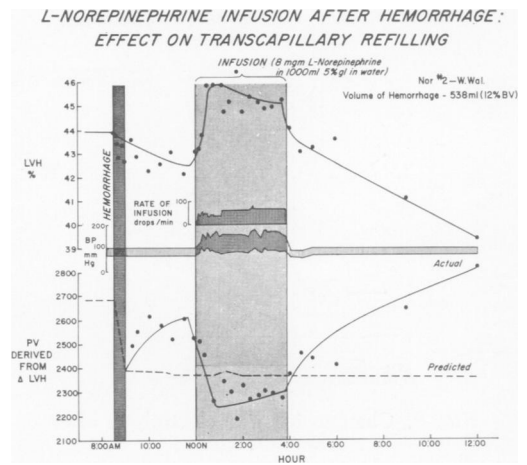


FIG. 7. LVH and plasma volume changes for the first 16 hours following a hemorrhage after which norepinephrine was infused.

lowered Na/K ratio varied from 36 to 60 hours. The aldosterone effect suggested by these alterations was not accompanied by changes in urinary levels of 17-hydroxysteroids or ketosteroids. Serum 17-hydroxysteroids and serum electrolytes were unchanged.

### Discussion

The data obtained in these experiments demonstrate the limits of the response of healthy man to nonshocking hemorrhage, and suggest some of the mechanisms operative in this response. We have used the term "transcapillary refilling" as descriptive of the phenomenon of plasma volume re-

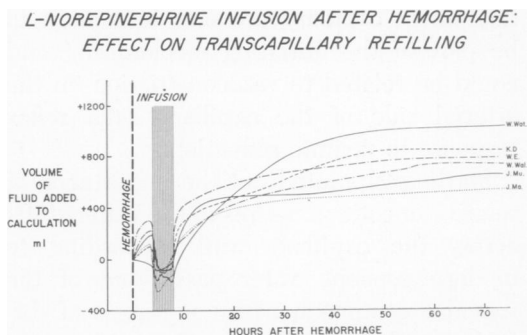


FIG. 8. Transcapillary refilling in the six subjects who had norepinephrine infusions after hemorrhage. Plasma volumes are calculated from LVH.



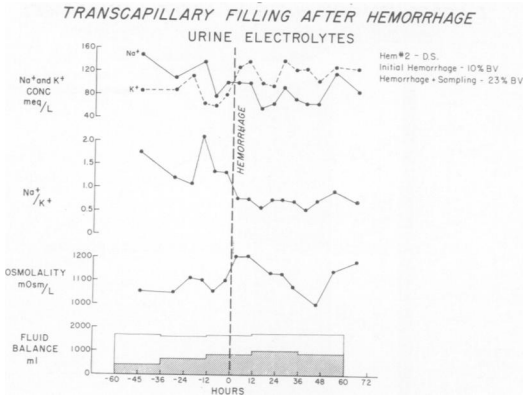


FIG. 9. Changes in urine electrolytes after hemorrhage.

plenishment, but without prejudice as to site or mechanism. The new water entering the plasma volume has come from an area not included in the dilution of plasma-volume tracers, such as T-1824 or radioalbumin; it may enter the bloodstream across peripheral capillaries, via central capillaries, via central capillaries (gut, liver) and thence by thoracic duct, or from the gut or other areas. In any event there is net water transport taking place and this across some rate-linking membranes, here collectively termed a "capillary."

The dependency of plasma dilution after hemorrhage on fall in arterial blood pressure, observed in the dog,<sup>10, 22, 25</sup> does not pertain to man. Reductions of blood volume of 10 per cent were sufficient to initiate the process, and complete refilling occurred even in the small bleeds. Reduction of capillary pressure is thought to be part of the initiating mechanism,<sup>1</sup> and could be related to vasoconstriction on the arterial side of the capillary as a reflex response to volume reduction.

Starling<sup>37</sup> pointed out the importance of relative oncotic pressures in the water shifts across the capillary wall. According to modern concept water passes out of the vascular compartment by a process of diffusion, and this is directly affected by pressure.<sup>8</sup> In the normal situation diffusion predominantly outward at the arterial end of the capillary, and diffusion predomi-

nantly inward at the venous end, reflect the relative hydrostatic and colloid osmotic pressures, and promote a constant balanced exchange of blood water with interstitial water.<sup>17</sup> Lowered capillary hydrostatic pressure affects this balance by favoring inward passage of fluid. The predominant colloid pressure favors diffusion inward toward the plasma also, so long as a clear gradient exists between the albumin concentration on the two sides of the capillary wall.

Evidence in man<sup>18</sup> and in experimental animals<sup>11, 23</sup> suggests that angiotensin increases vascular resistance by causing constriction of precapillary vessels, and that it lowers capillary hydrostatic pressure. If this substance is secreted in response to hemorrhage, it would tend to maintain the blood pressure and at the same time permit expansion of the plasma volume by lowering the capillary hydrostatic pressure.

Norepinephrine causes venular as well as precapillary constriction, and raises the capillary hydrostatic pressure, by a disproportionately high venular effect.<sup>11, 18, 23</sup> When the plasma colloid osmotic pressure is exceeded, the balance of water diffusion is outward and the plasma volume is reduced.

Aldosterone secretion is elevated by hemorrhage.<sup>2, 3, 14, 29, 30</sup> This is indicated in our data by reversal of the urinary  $\text{Na}^+/\text{K}^+$  ratio. Aldosterone secretion is sensitive to changes in extracellular fluid volume and is dependent on an intact kidney, but not on pituitary activity. Mulrow and Ganong<sup>29</sup> have shown that injection of angiotensin restores the aldosterone response to hemorrhage in nephrectomized dogs. Angiotensin appears to underly the chief homeostatic response to hemorrhage, by maintaining blood pressure, promoting repartition of extracellular water toward plasma, and inhibiting sodium and water loss by the kidney.

Plasma protein is added to the circulation after hemorrhage, in sufficient quantity to maintain the protein concentration con-

stant, after an initial fall.<sup>4, 11, 37</sup> Cope and Litwin<sup>9</sup> showed that the dog could restore the necessary amount of protein by way of the thoracic duct. Our data indicate a remarkable maintenance of plasma protein concentrations (both albumin and globulin) after an initial, minor reduction. Considering a mean transcapillary refill of 830 ml., this involves the movement of approximately 40 Gm. of albumin from extravascular sites. If a large component of this comes from some one visceral site (such as the liver) this connotes the storage of preformed plasma proteins at remarkably high concentrations, or its formation at a remarkable rate. By whatever mechanism man maintains his plasma protein concentration during the hemodilution process, this maintenance is necessary for continuation of the process. The rate of refilling is probably affected by the plasma protein concentration. In the earliest postbleed period, when the proteins are normal, or starting to be reduced, the refilling rate is highest. Poor response to hemorrhage by the nutritionally depleted individual may be related to ineffective expansion of the plasma volume, though this speculation requires documentation. In experimental animals, low plasma colloid osmotic pressure<sup>24</sup> and diminished transcapillary refilling<sup>36</sup> are factors in failure of survival.

The surgical patient who has undergone hemorrhage can be expected to have a prolonged period of hemodilution, lasting 36 or 48 hours, during which a continued fall in hematocrit does not necessarily signify continued or renewed hemorrhage. Until the dilution is complete, the hematocrit gives only a partial indication of the extent of hemorrhage.

Norepinephrine, used after hemorrhage, inhibits these normal homeostatic mechanisms, causing a reduced plasma volume at a time when volume expansion is most needed. The hematocrit is distorted upward because of the loss of plasma volume. One might argue that the rise in hematocrit

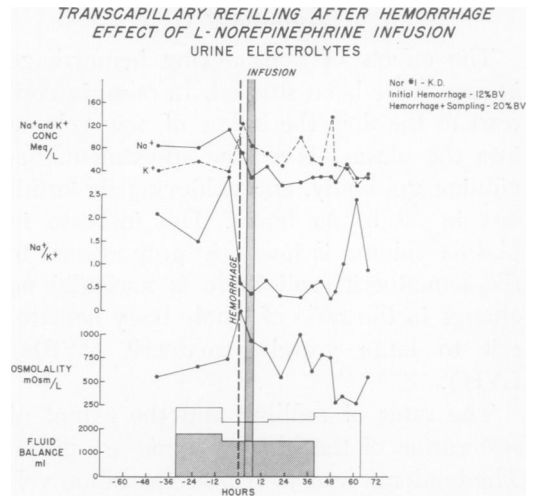


FIG. 10. Changes in urine electrolytes after hemorrhage and norepinephrine infusion.

under norepinephrine administration was factitial, due to erythrocyte *release* or plasma *trapping* in the bloodstream. Separate measurements of the plasma volume at the height of the norepinephrine effect corroborate this as a true reduction in the volume of plasma available for dye dilution. For such to be the result of intravascular *trapping*, one would have to postulate a sequestration of plasma without erythrocytes in a large area of the circulation; the findings are much more suggestive of a filtration or diffusion effect, plasma volume being lost from the circulation without red cells as a result of norepinephrine. As to erythrocyte *release*, the red cell volume remains unchanged over the short term postbleed period.

After cessation of norepinephrine there is a compensatory period of very rapid refilling, bringing the curve of plasma volume back to its expected level in an hour or less. This is of course accompanied by a fall in hematocrit, red cell count, or hemoglobin concentration. These data support the use of added volume to help support the patient during discontinuation of norepinephrine, and additionally account for the brisk fall in hematocrit often seen after norepinephrine is stopped.

### Summary

The effects of nonshocking hemorrhage in man have been studied. In man, in contrast to the dog, the inflow of new volume into the plasma is a slow adjustment, beginning gradually, and achieving its terminus in 36 to 48 hours. The increase in plasma volume is inversely proportional to the hematocrit, and there is normally no change in the ratio of whole body hematocrit to large vessel hematocrit (WBH/LVH).

The rates of refilling and the extent of restoration of the blood volume are given. The tendency was to restore the blood volume to its prebleed level at a mean rate of about 20 ml./hr.

Effects on the glomerular filtration rate were inconstant, but the urinary ratio of sodium to potassium concentration was always reduced, suggesting an aldosterone effect, probably secondary to angiotensin release.

Plasma protein concentrations were reduced at first, but then were restored to the circulation in sufficient quantity to maintain their concentrations in the face of continued hemodilution.

Norepinephrine caused reduction of the plasma volume, and reversed hemodilution in the posthemorrhage period, at the time of its peak rate. The effect of this vasoconstrictor in elevating the capillary hydrostatic pressure, and the reverse effect of angiotensin in lowering the hydrostatic pressure in the capillary, suggest that the balance of these two substances is instrumental in causing the observed water shifts.

Implications as to the clinical use of norepinephrine in patients following hemorrhage are discussed.

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#### DISCUSSION

DR. HENRY SWAN, II (Denver): In 1957 our group presented to this Association a standardized experimental preparation in the dog which consisted of acute rapid arterial bleeding of a selected

percentage of the measured blood volume of the animal, and we hoped that members of this Association would turn to the study of hemorrhage as contrasted to making observations on the artificially induced and maintained oligemic hypertension,