

# THE COLLAPSE PRODUCED BY VENOUS CONGESTION OF THE EXTREMITIES OR BY VENESECTION FOLLOWING CERTAIN HYPOTENSIVE AGENTS<sup>1</sup>

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It is well recognized that interruption of the lower thoracic and lumbar sympathetic nerves, or the administration of certain hypotensive drugs particularly sodium nitrite and the "sympatholytic" agents may cause hypotension and collapse in the erect position. It has been postulated that this hypotensive reaction is due to pooling of blood in the dependent parts of the body, particularly in the splanchnic vascular bed with consequent failure of venous return and, hence, of cardiac output (1).

During studies on the hemodynamic effects of hypotensive drugs in man we have observed sudden and marked reductions of arterial pressure frequently with collapse occurring in the supine position. This phenomenon was induced by subjecting the limbs to brief periods of venous congestion, after the administration of certain hypotensive agents (2). This paper presents data on the types of agents that cause this phenomenon as well as an analysis of the mechanisms whereby the effect is produced.

## MATERIALS AND METHODS

The subjects were patients both hypertensive and normotensive from the hospital wards. Arterial pressure was recorded either by the usual auscultatory method or optically with a Hamilton manometer connected to an 18 gauge needle inserted into the brachial artery.

With the patient in the supine position, inflatable cuffs connected to a large air reservoir bottle were applied proximally to both thighs and one arm and were held in place by covering the cuffs and adjacent skin with gauze bandage. In all of the hypertensive patients the limbs

were congested with a pressure of 100 mm. Hg and in the normotensive subjects at pressures of 60 to 80 mm. Hg. Before and after the administration of each of the various drugs tested the extremities were congested for five minutes unless collapse supervened. After each drug the blood pressure was recorded frequently. The point at which the blood pressure leveled off or began to rise was taken as the point for applying venous congestion. A similar procedure was used in the venesection experiments.

The volume of blood trapped in the congested extremities was determined according to the method of Ebert and Stead (3) following a congestion period of five minutes, instead of seven to 10 minutes as used by those investigators. The shorter congestion period may account for the fact that in the present experiments the volume of blood trapped in the extremities usually was smaller than that observed by Ebert and Stead.

Following the congesting period the pressure in the cuffs was raised to 250 mm. Hg after which the dye T-1824 was injected. Samples were drawn at eight and 10 minutes afterwards. The occluding cuffs were then released and further sampling was carried out at 18 and 20 minutes. The latter samples were used to determine total blood volume while the former were used to determine the volume of that portion of the body not removed from the general circulation by the occluding cuffs. It was found that the dye density values of the eight and 10 minute samples agreed closely with each other indicating that mixing was essentially complete at the end of eight minutes. Similarly the 18 minute were in good agreement with the 20 minute samples. The results of other investigations (4-7) also indicate that in normal subjects equilibration of dye is complete in less than eight minutes. Hence, it seems probable that this method was sufficiently accurate for the present purposes.

The segment plethysmograph used to determine changes in calf volume was the same as that described by Wilkins and Eichna (8) with the exception that proximal and distal blood pressure cuffs were not applied since in the present experiments the plethysmograph was used to determine volume changes rather than blood flow.

In the venesection experiments a 15 gauge needle was inserted into an antecubital vein and the blood introduced

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into a vacuum flask containing 130 cc. of acid citrate dextrose solution (ACD). Immediately following completion of the bleeding period the flask was inverted, and then pressurized by raising it and introducing air into it in order to hasten the return of blood to the circulation.

### RESULTS

#### *Effect of various hypotensive agents in the production of collapse during venous congestion of the extremities*

In the control period, prior to the administration of any drug only two of the 24 subjects exhibited a significant reduction of arterial pressure during congestion of the extremities for a five minute period. In these two cases (G. S. and J. L., Table I) the reductions in average ( $\frac{\text{systolic} + \text{diastolic}}{2}$ ) arterial pressure were 10 and 12 per cent, respectively. Neither of these patients exhibited signs of collapse.

Five patients who received sodium nitrite in doses of 90 to 210 mg. by mouth exhibited changes in average arterial pressure varying from +1 to -44 per cent (mean -25 per cent) during con-

gestion of the extremities. Three of these subjects developed marked hypotension and symptoms of collapse within two to three minutes after the congesting pressures were applied.

Five subjects were given 0.5 mg. of dihydroergocornine (DHO) intravenously. During congestion the changes in average arterial pressure in these patients varied between +6 and -48 per cent (mean -27 per cent). Three of these subjects developed signs of collapse prior to the end of the five minute congesting period.

In three subjects given tetraethylammonium (250 to 400 mg. intravenously) none developed collapse during congestion of the limbs although all exhibited reductions in average arterial pressure varying from -4 to -22 per cent (mean -15 per cent). However, all of the four subjects given the longer acting and more potent ganglionic blocking agent hexamethonium ( $C_6$ ) developed collapse within two to five minutes of venous congestion. The reduction of arterial pressure in this group of patients varied between -16 and -56 per cent (mean -37 per cent).

TABLE I

*The effect of various hypotensive agents on the arterial pressure during congestion of the extremities of unsympathectomized patients*

Pt.	Sex	Age	Drug	Dose and route	Control			Post-drug period			
					Arterial pressure		Change mean* arterial pressure	Arterial pressure		Change mean arterial pressure	Collapse
					Basal	After five min. of congestion		Basal	After five min. or less of congestion		
					<i>mm. Hg</i>	<i>mm. Hg</i>	<i>per cent</i>	<i>mm. Hg</i>	<i>mm. Hg</i>	<i>per cent</i>	
R. M.	M	24	Sodium nitrite	180 mg. P.O.	200/120	190/112	- 5	180/106	155/100	-11	0
A. A.	M	48	Sodium nitrite	120 mg. P.O.	226/128	246/146	+11	170/115	98/66†	-44	+
E. C.	F	43	Sodium nitrite	90 mg. P.O.	225/109	210/118	- 2	178/99	88/70‡	-43	+
M. S.	M	22	Sodium nitrite	180 mg. P.O.	118/68	114/64	- 4	96/50	68/40	-26	+
A. P.	M	28	Sodium nitrite	210 mg. P.O.	180/110	174/110	- 2	170/106	176/106	+ 1	0
K. M.	F	51	DHO	0.5 mg. I.V.	218/120	214/128	+ 1	184/94	90/56	-48	+
J. S.	F	45	DHO	0.5 mg. I.V.	194/110	192/102	- 3	174/90	176/99	+ 6	0
E. M.	F	29	DHO	0.5 mg. I.V.	204/104	191/112	+ 3	188/104	108/56	-43	+
J. G.	M	28	DHO	0.5 mg. I.V.	126/84	111/79	- 9	130/82	95/65	-25	0
S. K.	M	43	DHO	0.5 mg. I.V.	120/82	114/78	- 5	114/76	85/62	-23	+
R. K.	M	49	TEAC	300 mg. I.V.	197/120	212/133	+ 9	160/106	127/89	-19	0
E. S.	F	52	TEAC	250 mg. I.V.	255/142	252/149	+ 1	236/146	220/142	- 4	0
J. L.	M	28	TEAC	400 mg. I.V.	140/80	118/78	-12	128/80	100/62	-22	0
G. S.	M	42	C <sub>6</sub>	50 mg. I.V.	180/110	160/100	-10	160/100	80/60	-56	+
A. J.	F	49	C <sub>6</sub>	50 mg. I.V.	170/120	164/126	- 3	128/80	90/80	-25	+
T. B.	M	40	C <sub>6</sub>	50 mg. I.V.	170/110	155/120	- 2	110/80	85/75	-16	+
L. M.	M	37	C <sub>6</sub>	50 mg. I.V.	170/115	160/120	- 1	150/110	75/155	-50	+
S. W.	M	54	Sodium amytal	0.25 gm. I.V.	231/118	220/123	- 2	200/110	192/110	- 6	0
A. L.	M	27	Sodium amytal	0.75 gm. I.V.	130/96	122/92	- 5	128/100	118/100	- 5	0
E. S.	M	61	Sodium amytal	0.5 gm. I.V.	180/104	176/108	0	138/100	124/96	- 8	0
B. G.	M	38	Veratrone	0.8 cc. I.M.	210/128	204/124	- 3	164/96	162/100	+ 1	0
C. B.	F	56	Veratrone	1.0 cc. I.M.	272/180	276/182	+ 1	142/94	146/100	+ 4	0
J. Mc.	M	52	Vertavis	40 CRAW V.PO.	265/160	266/165	+ 1	155/117	145/131	+ 2	0
E. S.	F	52	Vertavis	40 CRAW V.PO.	255/142	252/149	+ 1	200/112	196/114	- 1	0

\* "Mean" arterial pressure =  $\frac{\text{svstolic} + \text{diastolic pressure}}{2}$ .

† Collapse occurred 2½ minutes after application of congesting pressure.

‡ Collapse occurred two minutes after application of congesting pressure.

TABLE II

*The amount of blood trapped in the extremities subjected to venous congestion before and after sodium nitrite, dihydroergocornine and hexamethonium*

Subject	Control			After drug			
	Volume of blood in trunk, head and arm	Total blood volume	Blood trapped in congested limbs	Drug dose and route	Volume of blood in trunk, head and arm	Total blood volume	Blood trapped in congested limbs
J. G.*	cc. 4,700	cc. 6,350	cc. 1,650	DHO 0.5 mg. I.V.	cc. 4,860	cc. 6,400	cc. 1,540
S. K.*	4,150	5,480	1,330	DHO 0.5 mg. I.V.	4,070	5,460	1,390
M. S.*	4,040	5,075	1,025	Sodium nitrite 210 mg. P.O.	4,055	5,020	965
R. M.*	2,990	4,230	1,240	Sodium nitrite 180 mg. P.O.	3,010	4,280	1,270
I. P.	5,540	6,660	1,120	Hexamethonium 50 mg. I.V.	5,450	6,540	1,090

\* Data on the changes in arterial pressure given in Table I.

No significant reductions of arterial pressure occurred during congestion of the extremities of three patients given 0.25 to 0.75 gm. of sodium amytal intravenously, two subjects given 0.8 or 1.0 cc. of Veratrone (tincture of veratrum viride) intramuscularly and two patients given 40 Craw units of Vertavis (whole powdered root and rhizomes of veratrum viride) orally. In all of the latter cases significant reductions of basal arterial pressure had occurred following the administration of veratrum viride.

The signs and symptoms related to the collapse state induced by sodium nitrite and the "sympatholytic" agents during congestion of the extremities resembled those observed in other types of acute hypotension such as carotid sinus and vaso-vagal syncope, or postural hypotension. The pulse pressure became small and bradycardia frequently developed. Pallor, yawning, sweating and vomiting sometimes occurred. The patients experienced faintness, giddiness and at times nausea.

For example, patient E. C. (Table I) who received 180 mg. of sodium nitrite by mouth 30 minutes prior to congestion exhibited a marked reduction of arterial pressure from 178/100 to 88/70 mm. Hg within three minutes after the venous tourniquets had been applied. Accompanying the hypotensive response there was profuse sweating, pallor and bradycardia. The patient complained

of faintness and nausea. Release of the congesting pressure at this time and tilting the patient into a five degree head-down position failed to relieve her symptoms. The arterial pressure continued to fall and one minute after releasing the pressure in the cuffs it was 48/33 mm. Hg and the heart rate was 58 per minute. Four minutes after releasing the congesting pressure the arterial pressure had risen to 110/78 mm. Hg and the heart rate to 72 per minute at which time the patient felt improved.

#### *The amount of blood trapped in the congested limbs*

In one hypertensive and four normotensive subjects the amount of blood trapped in the congested limbs was determined by the dye method of Ebert and Stead (3). In the control period the amount of blood present in both lower extremities and one upper extremity during congestion varied between 1,025 and 1,650 cc. with a mean of 1,273 cc. (Table II, Figure 1). There were no significant changes in arterial pressure. Two subjects received sodium nitrite, two were given DHO and one received hexamethonium. During the congestion period following these drugs all of the subjects exhibited significant reductions of arterial pressure and three developed marked hypotension and symptoms of collapse (Table II). The latter occurred two to

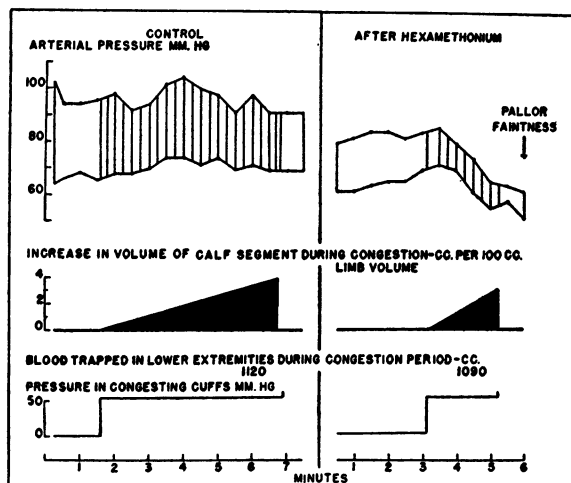


FIG. 1. CHART OF ARTERIAL PRESSURE, INCREASE IN VOLUME OF CALF SEGMENT, AMOUNT OF BLOOD TRAPPED IN THE EXTREMITIES AND CONGESTING CUFF PRESSURES BEFORE AND AFTER INTRAVENOUS HEXAMETHONIUM (50 mg.) IN SUBJECT I.P., NORMAL MALE, AGED 28

In the control period the arterial pressure was well maintained during venous congestion of the extremities for 5½ minutes. Following hexamethonium and 2½ minutes after the venous tourniquets had been applied, hypotension and collapse developed. However, the amount of blood trapped in the congested extremities was less and the increase in volume of the calf segment was not as great as in the control period.

four minutes after the beginning of congestion. This necessitated application of occluding pressure prior to the end of the five minute congestion period. This was done in order to prevent blood from either entering or leaving the limbs while the patient was tilted into a head-down position and allowed to recover during the time that the blood volume determinations were being completed.

The amount of blood present in the congested limbs during the experimental period varied between 965 and 1,540 cc. (mean 1,263 cc.). In two subjects there was a slight increase in the amount of blood trapped in the limbs in the post-drug as compared to the pre-drug congestion period and in three cases a slight decrease. In no case did the pre-and post-drug values vary from each other by more than 12 per cent.

#### *Changes in calf volume during venous congestion of the extremities*

In order to corroborate these observations indicating that no more blood is trapped in the limbs during venous congestion after as compared with before the administration of agents which induce "congestion collapse," the volume changes in the calf were measured using a plethysmograph. Hexamethonium was administered to all of the subjects.

In the control period the increase in volume of the calf segment during four and one-half to six and one-half minutes of venous congestion varied between 2.4 to 5.2 cc. per 100 cc. of limb volume (mean 3.8 cc.) (Table III, Figure 1). Hypotension did not occur in any of these subjects.

After hexamethonium five of the six subjects developed severe hypotension during periods of congestion of one and one-half to four minutes. The increase in calf volume varied between 2.0 and 3.6 cc. (mean 2.7 cc.). Subject P. G. did not develop severe hypotension during application of venous tourniquets for five and one-half minutes. The *rate of increase* in calf volume during congestion usually was greater after as compared to before hexamethonium (Figure 1). However, in

TABLE III

*The increase in volume of the calf segment during application of venous tourniquets before and after the administration of hexamethonium*

Subject	Control			After hexamethonium (50 mg. I.V.)		
	Increase in volume of calf segment	Duration of venous congestion	Development of hypotension	Increase in volume of calf segment	Duration of venous congestion	Development of hypotension
	cc. per 100 cc. limb volume	minutes		cc. per 100 cc. limb volume	minutes	
A. G.	3.0	5½	0	2.8	1½	+
I. P.	4.0	5½	0	3.0	2½	+
A. H.	5.2	6½	0	2.3	2½	+
P. G.	2.8	4½	0	5.0	5½	0
J. D.	3.0	5	0	3.6	4	+
L. B.	2.4	6½	0	2.0	1½	+

TABLE IV

*The effect of dihydroergocornine (DHO), hexamethonium (C<sub>6</sub>), and sodium nitrite on the arterial pressure and heart rate following venesection and subsequent return of the removed blood to the circulation*

Pt.	Drug, dose and route	Before drug		After drug and before venesection		During venesection				During return of removed blood			
		Arterial pressure	Heart rate	Arterial pressure	Heart rate	Blood re-moved	Time from beginning of venesection	Arterial pressure	Heart rate	Blood re-turned	Time from beginning of return	Arterial pressure	Heart rate
		mm. Hg	per min.	mm. Hg	per min.	cc.	minutes	mm. Hg	per min.	cc.	minutes	mm. Hg	per min.
L. H.	C <sub>6</sub> 50 mg. I.V.	170/100	82	140/80	86	100	2	128/80	92	100	2	130/70	81
						200	3	120/75	92	200	8	140/80	80
						300	4	115/75	100	300	16	150/85	80
						400	8	105/70	100	400	21	172/94	80
						500	12	98/60	80	500	26	180/96	82
J. B.	C <sub>6</sub> 50 mg. I.V.	220/120	88	140/90	84	100	1	120/80	84	100	1	90/65	84
						200	2	120/85	80	200	2	100/70	80
						300	5	115/75	80	350	4	130/90	80
						400	6	98/70	88	450	7	135/95	76
						500	8	80/65*	80	500	9	140/100	76
M. D.	DHO 0.5 mg. I.V.	130/100	84	130/100	84	100	2	115/85	80	100	3	110/80	88
						200	4	110/85	92	200	6	105/80	84
						300	7	108/82	96	300	7	100/85	80
						400	12	100/80	96	400	9	110/85	80
						500	15	96/72	104	500	12	110/90	72
M. C.	DHO 0.5 mg. I.V.	220/160	80	220/140	80	100	2	190/120	80	125	4	160/110	76
						200	4	140/105	76	250	9	180/120	76
						250	5	120/90*	80				
E. A.	NaNO <sub>2</sub> 210 mg. P.O.	122/82	94	122/82	96	100	2	108/84					
						200	5	110/82					
						300	9	108/78					
						400	17	105/72					
E. R.	NaNO <sub>2</sub> 240 mg. P.O.	240/140	60	180/120	84	100	1	180/120	92	120	2	135/95	80
						200	4	150/100	92	200	3	145/100	76
						300	7	150/110	96	300	7	145/110	80
						400	10	160/100	104	400	11	160/120	72
						525	15	125/85	84	525	15	160/120	72
W. O.	NaNO <sub>2</sub> 120 mg. P.O.	190/115	80	195/112	80	150	1	165/110	84	150	2	160/108	84
						300	2	155/110	88	400	4	150/110	80
						400	4	155/110	88	500	6	160/110	82
						500	6	155/110	88				

\* Yawning, pallor, feels faint.

four of the five patients who developed hypotension during the post-drug congestion period marked reduction in arterial pressure occurred before the *total* increase in calf volume was as great as that observed at the end of the pre-drug congestion period.

The estimation of the amount of blood trapped in the congested limbs as determined by the plethysmographic method agrees approximately with that obtained by the dye method. Previous studies estimate that about 750 cc. of blood are normally present in the lower extremities (3). The average amount of blood found in the congested extremities

was 1,270 cc. Thus, the excess of blood pooled out was approximately 1,270 - 750 or 520 cc. Using the plethysmographic method the average increase in calf volume during the control period was approximately 5.6 cc. per 100 cc. of limb volume. If the volume of both lower extremities is estimated to be approximately 10 liters the amount of blood pooled out would be 5.6 × 100 or 560 cc. It should be emphasized that this is a crude estimation since the plethysmograph measures the volume change in only one segment of the limb which may represent a selective rather than a representative portion of the vascular bed being congested.

*Effects of certain hypotensive drugs on the arterial pressure during venesection*

Seven patients, of whom five were hypertensive, were bled rapidly from an antecubital vein with removal of 250 to 525 cc. of blood (Table IV). Two patients received 0.5 mg. of dihydroergocornine intravenously, two were given 50 mg. of hexamethonium by the same route and three received 120 to 240 mg. of sodium nitrite orally. All of these patients exhibited reductions of average arterial pressure varying from  $-10$  to  $-42$  per cent; in five patients the reduction exceeded  $-24$  per cent. Two patients developed signs of collapse after withdrawal of 250 and 500 cc. of blood, respectively.

The arterial pressure did not fall precipitously at any point in the bleeding period. Instead there usually was a stepwise decrease with each 100 cc. of blood removed (Table IV and Figure 2). Similarly on returning the blood to the circulation the increase in arterial pressure paralleled the rate at which the blood was reinfused. Thus, there was no evidence of a critical amount of blood loss as in

untreated subjects beyond which "compensation" fails and the arterial pressure falls suddenly.

As a control the arterial pressures of eight blood donors were measured during venesection. No pretreatment with hypotensive agents had been given. The removal of 500 cc. of blood at a similar rate from each of the donors resulted in a decrease of average arterial pressure of  $-8$  to  $+2$  per cent (average  $-3$  per cent).

*Absence of congestion collapse after hypotensive drugs in partially sympathectomized subjects*

Eight hypertensive patients who had undergone either a lumbodorsal, or a transthoracic splanchnicectomy four months to five years previously were studied. Two patients received sodium nitrite in doses of 150 to 180 mg. orally, one received 0.3 mg. of the mixed dihydrogenated alkaloids of ergot (CCK) intravenously and five were given 50 mg. of  $C_6$  intravenously (Table V). In only two subjects were significant decreases in average arterial pressure observed ( $-11$  and  $-22$  per cent, respectively) during the post drug con-

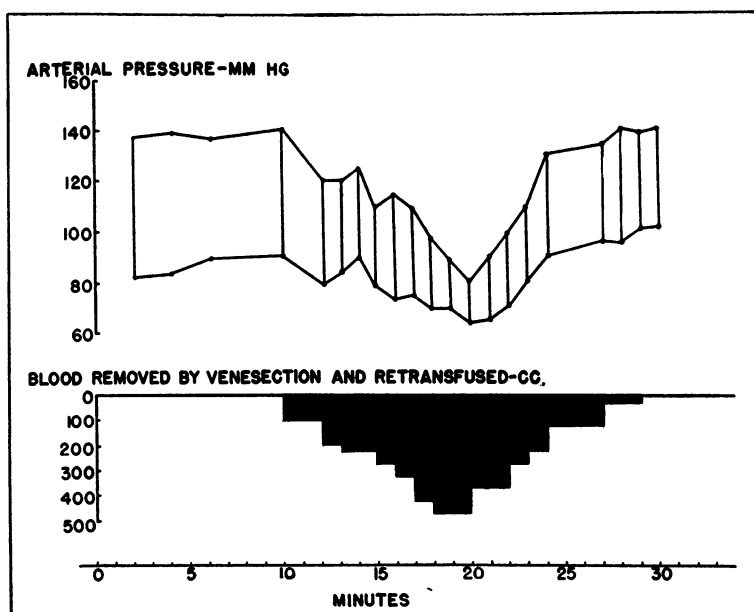


FIG. 2. CHART OF ARTERIAL PRESSURE AND THE AMOUNT OF BLOOD REMOVED BY VENESECTION AND RETRINFUSED IN PATIENT J. B., FEMALE, AGED 48

Hexamethonium (50 mg.) was given intravenously 30 minutes prior to beginning the venesection. Yawning, pallor and a feeling of faintness developed when the blood pressure fell to its lowest point.

TABLE V

*The effect of sodium nitrite, C<sub>6</sub> and CCK on the arterial pressure during congestion of the extremities of sympathectomized patients*

Pt.	Sex	Age	Drug	Dose and route	Control			Post-drug period			
					Arterial pressure		Change mean* arterial pressure	Arterial pressure		Change mean arterial pressure	Collapse
					Basal	After five min. of congestion		Basal	After five min. of congestion		
					mm. Hg	mm. Hg	per cent	mm. Hg	mm. Hg	per cent	
M. C.	F	44	Sodium nitrite	150 mg. P.O.	164/100	159/104	0	156/101	160/105	+ 3	0
P. D.	M	38	Sodium nitrite	180 mg. P.O.	170/110	168/108	-2	146/94	134/90	- 7	0
H. F.	M	36	CCK	0.3 mg. I.V.	212/128	215/135	+3	225/135	220/140	0	0
H. M.	F	43	C <sub>6</sub>	50 mg. I.V.	210/125	200/130	-1	150/90	160/95	+ 6	0
M. D.	F	44	C <sub>6</sub>	50 mg. I.V.	190/120	185/120	-1	140/100	130/100	- 4	0
D. H.	F	35	C <sub>6</sub>	50 mg. I.V.	220/140	205/140	-5	140/120	140/120	0	0
C. M.	M	47	C <sub>6</sub>	50 mg. I.V.	210/140	210/138	-1	170/125	140/120	-11	0
P. D.	M	38	C <sub>6</sub>	50 mg. I.V.	164/110	160/108	-2	124/95	90/60	-22	0

\* "Mean" arterial pressure =  $\frac{\text{systolic} + \text{diastolic pressure}}{2}$ .

gestion period. Neither of these subjects developed signs or symptoms of collapse. Six of the eight had significant reductions of basal arterial pressure following the hypotensive agents and all of these exhibited increased postural hypotension.

#### DISCUSSION

The development of collapse during venous congestion of the extremities has been observed in normal subjects (3) and in patients who have suffered recent blood loss (9). Our observations indicated, however, that patients given certain hypotensive agents are unusually susceptible to the development of collapse produced by venous tourniquets and/or hemorrhage. The type of hypotensive agents producing this phenomenon were those which also cause postural hypotension (10, 11), that is, sodium nitrite, hexamethonium, tetraethylammonium and the dihydrogenated alkaloids of ergot; whereas hypotensive drugs such as veratrum viride and sodium amytal which do not ordinarily cause postural hypotension also did not induce congestion collapse.

The increased susceptibility to collapse during venous congestion following sodium nitrite and the sympatholytic agents conceivably might be due to one of several mechanisms. Ebert and Stead have demonstrated that considerable amounts of blood may be trapped out of the central circula-

tion during venous congestion of the limbs (3). They showed that if venous tourniquets were applied for ten minutes or longer almost 30 per cent of the total blood volume may be present in the congested extremities resulting in collapse even in normal untreated subjects. It should be noted that the period of venous congestion had to be longer than five minutes to produce collapse in these untreated subjects. Since, in the present experiments with sodium nitrite and the "sympatholytic agents" hypotension appeared early in the congestion period it seemed possible that these agents induced greater pooling of blood in the congested extremities. This might have resulted from a reduction of "post-arteriolar tone" in the congested limbs produced by these drugs. The increased vascular capacity would thus produce critical loss of blood volume from the central circulation. However, this possibility was disproven by actual measurement of blood volume trapped in the limbs which demonstrated that despite the appearance of hypotension no more blood was trapped out during the post-drug as compared to the control congestion periods.

Plethysmographic measurement of the increase in volume of the calf during congestion also failed to reveal a greater increase in calf volume after as compared with before administration of these agents. In several instances the *rate* of increase in

calf volume was greater following the drug suggesting a decrease in arteriolar and/or post-arteriolar tone (or a failure of reflex arteriolar constriction in the limb). However, marked hypotension occurred before the *total* volume increase was as great as that achieved at the end of five minutes of congestion in the control period. Thus, the observed changes in calf volume provided additional confirmatory data that the collapse was not associated with increased amounts of blood trapped in the limbs.

The increased rate of blood loss to the extremities following these hypotensive agents may have contributed somewhat to the collapse reaction by producing a rapid decrease in venous return and hence of cardiac output. However, the venesection experiments demonstrated that increased rate of blood loss was not the major cause of the hypotensive reaction. Figure 2 shows that the arterial pressure fell despite gradual removal of 500 cc. of blood over a period of eight minutes, whereas a similar rate of removal in the control subjects of these venesection experiments had no significant effect on the arterial pressure.

Another possible explanation for the increased susceptibility to congestion collapse was that the hypotension was due to failure of homeostatic vasoconstriction either arteriolar, post-arteriolar or both, in areas other than in the congested limbs (12). The vascular system in essence is composed of a pump, an arterial conduit leading to a capillary reservoir and a return or venous conduit. The capillary reservoir which has a huge capacity in comparison to the total blood volume is capable of considerable variation in volume. If the reservoir were to enlarge to its full capacity blood would be lost from the large conduits, whereas if it became smaller an excessive amount of blood would be forced into the central circulation. If this closed system were static, blood loss would produce a fall in pressure throughout and a diminution of venous return. However, since the normal vascular system is dynamic, the capillary reservoir is capable within certain limits of reducing its capacity in proportion to the degree of blood loss. Thus, the venous conduit remains filled and venous pressure and return are maintained. Certain hypotensive agents by doing away with the ability to reduce the volume of the capillary beds convert the vascular

ture into a more static system with the result that during blood loss the pressure falls throughout and venous return fails.

If the collapse were due to failure of compensatory reactions to minor degrees of blood loss from the central circulation it would be expected that moderate blood loss by any route including venesection would produce a similar hypotensive reaction. After the administration of sodium nitrite, the mixed dihydrogenated alkaloids of ergot or hexamethonium, hypotension and collapse did occur following blood loss by venesection in amounts insufficient to induce significant hypotension in untreated individuals. These venesection experiments, therefore, provided direct evidence that the collapse during the post-drug congestion period was due to failure of compensatory vasoconstriction in the presence of relatively small amounts of blood loss.

The present data are not inconsistent with previous observations that sodium nitrite reduces "venous" (post-arteriolar) tone but does not prevent sympathetic vasoconstrictor reflexes involving the arterioles (10, 11). In the prior studies graded congesting pressures of 10 to 50 mm. Hg were applied for brief periods of only a few seconds to demonstrate the reduction in post-arteriolar tone (10). However, it must be emphasized that the congesting pressures of 60 to 100 mm. Hg used in the present experiments are far higher than those normally present in the capillaries and venules (13). When such pressures are applied for as long as five minutes maximum filling of the post-arteriolar vascular bed must occur whether or not sodium nitrite has been given. This accounts for the fact that no more blood was trapped out after as compared to prior to sodium nitrite. Collapse occurs in the post-nitrite congestion period not because of a greater total amount of blood pooled in the limbs but rather from failure of a compensatory reduction in the volume of the post-arteriolar vascular bed in areas other than in the congested limbs. Although this action of sodium nitrite is not definitely clarified the available data imply that while the drug does not prevent arteriolar constriction it must have some paralytic action on the post-arteriolar blood vessels (10). In this respect it differs from the sympatholytic agents which markedly inhibit reflex arteriolar constriction (11).



Perhaps of greater significance was the observation that withdrawal of a relatively small amount of blood by venesection, that is, 100 cc. or 2 to 3 per cent of the total blood volume, resulted in a perceptible decrement in arterial pressure after premedication with a hypotensive drug. This was particularly apparent after hexamethonium, a drug which apparently produces relatively complete sympathetic blockade in man (14). Such observations provide an index of the sensitivity of the homeostatic regulators of the circulation. These data suggest that in the normal, untreated individual losses of less than 5 per cent of the total blood volume stimulate compensatory decreases in the capacity of the vascular tree.

Following administration of adequate doses of the sympatholytic agents the subsequent level of arterial pressure depended in large measure on the position of the patient. A head down posture usually prevented marked hypotension while a slight head up tilt of the body precipitated collapse. In the supine patient following the administration of  $C_6$  marked reductions in arterial pressure could be induced either by tilting, venous tourniquets or moderate degree of blood loss by venesection. These observations are consistent with the concept that the sympathetic vasoconstrictor nerves and associated medullary vasomotor centers are primarily concerned with the rapid reflex adjustment of the capacity of the vascular system, toward regulation of arterial pressure under stress, rather than in the primary regulation of the "basal" level of blood pressure.

The resistance of partially sympathectomized subjects to collapse during venous congestion appears most likely to be related to the mechanisms which result in a gradual restoration of vascular "tone" in denervated areas. This resumption of tone is seen in the disappearance of increased blood flow in the forearm (15), in the hand (16), and in the hepatic-portal circuit (17) after regional sympathectomy as well as the gradual diminution of postural hypotension in patients who have undergone extensive splanchnicectomy (18). The mechanism whereby vascular tone is regained is unknown (19), but apparently, as evidenced by the present experiments, it results in attainment of at least partial homeostasis without dependence on local sympathetic vasoconstrictor reflexes.

# SUMMARY AND CONCLUSIONS

1. The prior administration of sodium nitrite, the dihydrogenated alkaloids of ergot, hexamethonium, and to a lesser extent tetraethylammonium to normotensive or hypertensive patients resulted in a state of increased susceptibility to the development of hypotension and collapse when the limbs were congested with venous tourniquets.

2. Veratrum viride and sodium amytal did not produce this effect.

3. Measurement of the volume of blood trapped in the limbs (dye method) and the increase in volume of the calf (plethysmograph) indicated that the hypotension and collapse were not due to pooling of excessive amounts of blood in the congested limbs.

4. The hypotension and collapse were due to failure of compensatory vasoconstriction in other areas than in the congested extremities following moderate blood loss. This was demonstrated by the observation that after the administration of sodium nitrite, the mixed dihydrogenated alkaloids of ergot or hexamethonium hypotension frequently with collapse occurred during venesections of only 250 to 525 cc. of blood.

5. After these drugs loss of as little as 2 to 4 per cent of the total blood volume frequently resulted in perceptible decrements of arterial pressure. Such observations illustrate the extreme sensitivity of the homeostatic vasoconstrictor mechanisms in the normal (untreated) individual.

6. Patients who had previously undergone lumbar or transthoracic sympathectomy were more resistant to hypotension during the post-drug congestion period than were non-sympathectomized subjects. This resistance probably was related to the well known return of independent vascular tone in sympathectomized areas.

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