Experimental Studies on the Relationship between the Elevated Venous Pressure and Osmolal Arterio-Venous Difference*

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For the water-balance across the capillary walls Starling's hypothesis has been widely accepted. Hayase and his coworkers reported that the osmolal arterio-venous difference (referred to hereafter as osmolal A-V difference) in the limbs of patients with congestive heart failure was often negative and that the venous pressure showed a rough negative correlation with osmolal A-V difference. In order to clarify the mechanisms underlying this phenomenon, the present author carried out a series of animal experiments where a balloon was inflated at various parts of the systemic or pulmonary venous system in dogs to increase the venous pressure of the up-stream regions. During the systemic venous congestion, the osmolal A-V difference shifted towards the negative side locally; in the case of the pulmonary venous congestion, the systemic osmolal A-V difference tended to shift towards the positive side. The negative shift of osmolal A-V difference caused by the elevation of the systemic venous pressure was inhibited by the pre-treatment with pentolinium or reserpine but it was not influenced by atropine or vagotomy. Therefore, the phenomenon in question appears to be related to the sympathetic nervous system. There are evidences indicating that the substance(s), responsible for the observed shift in osmolal A-V difference was mainly sodium.

The results shown in the present paper suggest that the increase in venous pressure is associated with a certain change in the capillary exchange of the peripheral circulation.

FOR water-balance at peripheral capillaries, Starling's hypothesis¹ has been widely accepted. This hypothesis states that both the amount of body fluid passing through capillary walls and the direction of this transfer are governed by the following driving forces: capillary pressure, tissue pressure, colloid osmotic pressure of blood plasma and colloid osmotic pressure of tissue fluid. According to this hypothesis, crystalloidal osmotic pressure of fluids exerts no influence on the fluid equilibrium across capillary

walls and an increase in venous pressure (that is, of capillary pressure) simply results in an increase of filtration of water and solutes from blood vessel into surrounding tissue. MAEKAWA and SAIMYOJI² reported that venous pressure was positively correlated with osmotic pressure of the venous blood plasma in patients with congestive heart failure in dehydrated state. HAYASE and his coworkers³⁻⁷ found that the peripheral osmolal A-V difference in patients of congestive heart failure often assumed negative values. Thus

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they found that, in patients with compensated or decompensated heart failure from valvular disease or congenital heart disease, the peripheral venous pressure was negatively correlated with the osmolal A-V difference. With the systemic venous congestion, the regional osmotic pressure of blood plasma was higher in the congested vein than in the inflowing arterial blood, making the osmolal A-V difference negative. These facts suggest that, under the systemic venous congestion, some substance(s) should be transferred from tissue to blood, or else, there should be a flow of water alone, or water in excess of solutes, from blood into tissue. It is highly likely that there is some abnormality in the tissue-blood-transfer of low molecular substances in the regional capillary vessels subjected to venous congestion. Redistribution of tissue blood flow

accompanying venous congestion was reported by JOHNSON et al^{8,9} and MELLANDER et al¹⁰ but no report is yet available about the tissue-blood-transfer of osmotically active substances in venous congestion. The experiments reported in the present paper attempt to establish factually the phenomena of the congestion-induced transfer of osmotically active substances described above and to clarify the underlying mechanism with a series of animal experiments.

MATERIALS AND METHODS

Mongrel dogs weighing 10 to 22 kg (mean: 14.5 kg) were employed. All dogs, except those reserpinized, were anesthetized with 25 to 30 mg/kg of intravenous pentobarbital. In reserpinized dogs, pentobarbital was used in doses about one third of this, intravenously, using the loss of corneal reflex as the end-point. Experimental arrangement is illustrated in Fig. 1. All experiments were performed on dogs breathing naturally through the cuffed endotracheal tube. Courmand's catheters (No. 8) provided with a balloon at the tip were introduced through the right external jugular vein into superior vena cava (SVC) (a little above the right atrium), right atrium (RA), inferior vena cava (IVC) (a little below the right atrium and above the diaphragm) or iliac vein, under fluoroscopic control. With balloon fixed at the desired position, it was inflated in order to increase the venous pressure upstreams, and the air contents of the balloon was regulated to keep the elevated venous pressure nearly constant. Peripheral venous pressure was measured at the right median vein and the right femoral vein using the water manometer. In the case of left atrial experiment, after a balloon-catheter was inserted into the left atrium (LA), another Courmand's catheter (No. 8) was advanced, via the right external carotid artery, into the left atrium until the tip was located close to the pulmonary veins beyond the balloon. The third catheter was advanced into RA via the right external jugular vein, and blood pressure of both right and left atria were recorded with electromanometers MP-24T, Nihon-Kohden Co., Ltd. Blood was sampled from T-tubes applied to the carotid artery and jugular vein and/or femoral artery and vein, using a syringe wetted with heparin before and after the elevation of venous pressure. The blood samples were immediately centrifuged at 2,000 r.p.m. for 20 minutes and blood plasma was separated. Osmotic pressure of the plasma samples were measured by Fiske's osmo-

Fig. 1. Experimental arrangement for the artificial production of systemic venous congestion. Under anesthesia with pentobarbital, a catheter provided with a balloon at the tip was introduced into SVC, RA, IVC or iliac V. as shown in the figure. Balloon inflation at one of these sites caused venous congestion in the tributaries of the occluded vein. Venous pressure were measured at median vein and femoral vein by a water manometer. The T-tubes and syringes applied to the carotid artery, jugular vein, femoral artery and vein are for blood sampling before and after the venous congestion.

meter, Model No. G-62. Since the plasma was allowed to contact with air during these procedures, the plasma was air-equilibrated. In some experiments, the plasma Na concentration was also measured by flame photometer, Instrumentation-Laboratory Model 143. All experiments were started after allowing 30 minutes to elapse after the surgical intervention, such as exposing and cannulating, with T-tubes, the femoral artery and vein as well as the carotid artery and jugular vein and advancing the balloon-catheters into the SVC, RA, IVC, iliac V. or LA. Once an experiment was started, no attempt was made to add anesthetics or switch to the use of an artificial respirator. The author simply excluded those dogs from the present consideration which began awakening from anesthesia or became breathless during the course of an experiment. Preliminary studies showed that, during venous congestion, there was no appreciable local hemoconcentration, as evidenced by alterations in A-V difference in hematocrit and plasma protein concentration. Pentolinium tartrate (Ansolsen), atropine sulfate and reserpine were employed in some experiments. Pentolinium tartrate was injected intravenously in dose of 1 mg/kg, atropine sulfate intramuscularly in dose of 1 mg/kg, reserpine was injected intramuscularly in dose of 0.5 to 0.3 mg/kg on the first day and 0.25 to 0.20 mg/kg on the next day, depending on the condition

of animal, and the experiment was carried on the third day.

RESULTS

I. Preliminary Experiment

i) Stability of osmolal A-V difference

Table I shows the results of a test of the reliability of Fiske's osmometer, the apparatus employed for measurement of osmotic pressure of blood plasma. In 9 tests with a standard solution of 100 mOsm/kg-H₂O the scatter of the readings was such that the standard deviation (SD) was 0.7 mOsm/kg-H₂O. For 8 tests with standard solution of 500 mOsm/kg-H₂O, the SD of the readings was 1.5 mOsm/kg-H₂O. The readings for the same sample of dog's plasma gave a SD of 0.9 mOsm/kg-H₂O in 12 tests. As described in METHODS, all samples of blood plasma for the measurements were air-equilibrated. The period of time from the blood sampling to the measurement of the osmotic pressure was 2.5 to 5 hours in all experiments.

Fig. 2 shows the time-course-change in the osmotic pressure of both arterial and venous blood plasma, studied in untreated dogs in the control state 4 times at intervals of 10 minutes. It is shown that the osmolal A-V difference remains almost constant, while the osmotic pressure of both arterial and venous blood plasma varied with time. Fig. 3 shows the time-course-

TABLE I STABILITY TESTS WITH STANDARD SOLUTION AND PLASMA

	Standard Solution		Plasma mOsm/kg-H ₂ O
	100 mOsm/kg-H ₂ O	500 mOsm/kg-H ₂ O	
	97.2	498.2	275.9
	98.0	500.2	276.0
	98.2	498.9	276.3
	99.0	499.0	275.4
	98.4	499.3	277.3
	97.5	499.9	277.0
	98.0	503.2	275.8
	100.0	500.0	277.3
	100.0		277.1
			276.6
			278.1
			278.2
Mean	98.5	499.8	276.7
SD	0.7	1.5	0.9
SE	0.2	0.5	0.3

SD: Standard deviation, SE: Standard error of mean

Fig. 2. Time-course-change in the osmotic pressures of arterial (solid lines) and venous (broken lines) blood plasma, recorded from femoral artery and vein, data from untreated dogs in the control state, studied 4 times at intervals of 10 minutes. While the osmotic pressures of both arterial and venous blood plasma varied with time, the osmolar difference between the artery and the vein (osmolar A-V difference) remained almost constant.

change of osmolar A-V difference studied in the control state just as in Fig. 2. Although the levels of the osmolar A-V difference were variable with individual animals, one and the same dog maintained a nearly constant value of osmolar A-V difference during the studied period of time. The bald line in Fig. 3 indicates the average extent of minute-to-minute variation in osmolar A-V difference above or below the control (time zero) level. Thus, in 8 tests the osmolar A-V difference varied with time with SD less than 0.5 mOsm/kg·H₂O.

ii) Time-course-changes in osmolar A-V difference during the venous pressure rise

With balloon stationed and inflated in IVC or iliac V., blood samples were collected from the femoral artery and the congested vein at different points of time. Fig. 4 shows the results of such a study; the abscissa gives time (minutes), and the ordinate gives, in upper part, osmolar A-V difference and, below, venous pressure. The bald line gives the mean values. The mean values of the osmolar A-V difference before the balloon inflation determined at four points of time, were 0.9, 1.1, 0.7 and 1.0 mOsm/kg·H₂O respectively, that is, almost constant for this period (Fig. 2

Fig. 3. Time-course-change in the osmolar A-V difference in the control state, constructed from data recorded from femoral artery and vein 4 times at intervals of 10 minutes. The bald line represents the mean values of osmolar A-V difference above or below the control level. It is seen that the variations of the osmolar A-V difference with time was within ± 0.5 mOsm/kg·H₂O.

and Fig. 3). The balloon was then inflated so as to keep the femoral venous pressure at the level of about 200 mmH₂O. Blood samples were

Fig. 4. Time-course-change in the osmolal A-V difference, recorded from femoral artery and vein, before, during and after the venous congestion produced by inflating a balloon in IVC or iliac vein. Fine solid lines indicate the data for balloon inflation in IVC; the broken lines indicate the data for balloon inflation in the iliac vein. The bold line represents the mean value. The osmolal A-V difference shifted towards the negative side during the venous congestion, becoming the most negative at about the end of 6 minutes after the start of venous congestion.

collected from femoral artery and vein at the end of 3, 6, 9, 12 and 15 minutes after the beginning of venous congestion, with the mean osmolal A-V difference values of -2.1 , -6.3 , -3.3 , -2.0 and -2.2 mOsm/kg-H₂O, respectively. When the balloon was deflated at the end of 15 minutes after the start of the inflation, the venous pressure returned to the control level immediately; blood samples obtained at the end of 5 and 10 minutes after the balloon deflation gave osmolal A-V difference of 0.1 and 0.1 mOsm/kg-H₂O, on average, respectively. Thus the osmolal A-V difference moved towards the negative direction after the onset of venous congestion, reaching the most negative level at the end of 6 minutes. It is recognized that measuring the osmotic pressure at a shorter time interval than this is desirable; however, frequent blood sampling can

produce undesirable effects on the animals, with as large as 12 cc of blood being required for each determination (the minimum amount of plasma necessary for the measurements with Fiske's osmometer was 2 cc). Therefore only minimum possible amount of bleeding was made. Where the osmolal A-V difference was negative to begin with, it became even more negative during the venous congestion. Accordingly, the venous pressure rise may be better said to make the osmolal A-V difference shift towards the negative side rather than that making it negative. In the following experiments, blood sampling during the venous congestion was made at about the end of 6 minutes after the start of venous congestion.

II. Osmolal A-V Difference and the Site of Venous Pressure Elevation

i) Right Atrium

Table II-a indicates the osmotic pressure of femoral arterial and venous blood in 12 dogs and the calculated osmolal A-V difference before and after the inflation of a balloon in the right atrium. While the osmolal A-V difference before the inflation was 0.2 mOsm/kg-H₂O on the average, it shifted to the negative side, that is, to -7.4 mOsm/kg-H₂O on an average during the venous congestion.

ii) Inferior Vena Cava

Table II-b shows the osmolal A-V difference of 10 dogs in which a balloon was located in IVC. Measurement of venous pressure was carried out on the femoral vein, and blood samples were obtained from femoral artery and vein. The mean osmolal A-V difference in the control period was 0.5 mOsm/kg-H₂O and it changed to -7.3 mOsm/kg-H₂O during the venous congestion.

iii) Superior Vena Cava

Table II-c indicates in the upper part, the results of studies in which a balloon was fixed in SVC. The venous pressure was recorded from the median vein; blood samples were obtained from carotid artery and jugular vein. While the mean value of the osmolal A-V difference was 0.2 mOsm/kg-H₂O in the control period, it moved into the negative direction, reaching -7.2 mOsm/kg-H₂O on average during the venous congestion.

iv) Iliac Vein

Table II-c shows in the lower part, the results of studies on 4 cases in which a balloon was located in the iliac vein. The venous pressure was measured from the femoral vein, and the blood samples were obtained from femoral artery and

TABLE II-a OSMOLAL A-V DIFFERENCE WITH OR WITHOUT VENOUS CONGESTION PRODUCED BY INFLATING A BALLOON AT VARIOUS SITES

Site of Balloon	No.	Control				Congestion			
		VP mmH ₂ O	Osmolality mOsm/kg-H ₂ O			VP mmH ₂ O	Osmolality mOsm/kg-H ₂ O		
			A	V	A-V		A	V	A-V
RA	1	38	288.2	290.8	-2.6	157	292.5	300.8	-8.3
	2	71	293.7	300.0	-6.3	200	287.5	304.0	-16.5
	3	70	293.3	292.0	1.3	145	293.9	298.8	-4.9
	4	76	294.2	295.0	-0.8	160	289.2	294.2	-5.0
	5	60	293.7	291.0	2.7	135	284.5	291.9	-7.4
	6	65	297.0	298.6	-1.6	155	281.7	289.5	-7.8
	7	60	292.0	289.0	3.0	140	285.3	291.8	-6.5
	8	70	273.0	268.9	4.1	170	265.5	274.5	-9.0
	9	45	293.4	291.9	1.5	120	292.2	296.6	-4.4
	10	35	300.7	303.1	-2.4	95	293.5	299.2	-5.7
	11	60	297.7	297.0	0.7	120	293.1	298.8	-5.7
	12	40	305.2	302.5	2.7	95	301.2	308.3	-7.1
Mean		58	293.5	293.3	0.2	141	288.3	295.7	-7.4
SD		14	7.7	8.8	3.0	30	8.9	8.4	3.2
SE		4	2.2	2.6	0.9	9	2.6	2.4	1.0

RA: Right atrium, VP: Venous pressure, A: Plasma osmolality of arterial blood
 V: Plasma osmolality of venous blood Sampling: Femoral A. and V., VP: Femoral V.

TABLE II-b

Site of Balloon	No.	Control				Congestion			
		VP mmH ₂ O	Osmolality mOsm/kg-H ₂ O			VP mmH ₂ O	Osmolality mOsm/kg-H ₂ O		
			A	V	A-V		A	V	A-V
IVC	1	50	292.9	295.5	-2.6	210	285.7	296.8	-11.1
	13	65	292.8	295.1	-2.3	125	292.0	297.6	-5.6
	15	40	298.9	297.9	1.0	135	297.9	302.7	-4.8
	16	32	282.9	281.8	1.1	180	283.0	292.8	-9.8
	17	30	291.3	290.1	1.2	150	286.2	293.2	-7.0
	21	40	294.2	293.7	0.5	150	292.0	298.4	-6.4
	22	40	289.5	287.0	2.5	235	287.5	298.4	-10.9
	23	20	299.3	299.1	0.2	180	299.4	306.0	-6.6
	24	35	295.2	293.3	1.9	170	288.1	291.0	-2.9
	25	5	301.7	299.8	1.9	195	295.8	303.9	-8.1
Mean		36	293.8	293.3	0.5	173	290.7	298.0	-7.3
SD		16	5.4	5.6	1.7	34	5.5	4.9	2.6
SE		5	1.7	1.8	0.5	11	1.7	1.6	0.8

IVC: Inferior vena cava Sampling: Femoral A. and V. VP: Femoral V.

TABLE II-c

Site of Balloon	No.	Control				Congestion			
		VP	Osmolality mOsm/kg-H ₂ O			VP	Osmolality mOsm/kg-H ₂ O		
		mmH ₂ O	A	V	A-V	mmH ₂ O	A	V	A-V
SVC*	14	47	295.0	297.8	-2.8	120	290.7	297.8	-7.1
	15	67	293.9	292.5	1.4	125	298.8	304.3	-5.5
	16	40	284.9	283.7	1.2	162	285.1	292.9	-7.8
	17	15	288.9	287.6	1.3	150	291.8	300.2	-8.4
Mean		42	290.6	290.4	0.2	139	291.6	298.8	-7.2
S D		23	4.6	6.0	2.0	20	5.6	4.7	1.2
S E		12	2.3	3.0	1.0	10	2.8	2.4	0.6
Iliac V.**	26	5	287.1	283.6	3.5	160	286.9	298.2	-11.3
	27	30	302.5	298.5	4.0	130	292.8	300.3	-7.5
	28	30	289.0	289.9	-0.9	440	286.5	291.7	-5.2
	29	30	303.0	301.7	1.3	350	293.3	302.2	-8.9
Mean		23	295.4	293.4	2.0	270	289.9	298.1	-8.2
S D		12	8.4	8.2	2.2	148	3.7	4.5	2.5
S E		6	4.2	4.1	1.1	74	1.9	2.3	1.3

SVC: Superior vena cava Iliac V.: External iliac vein Sampling: * External carotid A. and external jugular V., ** Femoral A. and V. VP: *Median V., **Femoral V.

vein. The mean osmolal A-V difference for the control period was 2.0 mOsm/kg-H₂O and it moved in the negative direction, reaching -8.2 mOsm/kg-H₂O during venous congestion. All other data are shown in the above tables.

Only mean values given in the foregoing tables were used in constructing the straight-lines in Fig. 5. This figure indicates that, irrespective of the site of balloon inflation, the values of osmolal A-V difference shifted, with significant difference, towards the negative side during the venous congestion.

In Figs. 6-A, B, and C, the ordinate gives the venous pressure and abscissa gives arterial blood plasma osmolality, venous blood plasma osmolality and osmolal A-V difference, respectively. The venous pressure was correlated with the osmotic pressure of arterial blood plasma with $r = -0.260$ ($P < 0.05$), i.e., a significant but weak negative correlation. The venous pressure was correlated with the osmotic pressure of venous blood plasma with $r = 0.373$ ($p < 0.01$), i.e., a positive correlation. The relation between the venous pressure and the osmolal A-V difference was with $r = -0.75$ ($p < 0.01$), i.e., a fairly strong, negative correlation.

III. Osmolal A-V Difference Inside and Outside of the Areas of Venous Congestion

Table III-a gives the data obtained in 4 dogs. First, a balloon was introduced, uninflated, into SVC, and blood samples were obtained from both carotid artery and jugular vein, as well as from femoral artery and vein at the same time. Under these circumstances, the venous pressure was 42 mmH₂O on an average for median vein and 35 mmH₂O for femoral vein. The mean values of osmolal A-V difference recorded from these sites were 0.3 and 1.8 mOsm/kg-H₂O, respectively. Then the balloon was inflated with the result that the venous pressure remained unchanged in femoral vein, while that of median vein increased, showing that the venous congestion occurred in upper half of the body; the mean value of the pressure in the median vein was 139 mmH₂O. Under these conditions, blood samples were collected in the same manner as before. The mean value of osmolal A-V difference obtained from carotid artery and jugular vein was negative, -7.2 mOsm/kg-H₂O, while that recorded from femoral artery and vein was positive, 2.6 mOsm/kg-H₂O; the lower half of the body was free from venous congestion, as evidenced by the

TABLE III-a OSMOLAL A-V DIFFERENCE INSIDE AND OUTSIDE OF THE AREAS OF VENOUS CONGESTION

Site of Balloon	No.		VP (Median V.) mmH ₂ O	Osmolality Carotid A. and Jugular V. mOsm/kg-H ₂ O			VP (Femoral V.) mmH ₂ O	Osmolality Femoral A. and V. mOsm/kg-H ₂ O		
				A	V	A-V		A	V	A-V
SVC	14	Cont.	47	295.0	297.8	-2.8	28	294.9	290.2	4.7
		Cong.	120	290.7	297.8	-7.1	40	296.3	292.9	3.4
	15	Cont.	67	293.9	292.5	1.4	67	294.7	293.4	1.3
		Cong.	125	298.8	304.3	-5.5	51	303.0	300.3	2.7
	16	Cont.	40	284.9	283.7	1.2	30	291.1	289.5	1.6
		Cong.	162	285.1	292.9	-7.8	10	286.9	285.8	1.1
	17	Cont.	15	288.9	287.6	1.3	15	287.1	287.4	-0.3
		Cong.	150	291.8	300.2	-8.4	0	285.4	282.0	3.4
Mean		Cont.	42	290.7	290.4	0.3	35	291.9	290.1	1.8
SD			21	4.6	6.1	2.0	22	3.7	2.5	2.1
SE			11	2.3	3.1	1.0	11	1.9	1.3	1.1
Mean		Cong.	139	291.6	298.8	-7.2	25	292.9	290.3	2.6
SD			20	5.6	4.7	1.2	24	8.3	8.0	1.1
SE			10	2.8	2.4	0.6	12	4.2	4.0	0.6

Cont.: Control Cong.: Congestion

TABLE III-b

Site of Balloon	No.		VP (Median V.) mmH ₂ O	Osmolality Carotid A. and Jugular V. mOsm/kg-H ₂ O			VP (Femoral V.) mmH ₂ O	Osmolality Femoral A. and V. mOsm/kg-H ₂ O		
				A	V	A-V		A	V	A-V
IVC	13	Cont.	35	290.6	289.7	0.9	65	292.8	295.1	-2.3
		Cong.	20	291.3	291.0	0.3	125	292.0	297.6	-5.6
	15	Cont.	20	298.2	298.1	0.1	40	298.9	297.9	1.0
		Cong.	33	301.2	298.9	2.3	135	297.9	302.7	-4.8
	16	Cont.	40	294.9	292.7	2.2	32	282.9	281.8	1.1
		Cong.	2	286.0	287.4	-1.4	180	283.0	292.8	-9.8
	17	Cont.	20	285.5	284.0	1.5	30	291.3	290.1	1.2
		Cong.	0	286.3	284.5	1.8	150	286.2	293.2	-7.0
Mean		Cont.	29	292.3	291.1	1.2	42	291.5	291.2	0.3
SD			10	5.5	5.9	0.9	16	6.6	7.0	1.7
SE			5	2.8	3.0	0.5	8	3.3	3.5	0.9
Mean		Cong.	14	291.2	290.5	0.7	148	289.8	296.6	-6.8
SD			15	7.0	6.2	1.6	24	6.6	4.6	2.2
SE			8	3.5	3.1	0.8	12	3.3	2.3	1.1

Fig. 5. Osmolal A-V difference and venous pressure before and after the venous congestion. The mean data for balloon inflation in SVC, RA, IVC, or iliac vein are given. Irrespective of the site of balloon inflation, the osmolal A-V difference shifted towards the negative side during the venous congestion.

femoral venous pressure of 25 mmH₂O. The balloon was then deflated to allow the venous pressure of median vein to return to the normal level. After 30 minutes the balloon was placed in IVC, and blood sampling was carried out without the inflation of the balloon. The osmolal A-V difference of both head and the hind leg was normal, 1.2 mOsm/kg·H₂O and 0.3 mOsm/kg·H₂O, respectively. After the inflation of the balloon, blood sampling was performed in the same manner as described above. The pressure of median vein remained unchanged but that of femoral vein increased, indicating that the venous congestion occurred in the lower half of the body. The results obtained are shown in Table III-b. The neck vessels gave an osmolal A-V difference of 0.7 mOsm/kg·H₂O, a normal osmolal A-V difference value for the upper half of body without venous congestion. By contrast, the osmolal A-V difference recorded from the congested femoral vessels was negative, -6.8 mOsm/kg·H₂O. Other data are shown in the tables.

From these findings it is concluded that the value of the osmolal A-V difference becomes negative only at the area where the venous pressure is increased, i.e. a fact which suggests that the change of osmolal A-V difference caused by the increase of venous pressure depends on some local mechanisms.

Fig. 6. Relationship between the venous pressure and plasma osmolality. (A) Venous pressure versus arterial blood plasma osmolality (B) Venous pressure versus venous blood plasma osmolality (C) Venous pressure versus osmolal A-V difference (Osm A-V)

IV. Investigations on Pulmonary Circulation: osmolal A-V difference during the elevation of left atrial pressure

A catheter provided with a balloon at the tip was advanced into LA via the left external carotid

TABLE IV OSMOLAL A-V DIFFERENCE IN THE CONTROL AND INFLATING A BALLOON AT LA OR RA

Site of Balloon	No.	Control				Congestion			
		Pressure mmHg		Osmolality mOsm/kg-H ₂ O		Pressure mmHg		Osmolality mOsm/kg-H ₂ O	
		RA	LA	A	V	RA	LA	A	V
LA	31	0	8	297.1	300.5	0	13	296.2	297.9
	32	3	6	292.3	297.8	4	10.5	293.9	296.0
	33	4	10	294.9	292.9	4	20	298.8	294.5
					2.0				4.3
Mean		2.3	8.0	294.8	297.1	2.7	14.5	296.3	296.1
SD		2.1	2.0	2.4	3.8	2.3	4.9	2.4	1.7
SE		1.2	1.2	1.4	2.1	1.3	2.8	1.4	0.9
RA	31	0	7.5	296.4	296.1	9	6	295.9	300.9
	32	3	6	296.7	296.0	10	6	296.1	300.1
	33	2	4	300.2	297.3	7	4	294.3	301.8
					0.3				-5.0
					0.7				-4.0
					2.9				-7.5
Mean		1.7	5.8	297.8	296.5	8.7	5.3	295.4	300.9
SD		1.5	1.7	2.1	0.7	1.5	1.6	0.9	0.8
SE		0.9	1.0	1.2	0.4	0.9	0.9	0.6	0.5

LA: Left atrium, RA: Right atrium, Sampling: Femoral artery and vein

artery and, at the same time, pressure-measuring catheters were advanced into RA and LA via the right external jugular vein and the right external carotid artery, respectively. First, without inflating the LA balloon, blood samples were collected from femoral artery and vein, and osmolal A-V difference was calculated. The results obtained are shown in Table IV. P_{RA} was 2.3 mmHg on an average and P_{LA} was 8 mmHg. Osmolal A-V difference was $-2.3 \text{ mOsm/kg}\cdot\text{H}_2\text{O}$. After inflating the balloon in LA, P_{LA} was increased to 14.5 mmHg on an average, while P_{RA} was almost unchanged (2.7 mmHg on an average), indicating that an isolated pulmonary venous congestion was produced. At the end of 6 minutes after the balloon inflation, that is, with the same timing as in the case of systemic venous congestion, the blood samples were collected from the systemic circulation. The osmolal A-V difference of the femoral vessels was $0.2 \text{ mOsm/kg}\cdot\text{H}_2\text{O}$ on an average.

In the dogs employed in the experiment described just above, the balloon was removed from LA and introduced into RA. After 30 minutes, the systemic venous congestion were produced by the RA balloon inflation. The results obtained are shown in the lower part of Table IV. The osmolal A-V difference recordable from femoral artery and vein changed from 1.3 to $-5.5 \text{ mOsm/kg}\cdot\text{H}_2\text{O}$ with the RA balloon inflation.

This study shows that the value of osmolal A-V difference recordable from femoral artery and vein shifts towards the positive side during the pulmonary venous congestion, a tendency just reverse of what is seen with the systemic venous congestion.

V. Autonomic Nerves and the Shift of Osmolal A-V Difference during the Venous Pressure Elevation

i) Effects of pentolinium and reserpine

Table V-a shows, in upper part, the results of 6 experiments with pentolinium. Under monitoring the femoral arterial pressure with an electromanometer, 1 mg/kg of pentolinium tartrate was slowly injected intravenously in 6 dogs. The blood pressure decreased from 142/106 down to 42/15 on an average and remained there almost constant at the end of about 10 minutes after the injection. At this state (control state), blood sampling was performed, with venous pressure of $50 \text{ mmH}_2\text{O}$ on an average and the osmolal A-V difference of $0.5 \text{ mOsm/kg}\cdot\text{H}_2\text{O}$. The bal-

loon was then inflated in order to increase the pressure in femoral vein up to $127 \text{ mmH}_2\text{O}$ on the average. The osmolal A-V difference obtained under this circumstance was $2.0 \text{ mOsm/kg}\cdot\text{H}_2\text{O}$, indicating that the osmolal A-V difference was practically unaffected by venous congestion in dogs pretreated with pentolinium. Table V-a shows, in lower part, the result of 3 experiments carried out with reserpinized dogs. The doses of reserpine used were described in METHOD. The mean venous pressure was $33 \text{ mmH}_2\text{O}$ and the mean osmolal A-V difference was $0.6 \text{ mOsm/kg}\cdot\text{H}_2\text{O}$ in the control state; with venous congestion of $85 \text{ mmH}_2\text{O}$ on the average, the osmolal A-V difference was $1.5 \text{ mOsm/kg}\cdot\text{H}_2\text{O}$. It was thus shown that the osmolal A-V difference was unaffected by the increase of venous pressure when the animals have been pretreated with reserpine.

ii) Atropine and cervical vagotomy

One mg/kg of atropine sulfate was injected intramuscularly in 3 dogs and blood sampling was performed after a sufficient degree of mydriasis was achieved at the end of about 20 to 30 minutes after the injection. The results obtained are shown in the upper part of Table V-b. With average venous pressure of $28 \text{ mmH}_2\text{O}$, the osmolal A-V difference was $0.6 \text{ mOsm/kg}\cdot\text{H}_2\text{O}$. The osmolal A-V difference was $-4.4 \text{ mOsm/kg}\cdot\text{H}_2\text{O}$ on an average when the venous congestion of $150 \text{ mmH}_2\text{O}$ on an average was produced.

In 4 dogs the vagus nerves were cut at the both sides of the neck and similar experiments to those described above were carried out at the end of about 20 to 30 minutes after the vagotomy. The results obtained are shown in the lower part of Table V-b. Before the venous congestion, the mean venous pressure was $56 \text{ mmH}_2\text{O}$ and the osmolal A-V difference was $1.5 \text{ mOsm/kg}\cdot\text{H}_2\text{O}$. After the venous congestion with venous pressure of $124 \text{ mmH}_2\text{O}$ on an average, the mean osmolal A-V difference was $-8.4 \text{ mOsm/kg}\cdot\text{H}_2\text{O}$.

Thus in dogs pretreated with atropine or vagotomy, the values of osmolal A-V difference moved in the negative direction following the increase of venous pressure just as in the control dogs.

The relationships between the osmolal A-V difference and venous pressure after the pretreatment with pentolinium, reserpine, atropine or vagotomy are illustrated in Fig. 7. This result indicates that the change of osmolal A-V difference produced by the increase of venous pressure

TABLE V-a INFLUENCE OF VENOUS CONGESTION ON OSMOLAL A-V DIFFERENCE AND ITS MODIFICATION BY AUTONOMIC INNERVATION

Autonomic Intervention	No.	Control				Congestion			
		VP mmH ₂ O	Osmolality mOsm/kg-H ₂ O			VP mmH ₂ O	Osmolality mOsm/kg-H ₂ O		
			A	V	A-V		A	V	A-V
<i>Pentolinium Tartrate</i>	7	52	292.4	291.8	0.6	98	287.1	284.6	2.5
	8	60	272.7	268.9	3.8	210	268.3	263.8	4.5
	9	45	301.7	299.5	2.2	95	293.8	293.2	0.6
	10	40	298.8	301.4	-2.6	130	295.5	295.3	0.2
	11	40	291.5	290.0	1.5	86	294.5	293.6	0.9
	13	65	292.8	295.1	-2.3	145	293.8	290.8	3.0
<i>Mean</i>		50	291.6	291.1	0.5	127	288.8	286.8	2.0
<i>S D</i>		10	10.1	11.6	2.5	46	10.4	11.8	1.6
<i>S E</i>		4	4.1	4.8	0.4	18	4.3	4.8	0.7
<i>Reserpinized</i>	18	30	310.1	307.2	2.9	95	324.4	319.8	4.6
	19	25	294.3	294.5	-0.2	70	293.8	293.6	0.2
	20	45	292.5	293.4	-0.9	90	287.0	287.3	-0.3
<i>Mean</i>		33	298.9	298.3	0.6	85	301.7	300.2	1.5
<i>S D</i>		10	9.6	7.6	2.0	13	19.8	17.1	2.7
<i>S E</i>		6	5.5	4.4	1.2	8	11.4	9.9	0.7

Balloon: Right atrium, Sampling: Femoral artery and vein

TABLE V-b

Autonomic Intervention	No.	Control				Congestion			
		VP mmH ₂ O	Osmolality mOsm/kg-H ₂ O			VP mmH ₂ O	Osmolality mOsm/kg-H ₂ O		
			A	V	A-V		A	V	A-V
<i>Atropine Sulfate</i>	15	40	293.4	292.7	0.7	140	290.5	295.7	-5.2
	16	25	282.5	280.6	1.9	165	286.4	290.9	-4.5
	17	20	286.9	287.8	-0.9	145	294.5	297.9	-3.4
<i>Mean</i>		28	287.6	287.0	0.6	150	290.4	294.8	-4.4
<i>S D</i>		10	5.4	6.0	1.3	13	4.0	3.5	0.9
<i>S E</i>		6	3.2	3.5	0.7	8	2.3	2.9	0.5
<i>Vagotomy</i>	7	65	280.6	277.4	3.2	132	287.2	291.1	-3.9
	9	45	291.3	290.0	1.3	90	295.0	302.1	-7.1
	11	75	292.3	293.2	-0.9	180	298.8	310.4	-11.6
	12	70	307.4	305.0	2.4	95	300.7	311.7	-11.0
<i>Mean</i>		56	292.9	291.4	1.5	124	295.4	303.8	-8.4
<i>S D</i>		16	10.9	11.3	1.8	41	5.9	9.4	3.6
<i>S E</i>		8	5.4	5.6	0.9	21	3.0	4.7	1.8

Fig. 7. Relationships between the osmolal A-V difference and venous pressure after the pretreatment with pentolinium, reserpine, atropine and vagotomy. Data for normal dogs are also shown. Balloon was inflated in RA. Venous congestion caused no change in osmolal A-V difference in dogs pretreated with pentolinium or reserpine, while atropine or vagotomy did not modify the usual negative shift of osmolal A-V difference upon venous congestion.

requires an intact sympathetic nervous system, while the parasympathetic nervous system has nothing to do with this phenomenon.

VI. Relationship between Osmolal A-V Difference and A-V Difference of Sodium Concentration (Na A-V)

Fig. 8 shows the data obtained in one experiment, where a balloon was inserted into IVC and the osmotic pressure was recorded from femoral artery and vein before and after the increase of venous pressure. At the same time, A-V difference of sodium concentration (referred hereafter as Na A-V) was also measured. In the upper half, Fig. 8 indicates the recorded osmotic pressure; it is shown that the osmolal A-V difference became negative after the venous congestion. In the lower half, Fig. 8 shows the Na A-V of blood plasma; it is shown that the osmolal A-V difference is numerically almost equal to Na A-V. Short horizontal lines drawn on both sides of the curves indicate the mean values of the arterial and venous osmotic pressure and of the Na A-V

Fig. 8. An experiment showing the relationship between the osmolal A-V difference and sodium A-V difference during the venous congestion. The curves were constructed from data obtained in one dog with IVC balloon and blood sampling from femoral artery and vein. The solid lines represent arterial blood, and broken lines represent venous blood. The mean values are indicated by short horizontal lines on the left (control period) and right (venous congestion) side of the curves. The shaded areas represent a negative A-V difference in osmolality and sodium concentration. It is seen that the osmolal A-V difference is numerically almost equal to sodium A-V difference.

TABLE VI. OSMOLAL A-V DIFFERENCE VERSUS SODIUM A-V DIFFERENCE

No.		VP mmH ₂ O	Osmolality mOsm/kg·H ₂ O			Sodium mEq/L		
			A	V	A-V	A	V	A-V
4	Cont.	76	295.0	294.2	0.8	110.8	102.3	8.5
	Cong.	160	289.2	294.2	-5.0	110.8	107.5	3.3
5	Cont.	60	293.7	291.0	2.7	110.9	108.6	2.3
	Cong.	135	284.5	291.9	-7.4	103.6	113.9	-10.3
7	Cont.	60	292.0	289.0	3.0	111.5	111.5	0
	Cong.	140	285.3	291.8	-6.5	115.2	118.9	-3.7
11	Cont.	60	297.7	297.0	0.7	163.5	159.7	3.8
	Cong.	120	293.1	298.8	-5.7	167.0	175.5	-8.5
22	Cont.	35	294.2	290.9	3.3	143.4	143.4	0
	Cong.	200	294.6	297.8	-3.2	140.2	147.4	-7.2
23	Cont.	23	298.5	298.1	0.4	149.5	149.0	0.5
	Cong.	156	297.0	300.9	-3.9	146.4	151.5	-5.1
24	Cont.	35	295.0	293.9	1.1	158.9	150.3	8.6
	Cong.	175	294.4	296.1	-1.7	156.9	153.8	3.1
25	Cont.	8	300.0	298.6	1.4	155.1	154.5	0.6
	Cong.	208	293.8	297.5	-3.7	154.0	156.5	-2.5
Mean	Cont.	45	295.8	294.1	1.7	137.9	134.9	3.0
SD		44	2.7	3.6	1.1	23.0	23.4	3.8
SE		16	0.9	1.2	0.4	8.7	8.3	1.3
Mean	Cong.	162	291.5	296.1	-4.6	136.8	140.6	-3.8
SD		31	4.6	3.3	1.8	23.8	24.2	5.0
SE		11	1.6	1.2	0.7	8.4	8.5	1.8

Balloon: IVC Sampling: Femoral artery and vein VP: Femoral vein

before and after the venous congestion. Namely, before the congestion, the Osm A was 298.5; Osm V, 298.1; osmolal A-V difference, 0.4 mOsm/kg·H₂O; Na A, 149.5; Na V, 149.0; Na A-V, 0.5 mEq/L. After the congestion, Osm A was 297.0; Osm V, 300.9; osmolal A-V difference, -3.9 mOsm/kg·H₂O; Na A, 146.4; Na V 151.5; Na A-V, -5.1 mEq/L.

Table VI lists the observed values of Osm A, Osm V, Na A and Na V before and after the increase of venous pressure in 8 dogs. Before the congestion, the average osmolal A-V difference was 1.7 mOsm/kg·H₂O and that of Na A-V was 3.0 mEq/L. After the congestion, osmolal A-V difference was -4.6 mOsm/kg·H₂O and Na A-V was -3.8 mEq/L on the average.

Fig. 9 was constructed from the values of

osmolal A-V difference and Na A-V compiled in Table VI. The straight lines drawn from open circles to solid circles in this figure represent the observed shifts from the normal state to the state of venous congestion. The bald line in the figure connects the point of the mean of the osmolal A-V difference for the normal state and the point of the mean for the state of venous congestion. Inspection this figure would indicate that, during venous congestion, both osmolal A-V difference and Na A-V shifted towards the negative side with mean vectorial angle of about 45 degrees.

DISCUSSION

As to the reliability of Fiske's osmometer, Table I showed that the higher the osmotic pres-

Fig. 9. Osmolal A-V difference plotted against the simultaneously measured sodium A-V difference. Open circles represent the control state and solid circles represent the state of venous congestion. A bold line connects the point of the mean of the control data and the point of the mean of the data obtainable during venous congestion. That both osmolal A-V difference and sodium A-V difference shifted towards the negative direction with numerically 1 : 1 correspondence in many instances is reflected in the direction of the mean "vector", intersecting with abscissa with angle of 45 degrees.

sure to be measured, the larger the SD for the same sample. However, the measurements on dog's blood plasma were reproducible with SD of 0.9 mOsm/kg-H₂O. Therefore, given a difference in osmolal A-V difference that exceeds 1.8 mOsm/kg-H₂O, one can be reasonably sure that a significant change took place.

When the conditions of the animal were allowed to stabilize during the period of 30 minutes after the completion of surgical interventions, such as anesthesia with pentobarbital, exposure of femoral artery and vein, application of T-tubes for blood sampling, and the introduction of balloon-catheters into major vessels, such as IVC and iliac vein, the osmolal A-V difference recorded from femoral artery and vein remained almost unchanged with fluctuations less than 0.5 mOsm/kg-H₂O; however, the osmotic pressure of femoral arterial or venous blood changed with time. The observed periodicity and amplitude of the last-mentioned change was variable, but this was not the topic of the present author's concern. The values of osmolal A-V difference obtainable immediately after the surgical operations were both unstable and variable. Similarly variable were the values of osmolal A-V difference obtained in case pentobarbital was added during the course of one experiment or when the artificial respirator was called into action to give oxygen because of excessive anesthesia and respiratory stand-still; in such cases osmolal A-V difference

changed by more than 2.0 mOsm/kg-H₂O. Therefore, neither addition of pentobarbital during the course of one experiment nor switching to the use of a respirator was done in the present studies. The period of time required from the beginning to the end of an experiment was about 1 to 1.5 hours, including the time allowed to elapse after the surgical operation was over.

There were 3 dogs exceptional in that the values of osmolal A-V difference were negative already before producing any venous congestion. Two of the three dogs had osmolal A-V difference of -0.9 and -1.1 mOsm/kg-H₂O, respectively, but no special meaning may be attached to these readings, because they are not outside of the limit of errors inherent to Fiske's osmometer. The third one had osmolal A-V difference of -3.5 mOsm/kg-H₂O that was significantly negative. However the osmolal A-V difference was stable at this negative level. It may be appropriate to note, here, that there was a dog showing, consistently, a high positive value of osmolal A-V difference, i.e., 4.0 mOsm/kg-H₂O before producing any venous congestion. Implications of these findings are not clear at present. In most cases, the readings of osmolal A-V difference in the control state were within ± 2.0 mOsm/kg-H₂O.

Time-course of the osmolal A-V difference change deserves a mention. With a balloon introduced into IVC or iliac V., the osmolal A-V difference was measured before and after the elevation of venous pressure. As indicated in Fig. 4, the osmolal A-V difference became the most negative at the end of 6 minutes after the beginning of venous congestion. When the venous pressure was restored back to normal by deflating the balloon, the osmolal A-V difference readings were also restored to the normal level. However, there was a certain time-lag between the venous pressure and the value of osmolal A-V difference. Upon the inflation of a balloon, the venous pressure rose immediately, but the osmolal A-V difference remained normal even at the end of 3 minutes after the beginning of the venous congestion; after 6 minutes, the recorded osmolal A-V difference was invariably more negative than in the control state. This fact suggests the presence of a mediator between the elevation of venous pressure and the negative shift of osmolal A-V difference. It is recognized by many investigators that anaerobic metabolism is accelerated when a patient suffering from heart failure performs physical exercise.^{11,12} ISER¹³

observed that there was an increase in osmotic pressure, Na concentration, lactate/pyruvate ratio and the hematocrit in arterial blood during physical exercise. He thought this to be due to an increase in anaerobic metabolism of skeletal muscle, drawing water from blood plasma into cells, resulting in a decrease in blood volume. Since this type of change was observed in 17 cases of heart diseases as well as 8 cases of non-cardiac diseases in a similar manner, this phenomenon can hardly be considered specific to the patho-physiological change prevailing in the congestive heart failure. However, it may be that an increase of venous pressure brings forth a metabolic abnormality in the regional tissue, resulting in a time-lag between the change in venous pressure and that of osmolal A-V difference.

It was also observed that, while venous pressure was normalized immediately after deflating a balloon, the osmolal A-V difference was returned to the control level only gradually.

As shown in Fig. 4, the values of osmolal A-V difference decrease with time after producing venous congestion, and the curve tended to level off, with a plateau, at the end of 12 or 15 minutes; but the venous congestion was discontinued at this stage. The data for a longer venous congestion are shown in Fig. 10 where the changes in osmolal A-V difference were followed for 60 minutes of venous congestion. During the period of the venous congestion, the values of osmolal A-V difference were well on the negative side, different significantly from the control level. This fact seems to be the counterpart of the clinical observation that the patients with congestive heart failure persistently exhibit negative values of osmolal A-V difference for a long period. It is concluded from these foregoing results that the osmolal A-V difference, at least in the region subjected to venous congestion, for example, in tributaries of femoral vein when a balloon is inflated to in IVC or iliac V. was distinctly on the more negative side than in the control period.

Fig. 5 and Table II indicate the change in the osmolal A-V difference value that occurs when a balloon is inflated in places other than the IVC or iliac vein, for instance, RA or SVC. Inspection of this figure and table would indicate that the negative shift of osmolal A-V difference upon the elevation of venous pressure is a ubiquitous phenomenon, seen not only with the congestion of IVC or iliac vein but also with congestion

Fig. 10. Osmolal A-V difference before and during the venous congestion of 60 minutes' duration, an experiment with a balloon in IVC and blood sampling from the femoral artery and vein. The osmolal A-V difference stayed consistently negative during 60 minutes' period of venous congestion.

anywhere between the right atrium and periphery.

While the values of osmolal A-V difference shifted towards the negative side in places subjected to congestion, what happens in osmolal A-V difference in places not subjected to venous congestion? Data shown in Table III answered this question. It was thus shown that the negative shift of osmolal A-V difference occurred only in the regions where the venous pressure was increased. From these findings, it may be concluded that the negative shift of osmolal A-V difference caused by the elevation of venous pressure is clearly a local phenomenon. HENRY, GAUER and REEVES¹⁴ localized their stretch receptor, sensing the amount of circulating blood volume, in the left atrium. If there should be any osmoreceptor triggered by venous pressure change, it should not be localized to one place, but distributed throughout the venous systems.

Inspection of Fig. 6 would suggest that the negative shift of osmolal A-V difference accompanying increased venous pressure is due to decreased osmotic pressure of arterial blood plasma and increased osmotic pressure of venous blood plasma, the latter probably playing the main role.

Discussion up to this point centered around the problem of the systemic venous congestion, with attendant negative shift of osmolal A-V difference. With pulmonary venous congestion produced by a balloon inflated in the left atrium, the result was just opposite to that obtainable with systemic venous congestion, as shown in Table IV. The osmolal A-V difference recorded from femoral artery and vein shifted towards the

positive side during the pulmonary venous congestion, a phenomenon just reverse to what is seen during the systemic venous congestion. In this experiment, left atrial pressure was slightly high, but the fractional contribution of the physiological pressure difference between RA and LA, and the effect of artificially induced aortic insufficiency and mitral insufficiency, by 2 catheters inserted into LA, is not known. The positive shift of systemic osmolal A-V difference in response to the pulmonary venous congestion was small in magnitude in comparison with the negative shift of osmolal A-V difference accompanying systemic venous congestion, the change being not significant, judging from the precision of measurements, with Fiske's osmometer. However, it may be safely stated that osmolal A-V difference tended to move towards the positive side. LEVINE¹⁵ reported that the pericapillary force in the pulmonary interstitium is changed significantly during the pulmonary venous congestion. PEARCE¹⁶ found that the pulmonary venous congestion produced by epinephrine or alloxan infusion was associated with a loss of sodium from blood stream. He thought that this sodium loss may represent binding by some extravascular locus or it may be related to alveolar wall injury.

Disagreement between the present result and the data of PEARCE who found sodium loss in pulmonary edema can not be accounted for at present, but it may be due to the difference in experimental conditions employed.

Alterations in osmolal A-V difference induced by venous pressure rise were studied after blocking the function of the autonomic nerves, with results shown in Fig. 7 and Table V. The negative shift of osmolal A-V difference caused by the elevation of venous pressure was inhibited completely by the pretreatment with pentolinium or reserpine. These facts suggested that the negative shift of osmolal A-V difference produced by venous pressure rise was under the influence of autonomic nerves, especially the sympathetic nervous system. It is known that the clinical manifestations of congestive heart failure are heavily influenced by the activity of sympathetic nervous system. For instance, there is a fact that the congestive heart failure is aggravated by the administration of guanethidine¹⁷ or reserpine,¹⁸ indicating that the circulatory functions depend more heavily on the sympathetic nervous system in these patients than in healthy persons. The amount of nor-epinephrine excret-

ed in urine was reported^{18,19} to be increased in patients with congestive heart failure of class III or IV of New York Heart Association classification; the concentration of nor-epinephrine in blood plasma increased to a greater extent during physical exercise in the patients with heart failure than in healthy persons.²⁰ These facts suggest the importance of the sympathetic nervous system in the regulation of blood circulation in congestive heart failure. Should the negative shift of osmolal A-V difference accompanying the systemic venous congestion be a kind of physiological reactions, as would be discussed latter, it is not surprising that this response is inhibited by blockade of the sympathetic nervous system.

The administration of atropine or vagotomy did not influence the usual negative shift of osmolal A-V difference upon the elevation of venous pressure; therefore, it seems that the parasympathetic nervous system has no contribution to the phenomenon in question.

In dogs pretreated with pentolinium and, especially, reserpine, the present author found that the venous pressure did not rise rapidly upon the inflation of balloon; when inflation was carried further, dogs often died. This is probably due to an excessively reduced tone of venous vessels brought about by blockade of the sympathetic nervous system. In reserpinized dogs, it was difficult to increase the venous pressure sufficiently, because many dogs so pretreated died upon inflation of a balloon; the venous pressure obtainable after the balloon-inflation was in the region of 95, 70, and 90 mmH₂O, that is, values not very high. They are not too low, either, because there were some untreated dogs (No. 10 and 12) where osmolal A-V difference shifted in the negative directions with this degree of venous pressure rise. However, the venous pressure had better be elevated above 100 mmH₂O for the induction of changes in osmolal A-V difference.

It is naturally desirable to identify the substance(s) responsible for the change in osmolal A-V difference. The present author attempted to approximate the substance(s) by some experiments, although number of observations was limited. Fig. 8 represents such a study. It is noticed that the osmolal A-V difference shifted towards the negative side by the same numerical amount as Na A-V shifted towards the negative side during the venous congestion. While it is naively expected that Na⁺ moves accompanied by Cl⁻, the fact that the change in osmolal A-V

difference was numerically almost the same with the change in Na A-V, suggests that the "active" substance in question is not in the form of strong electrolyte with chloride partner, like NaCl, which produces two ions from one molecule; instead, a substance in the form of Na X, composed of Na as the main element and X, poorly dissociable partner, must be invoked. Fig. 9 summarized the relation between osmolal A-V difference and Na A-V; the grand mean "vector" formed an angle of 45 degree with the abscissa, indicating the equality of osmolal A-V difference change with Na A-V change in many cases of venous congestion. Further investigations are required to identify the substance(s) responsible for the observed change in osmolal A-V difference, including measurements of A-V difference of many other molecules and ions.

One of the greatest problems on the pathological physiology of congestive heart failure is the problem of the elevation of venous pressure, edema formation and accumulation of water and NaCl. Generally, veins and venous capillaries constitute the largest reservoir of blood in the body; when venous pressure is increased in a part of the body, the venous bed in that region is expanded and accommodates a large amount of blood. Since the compliance, $\Delta V/\Delta P$, of the entire systemic venous system in human beings is estimated to be about 100 ml/mmHg, from values recorded from the upper arm vein by WOOD,²¹ it follows that the total systemic venous system is capable of accommodating 1,500 ml of extra blood when systemic venous congestion elevates the venous pressure by 15 mmHg. Therefore, it is theoretically possible that the entire blood in the heart, pulmonary vessels and systemic arterial system is drained almost completely into the systemic venous system with a rise of venous pressure by 15 mmHg. Such a "bleeding into his own venous system" obviously threatens life. Therefore, living organism should have a mechanism to reduce the capacity of the systemic venous system to protect his life during the systemic venous congestion. As such protective mechanisms, the following two events have been thought to occur in local venous beds subjected to an increase of venous pressure: a) venoarteriolar reflex²² or myogenic response,⁹ where the venous congestion leads to the contraction of arterioles, thus impeding the entry of arterial blood, and b) contraction of precapillary sphincters, impeding the entry of blood into capillaries that are engaged in blood-tissue ex-

change. It was thus observed by MELLANDER¹⁰ in human legs and by JOHNSON⁸ in dog's intestine that the coefficient of filtration decreased in response to venous congestion. They ascribed this phenomenon to a decrease in the capillary surface area available for fluids movement. BAKER²³ studied, using dog's forelegs, the influence of the elevation of venous pressure, in the range of 5 to 35 mmHg, on the exchange of low-molecular substance across capillary walls and the filtration of body fluid. The results he obtained showed that the coefficient of filtration fell markedly and the diffusion capacity (the product of permeability, P and capillary surface, S) was reduced slightly, suggesting that the blood stream fairly large number of minutes blood vessels came into standstill, trapping blood, and that the blood stream was redistributed in favor of nonexchange vessels. Thus an increase in venous pressure produces a local circulatory state with reduced rate of inflow of blood into capillaries and decreased fluid filtration. The negative shift of osmolal A-V difference accompanying the elevation of venous pressure can not be explained solely in terms of increased filtration; instead, increased transfer of some substance (probably Na⁺) from tissue to blood must be invoked, or else, preferential exit of water from blood into tissue space, unattended by solutes, must be invoked. It is tempting to speculate on the mechanism of the phenomenon in question. It may be that the elevation of the venous pressure activates some kind of "receptor" distributed throughout the systemic venous system. It is also possible that the venous congestion produces some changes in trans-capillary exchange via the route of sympathetic nervous system. It was suggested, earlier in this report, that some substance(s), probably in the form of Na X, shift(s) from tissue to blood in rates exceeding the rate of its shift in opposite direction, resulting in a higher concentration of Na in venous blood than in arterial blood, hence a negative shift of osmolal A-V difference.

If the osmotically active substance in question should remain in the circulating blood for a long time after it was drawn into the blood stream, the osmotic pressure of the entire blood in the circulatory system should increase perpetually. Therefore, the osmotically active substance should be released from blood into pulmonary interstitium, causing the systemic arterial blood to become lower than the systemic venous blood in osmolality. It may be that the substance released into the pulmonary interstitium is

Fig.11. Blood-tissue transport of osmotically active substance(s) illustrated with a hypothetical model. Data in control state, during systemic and pulmonary venous congestion are shown. The osmotically active substance(s), probably in the form of Na X, is given as Na, with the predominant direction of transport shown by large arrows.

During the systemic venous congestion, "Na" is absorbed from "edematous" peripheral tissue into the blood stream and released into the pulmonary interstitium. It seems to be brought back to the venous system via lymph duct. During the pulmonary venous congestion, there were suggestive evidences that "Na" is absorbed from "edematous" pulmonary tissue into the blood stream and released into the systemic interstitium.

brought back to the venous system via lymph ductus. Such is a possible model of the circulation in the presence of the systemic venous congestion. The results shown in Table IV for the pulmonary venous congestion lend support to this hypothetical model. Fig. 11 illustrates this model schematically. It should be noted that this model is only hypothetical one and that there are needs of further investigations before the final conclusion can be drawn.

SUMMARY

In order to delineate the observation, made by HAYASE and his coworkers, that the patients with congestive heart failure often had negative A-V difference in plasma osmolality (osmolal A-V difference), the present author studied the osmolal A-V difference with or without systemic venous congestion in anesthetized dogs by means of balloons inflated at various sites of the venous system. The plasma osmotic pressure, and the osmolal A-V difference in various conditions

were studied.

1. The values of osmolal A-V difference shifted towards the negative side during the systemic venous congestion at those areas subjected to the venous pressure elevation. This phenomenon was seen irrespective of the site of the balloon inflation, such as superior vena cava, inferior vena cava, iliac vein or right atrium.
2. The value of osmolal A-V difference shifted towards the negative side only at the areas where the venous pressure was increased, and not in those areas free from venous congestion. It is concluded that the negative shift of osmolal A-V difference during venous congestion is a strictly localized phenomenon.
3. There was a time-lag between the venous pressure elevation and the change in osmolal A-V difference, suggesting the presence of some mediator(s) that lie between the two processes.
4. During the pulmonary venous congestion, osmolal A-V difference showed a tendency to shift towards the positive side from the control

level.

5. The negative shift of osmolal A-V difference caused by the elevation of the systemic venous pressure was inhibited by the pre-treatment with pentolinium tartrate or reserpine but it was not influenced by atropine or vagotomy. Therefore, the phenomenon in question appears to be related to the sympathetic nervous system.

6. There were suggestive evidences that the substance responsible for the observed shift in the osmolal A-V difference during the venous congestion is a weakly dissociable electrolyte in the form Na X.

It is probable that the elevation of the venous pressure produces some changes in the transcapillary exchange other than an increased fluid filtration and that this is the cause of the alteration in osmolal A-V difference.

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