Studies on the Relationship between Venous Pressure and Arterio-Venous Difference of Plasma Osmolality in Congestive Heart Failure

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In order to clarify the significance of the peripheral circulation in the congestive heart failure, a study was made of the relationship between the elevated venous pressure and the osmolality of the arterial and venous blood plasma, with emphasis on the osmolal arterio-venous difference in the patients with congestive heart failure. Day-to-day variations were delineated, and disease-specific features of the plasma osmolality were studied statistically. Elevated systemic venous pressure tended to be associated with a shift of the osmolal arterio-venous difference towards the negative side; this tendency was noticed, with statistical significance, in the patients with valvular and congenital heart diseases. This tendency was absent in the patients with pleuro-pericardial effusion. With regard to the correlation between the plasma osmolality and systemic venous pressure, a positive correlation was noticed, to some extent, only in the patients with valvular and congenital heart diseases.

These observations suggest that the venous congestion produces a tissue-to-blood gradient of osmotically active substance(s) in the tributary veins, leading to an altered trans-capillary exchange.

CAPILLARY vessels are the site of bi-directional diffusion, net filtration and reabsorption,¹⁻⁴ transport through "leaks"⁵ or, to a lesser extent, by cytoplasmic vesicle as suggested by MAYERSON et al.⁶ According to Starling's hypothesis,¹ the water balance at capillaries depends on the net effect of four interdependent forces: capillary pressure, tissue pressure, colloid osmotic pressure of blood plasma and tissue fluids. This concept, extended by PAPPENHEIMER,³ predicts that, during ultrafiltration of plasma through capillary membranes, water and small-sized solutes normally move virtually together, without appreciable molecular sieving. This means that the net filtration or reabsorption of body fluids, per se, almost never gives rise to an appreciable concentration difference of small-sized molecules

between arterial and venous blood.

MAEKAWA and SAIMYOJI⁷ reported that peak of the excretion of osmolal substances proceeded that of water when water load was placed on cardiac patients of slightly congestive state. This fact could not be explained solely in terms of the antidiuretic hormone. They referred, furthermore, to relationship between venous pressure, plasma osmolality, and serum level of antidiuretic hormone. They found a roughly positive correlation between venous pressure and plasma osmolality of venous blood, and also a correlation, although not statistically significant, between venous pressure and serum level of antidiuretic hormone. These facts suggest a possibility that the elevation of systemic venous pressure, per se, induces a change in the transportation of osmolal

(Received for Publication, October 5, 1970)

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* The outline of this work was reported at the 32th Annual Meeting of Japanese Circulation Society in Kurume, March 28, 1968, and 66th Annual Meeting of Japanese Society of Internal Medicine in Sendai, April, 1969, and 34th Annual Meeting of Japanese Circulation Society in Kobe, March 27, 1970, and 67th Annual Meeting of Japanese Society of Internal Medicine in Fukuoka, April 1, 1970.

TABLE I CARDIAC PATIENTS CLASSIFIED BY BASIC DISEASE

			sum
<i>Congenital Heart Disease</i>	<i>ASD</i>	3	6
	<i>VSD</i>	2	
	<i>PDA</i>	1	
	<i>Miscellaneous</i>	0	
<i>Valvular Heart Disease</i>	<i>Mitral Valve Lesion</i>	21	30
	<i>Aortic Valve Lesion</i>	2	
	<i>Combined Valve Lesion</i>	4	
	<i>Miscellaneous</i>	3	
<i>Hypertensive-arteriosclerotic Heart Disease</i>			16
<i>Pleuro-pericarditis</i>	<i>Cancer</i>	1	4
	<i>Tuberculosis</i>	2	
	<i>Miscellaneous</i>	1	
<i>Sum</i>			56

ASD: Atrial septal defect VSD: Ventricular septal defect

PDA: Patent ductus arteriosus

TABLE II CARDIAC FUNCTION AND BASIC DISEASE OF THE PATIENTS

<i>Cardiac Function (NYHA)</i>	<i>Valvular Heart Disease and Congenital Heart Disease</i>	<i>Hypertensive-arteriosclerotic Heart Disease</i>	<i>Pleuro-pericardial Effusion</i>	<i>Sum</i>
<i>I</i>	0	0	0	0
<i>II</i>	16	3	0	19
<i>III</i>	7	11	1	19
<i>IV</i>	13	2	3	18
<i>Sum</i>	36	16	4	56

substances between the blood and tissue.

This paper describes the result of a study made on the venous pressure and plasma osmolality, particularly the difference in osmolality between the arterial and the venous blood plasma, arterial minus venous.

SUBJECTS AND METHOD

Fifty six consecutive cardiac patients with or without congestive heart failure were included in this study. Table I indicates that they can be classified by basic diseases into 3 groups, i.e. 36 patients with congenital and valvular heart diseases, 16 patients with hypertensive-arteriosclerotic heart diseases and 4 patients with exudative pleuro-pericarditis. Their cardiac functions, taking the worst condition encountered in the entire period of the admission, were summa-

rized in Table II. Thus, each one third of the patients was placed in classes II, III, and IV (NYHA). The venous pressure was measured by a water manometer at the antecubital vein in the supine position. The reference point was set at the level 4 cm behind the sternal margin of the anterior chest wall. The osmolality of air-equilibrated plasma was measured by Fiske osmometer, using both arterial and venous blood, which were simultaneously sampled from the brachioradial artery and antecubital vein with syringes wetted with heparine. The measurements of the venous pressure and plasma osmolality were made in one and same patient successively on the same day or at least within two days.

RESULT

I. Preliminary Study

TABLE III PLASMA OSMOLALITY OF ARTERIAL AND VENOUS BLOOD OF NORMAL SUBJECTS

with Tourniquet			without Tourniquet			
<i>A</i>	<i>V</i>	<i>A - V</i>	<i>A</i>	<i>V</i>	<i>A - V</i>	
281.1	284.9	-3.8	290.3	291.0	-0.7	
293.5	295.5	-2.0	294.5	292.9	1.6	
294.5	298.0	-3.5	298.0	296.0	2.0	
281.5	283.0	-1.5	292.2	289.0	3.2	
297.9	298.5	-0.6	294.9	291.9	3.0	
282.8	283.2	-0.4	288.2	288.8	-0.6	
277.9	277.4	0.5	282.0	282.1	-0.1	
291.7	291.5	0.2	281.1	279.0	2.1	
275.2	278.1	-2.9	276.7	274.5	2.2	
285.5	288.5	-3.0	270.8	270.0	0.8	
288.8	286.9	1.9	270.0	269.2	0.8	
296.2	294.2	2.0				
288.1	291.9	-3.8				
288.5	291.6	-3.1				
295.2	297.0	-1.8				
270.4	274.8	-4.4				
273.1	275.0	-1.9				
270.1	273.2	-3.1				
290.1	290.5	-0.4				
282.3	284.2	-1.9				
271.0	272.2	-1.2				
273.5	274.5	-1.0				
<i>Mean</i>	283.9	285.5	-1.6	285.3	284.0	1.3
<i>SD</i>	8.7	8.4	3.1	9.4	9.1	1.3
<i>SE</i>	1.8	1.8	0.6	2.8	2.7	0.4

A: Plasma osmolality of arterial blood V: plasma osmolality of venous blood
A-V: Osmolal A-V difference SD: Standard deviation SE: Standard error of mean

This study was performed for the purpose of investigating whether the usage of a tourniquet around the upper arm would have any effect on the measured value of plasma osmolality or not. The patients with pulmonary tuberculosis of mild degree were subjected to examination. The results are shown in Table III. The venipuncture was made with tourniquet in 22 patients. The plasma osmolality of the arterial blood was 283.9 ± 1.8 mOsm/kg-H₂O (Mean $\pm$ SE), and that of the venous blood was 285.5 ± 1.8 mOsm/kg-H₂O. The difference in plasma osmolality between the arterial and venous blood (osmolal A-V difference) was calculated to be -1.6 ± 0.6 mOsm/kg-H₂O. On another series of 11 cases the venipuncture was made and blood samples

were collected without tourniquet. The plasma osmolality of the arterial and venous blood were, respectively, 285 ± 2.8 , 284.0 ± 2.7 mOsm/kg-H₂O. The osmolal A-V difference was 1.3 ± 0.4 mOsm/Kg-H₂O.

It can be said that the osmolality of venous blood was higher with compression of the upper arm by a tourniquet than without it, that the osmolal A-V difference shifted towards negative side with tourniquet. In all studies to follow, the blood samples were collected without tourniquet.

II. Illustrative Cases of Congestive Heart Failure

Case 1, age 39, male. Admission; January 7, 1970. Clinical diagnosis; congestive heart failure, arterial fibrillation and mitral insufficiency.

Chief complaints; orthopnea and generalized edema. He complained of palpitation and breathlessness after exertion for the last 3 years. Since the beginning of the last December, his condition became worse. Paroxysms of nocturnal cough and edema of the face and the legs appeared. Before admission he was forced to stay in bed because of orthopnea.

On physical examination, the respiration was 36/min. The pulse was irregular and the rate was 75/min, with pulse deficit of 45/min. The blood pressure was 120/78 mmHg. On auscultation, pansystolic murmur was clearly heard at the apex and the base. The liver was palpable 10 cm below the right costal margin, but no pulsation was noticed.

The roentgenogram showed marked cardiomegaly (cardio-thoracic ratio: 0.59) and showed increased pulmonary vascular markings. The venous pressure was 240 mmHg. The plasma osmolality of arterial and venous blood were 294.0 and 301.0 mOsm/kg-H₂O respectively. The osmolal A-V difference was thus -7.0

mOsm/kg-H₂O.

The clinical course is shown in Fig. 1. Namely, his condition was gradually improved under diet control and the administration of digitalis and diuretics. The elevated venous pressure was lowered to normal within 15 hospital days. The plasma osmolality of arterial and venous blood were reduced and osmolal A-V difference shifted from negative to positive value.

Case 2, age 28, female, was a woman admitted to this hospital on October 23, 1969 for detailed examination of her heart. While attending the middle school, she joined the swimming team. But cardiac enlargement was noticed at that time. Since this September she sometimes complained of slight fever and general fatigue. Since the end of the October she felt palpitation upon exertion and edema appeared in the face in the early morning.

On physical examination, the respiratory rate was 30/min and the heart rate was 110/min. The blood pressure was 130/45 mmHg. Palpation of the thorax revealed a thrill at the pulmonic orifice

Fig.1. Clinical course of Case 1

MI: Mitral insufficiency

NYHA: New York Heart Association Classification

VP: Venous pressure

BP: Blood pressure

Fig. 2. Clinical course of Case 2

PDA: Patent ductus arteriosus

area. On auscultation, there was a continuous, machinery murmur, grade 4/6, along the left sternal border. The electrocardiogram showed RVH. The chest roentgenogram showed cardiomegaly (CTR; 0.67) with prominent arc II and marked pulmonary vascular markings. The clinical diagnosis was patent ductus arteriosus.

During hospitalization for the cardiac catheterization, she accidentally caught common cold. Hence her cardiac function became rapidly deteriorated. The changes in plasma osmolality and related data are showed in Fig. 2. The venous pressure began to be elevated about at the 40th day. The plasma osmolality of venous blood gradually increased since admission, but not in arterial blood. The osmolal A-V difference became negative in association with the elevation of the venous pressure.

Case 3, age 31, male. He was admitted on May 9, 1967 with complaints of exertional dyspnea. The patient received drug therapy for half a year in 1965. From the last October till this February the patient received medical treatment under the diagnosis of pleurisy, but became aware of exertional dyspnea and edema in the face and the lower extremities.

On physical examination, the respiratory rate was 24/min and the heart rate was 110/min. The blood pressure was 118/106 mmHg. On auscultation the heart sound was distant but no murmur was audible. On percussion of the chest, the cardiac dullness could not be outlined. The liver was palpable 5 cm below the right costal margin. The roentgenogram showed pleuro-pericardial effusion. The electrocardiogram showed negative or flat T waves in the all leads, and low amplitude. The right cardiac catheterization (May 20, 1967) revealed no particular findings, and the pulmonary capillary pressure could not be measured. The radiocardiogram (May 16, 1967) revealed that the blood volume, cardiac index and stroke volume were 5.39 L/min, 3.8 L/min/M² and 68 ml respectively. Clinical diagnosis was exsudative tuberculous pleuro-pericarditis with cardiac tamponade.

The clinical course and treatment is shown in Fig. 3. On admission, the venous pressure was 173 mmH₂O and the osmolal A-V difference was -9.8 mOsm/kg-H₂O. Edema and dyspnea gradually disappeared, but pulmonary rale was heard throughout the course. The venous pressure did not decrease, fluctuating between 162 and 236

K. S. age 31 Male Pleuro-Pericarditis

Treatment	Furosemide 40 mg			Furosemide 40 mg			
	Streptomycin 1.0 g Para-aminosalicylic acid 8.0 g Isonicotinic acid hydrazid 0.4 g						
Pleural Punction	500	800	1000	1000	1000 1000 400 800 (cc)		
Osmolality A (mosm/kgH ₂ O) V A-V	276.0	272.9	273.0	284.0	281.2		
	285.8	271.6	273.0	280.6	284.1		
	-9.8	1.3	0	3.4	-2.9		
V P (mmH ₂ O)	173	162	210	176	236		
B P (mmHg)	118/106	118/88	106/86		108/90		128/94
Serum Protein	8.2 (mg/dl)				7.3		
Na	142	141	144	140	138		
Serum K (mEq/l)	3.6	3.8	3.1	3.9	3.7		
Dyspnea
E d e m a
R a l e
Fluid Intake
Urine Volume (cc)
Hospital Days	1	5	10	15	20	25	30 35

Fig.3. Clinical course of Case 3

Fig.4. Relationship between the venous pressure and plasma osmolality (total of the patients)
 (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)

mmH₂O. Excepting for the first measurement, the measured osmolal A-V difference was positive or slightly negative throughout the course of his disease.

Comment: There were found a negative correlation between the venous pressure and the value of the osmolal A-V difference in case 1 and 2, whereas case 1 was observed in decrescendo phase but case 2 in crescendo phase of congestive heart failure. There was no such correlation in case 3. The presence of such two types of the correlation suggests to the authors that the correlation should be investigated from the point of view of basic diseases.

III. Statistical Observations

1. Observations on the total of the patients

The measurements of venous pressure and plasma osmolality of both arterial and venous blood were performed 143 times on 56 cases with heart diseases as indicated in Table I. As shown in Fig. 4-A, B, C, there was no correlation between the venous pressure level and the plasma osmolalities of either arterial or venous blood ($r = 0.028$, $p > 0.05$ and $r = 0.103$, $p > 0.05$). But it can be seen that a negative correlation was found to some extent between the venous pressure and the osmolal A-V difference ($r = -0.442$, $p < 0.01$).

2. Observations on the patients classified by basic diseases

All the subjects were classified by their basic disease into 3 groups as shown Table I, i.e. group I, congenital and valvular heart diseases, number of patients, 36 and number of measurements, 90; group II, hypertensive-arteriosclerotic heart diseases, number of patients, 16 and number of measurements, 31; group III, pleuropericardial effusion, number of patients, 4 and number of measurements, 22. There was a weak correlation ($r = 0.288$, $p < 0.01$) between venous pressure and arterial blood osmolality in group I (Fig. 5-A), but there was no such correlation in the remaining groups, group II and III (Fig. 6-A, Fig. 7-A). This was true for the venous blood in group II and III (Fig. 6-B, Fig. 7-B), but a roughly positive correlation between venous pressure level and venous blood osmolality occurred in group I (Fig. 5-B). A statistically significant, negative correlation was found between venous pressure level and the osmolal A-V difference in group I ($r = -0.629$, $p < 0.01$) (Fig. 5-C). There was no significant relation between venous pressure and the osmolal A-V difference in group II

Fig. 5. Relationship between the venous pressure and plasma osmolality (Group I: congenital and valvular heart diseases)
(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)

Fig. 6. Relationship between the venous pressure and plasma osmolality (Group II: hypertensive-arteriosclerotic heart diseases)
 (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)

Fig. 7. Relationship between the venous pressure and plasma osmolality (Group III: pleuro-pericarditis)
 (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)

($r = -0.353$, $p > 0.05$) and in group III ($r = -0.063$, $p > 0.05$).

DISCUSSION

This study revealed that there is a roughly negative correlation between the venous pressure level and the osmolal A-V difference in cardiac patients in general. When the result was analyzed on the basis of each basic disease, the venous pressure level showed a roughly negative correlation with osmolal A-V difference in congenital and valvular heart diseases, to a lesser extent in hypertensive-arteriosclerotic heart diseases, and never in exsudative pleuro-pericarditis. In the first group the correlation was statistically significant, but in the following two groups the correlation may be by chance. Between the venous pressure level and the either arterial or venous blood plasma osmolality, there was found a positive correlation in group I but not in group II and III. The results obtained in group I are in agreement with the report by MAEKAWA and SAIMYOJI.⁷ Fig. 4, 5, 6, and 7 show the different degrees of correlation, among 3 types of heart diseases, between the venous pressure level and the plasma osmolality and the osmolal A-V difference. The precise mechanism responsible for the observed difference remains unknown, but some discussion will be attempted later.

The authors would like to emphasize the concurrence of the venous pressure elevation and negative osmolal A-V difference. This reversal of osmolal A-V difference with venous hypertension appears to be a locally elicited phenomenon for following two reasons, i.e., 1) the osmolal A-V difference shifted towards negative side by compression of the arm vein as indicated previously in the preliminary observation, 2) the osmolal A-V difference related to the venous pressure level but not to the absolute values of plasma osmolality of arterial and/or venous blood.

The principal factors regulating the exchange of fluids (by bulk flow) across the capillary walls were stated by STARLING.¹ The Starling's hypothesis is the basis of our knowledge about the net movement of fluid across capillary walls under normal and disturbed condition, and its validity was given substantial experimental support by LANDIS⁸ PAPPENHEIMER and SOTO-RIVERA⁹ characterized the diffusion and filtration across capillary walls by use of osmotic transient and isogravimetric method, where capillary pressure was determined indirectly from

arterial and venous pressure in the presence of constant precapillary and postcapillary resistance. MELLANDER et al.¹⁰ emphasized the importance of vascular adjustments to increased transmural pressure in the homeostasis of vascular, as against blood, volume in cat and man. According to Starling-Landis-Pappenheimer's hypothesis,¹⁻⁴ the ultrafiltrate and blood plasma have nearly the same composition so far as small-sized solutes are concerned, unless the rate of filtration is exceedingly high. This means that plasma osmolality of arterial and venous blood obtained from one and the same tissue or organ should be nearly equal, unless there is either addition to, or uptake from, the blood stream.

The venous congestion causes the leakage of serum proteins into the extracellular space.¹¹ In this case the plasma osmolality of venous blood should be smaller than of arterial blood by GIBBS-DONNAN's rule.¹² For example; suppose that the arterial plasma, composed of 164 mEq/L of cations, 147 of anions and 17 of protein, was deprived of 7 mEq/L of protein during passage through the capillaries embedded in the interstitial fluids composed of 152 mEq/L of cations and 152 of anions. The outflowing venous blood would have a composition of cation 159 mEq/L, anion 149 mEq/L and protein 10 mEq/L, while the interstitial fluid now have the composition of cations 157 mEq/L, anions 150 and protein 7. The arterial blood now has 328 mEq/L of ions, while the venous blood has 318 mEq/L of ions in the presence of such protein-losing congestive state. Obviously, the difference in plasma osmolality between arterial and venous blood, such as found by the present authors in the cardiac patients can not be explained in terms of either the "molecular sieving" effect of excessive capillary filtration or protein-losing capillaries and Donnan equilibrium.

Our results will have to be explained by postulating that, in tissue under the venous congestion, there is a net movement of osmotically active substance(s) in the direction of tissue to blood. The responsible mechanism may be (a) increased exit of sodium ions from cells or (b) increased entry of pure water into cells.

According to Starling's hypothesis,¹ when there is a difference in concentration of inert molecular species across the capillary membrane, the molecules tend to diffuse from the site of higher concentration to the side of lower concentration across the membrane, and the concentration gradient of the molecules across the

capillary membrane results in osmotic withdrawal of fluid in the direction opposite to that of diffusion. Both processes continue until the concentration gradient across capillary wall approaches zero. No substance was added exogenously to any side, inside or outside of the capillary, in our system. ISERI et al.¹³ observed in cardiac as well as noncardiac patients, a significant decrease in plasma volume and significant increases in arterial plasma sodium concentration, osmolality, blood hematocrit reading, lactate-pyruvate ratio after the exercise. They suggested that an increased rate of anaerobic muscle metabolism causes the migration of water from plasma in to the cells, presumably from increased cellular osmolality. No data about tissue metabolism are available in the present study, but a speculation that venous pressure elevation would give the local tissue cells the same effect as exercise may be the one which should be examined in future.

According to our experimental studies on dogs,¹⁴ sodium ion, in the form of a poorly dissociable electrolyte, is the most probable osmolal substance responsible for the osmolal A-V difference. In the "hindlimb" preparation of dogs, the authors¹⁵ found a decrease in the fractional extraction of ²²Na following the elevation of venous pressure by using indicator diffusion method. Details of this will be reported by our coworkers, KONDO¹⁶ and IMAO.¹⁷ A similar result was reported by BAKER¹⁸ with dogs' foreleg. These results differ from the results of PEARCE¹⁹ on the lungs made edematous with hypervolemia plus epinephrine or with alloxan. He observed a reduced sodium recovery from edematous lungs compared with normal by the same method. He suggested that sodium loss represents binding by some extravascular locus and may be related to the extent of alveolar wall injury. This difference may be due to the difference of organs used or condition of the preparation.

The correlation between the shift to negative side of osmolal A-V difference and venous pressure was statistically significant in the group of congenital and valvular heart diseases, but not in the group of pleuropericardial effusion. The arterial osmolality was higher than the venous irrespective of venous pressure in the majority of the last group (Fig. 3, Fig. 7-A, B, C). Although there is a lack of substantial data on systemic and pulmonary circulation, it is reasonably presumed that the patients with pleuropericardial effusion had predominantly "left

heart failure". Elevated left atrial pressure may cause the plasma osmolality of pulmonary venous blood (systemic arterial blood) to rise above the level of the systemic venous blood, resulting in a positive osmolal A-V difference by definition, if the same events should take place in the pulmonary circulation as in the systemic circulation. The effect of negative osmolal A-V difference induced by the venous pressure elevation in the systemic circulation would be eliminated during passage of blood through the less congested pulmonary circulation by the mechanism of either loss of osmolal species in the lungs in the direction of blood to tissue or migration of water from tissue to blood; a chain of events just opposite to this may take place in the presence of venous congestion in the pulmonary circulation. Such see-saw phenomenon may play an important role in the homeostasis in the plasma osmolality and thus blood volume.

SUMMARY

A study was made of the relation between the venous pressure determined in cardiac patients and the plasma osmolality, its A-V difference, determined simultaneously or at a near-by point of time, in the same patients.

The results were as follows:

1. A total of 143 pairs of determinations (of venous pressure and osmolal A-V difference) made in 56 cardiac patients revealed that there was a roughly negative correlation ($r = -0.442$, $p < 0.01$) between the venous pressure and osmolal A-V difference. There was no statistically significant correlation between the venous pressure and arterial blood or venous blood osmolality in the totality of the patients.
2. There was a moderate negative correlation between the venous pressure and osmolal A-V difference ($r = -0.629$, $p < 0.01$) in the patients with congenital and valvular diseases. The coefficient of correlation was $r = -0.353$ and $r = -0.063$ in hypertensive-arteriosclerotic heart disease and pleuro-pericardial effusion.
3. The effect of compressing the upper arm with a cuff on the osmolality of the local venous blood was studied in normal individuals. Venous congestion caused the blood osmolal A-V difference to shift towards the negative side.

These facts suggest that the congestive heart

failure is associated with a local alteration in the tissue-blood transport of osmotically active substance(s). It is also suggested that the some local change may involve both systemic and pulmonary circulatory system.

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