Peripheral Vascular Permeability following a Thermal Injury to the Airway

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Effects of thermal injury to the airway on the vascular permeability in the region of head and neck, were studied in the canine models. The thermal airway injury was produced by an inhalation of a gas burner's flame through the metallic tracheostomy cannula. The changes in vascular permeability were evaluated by calculating the reflection coefficient, which was obtained by the protein washdown technique into lymph. The reflection coefficient after the flame inhalation did not show any increases, while it increased significantly after a histamine infusion into the carotic artery. We concluded, that the vascular permeability in the unburned area does not increase at least in the first 3 hr after a thermal injury to the airway. (Key words: capillary permeability, inhalation burn, reflection coefficient, Lymph protein concentration)

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Increases in the peripheral vascular permeability[1,2] have been reported in many pathological conditions, including sepsis, hemorrhagic shock, acute pancreatitis and burns, and how to overcome the period of increased vascular permeability is one of the most important therapeutic problems in the field of acute medicine. However, recognition of an increased vascular permeability is very difficult, especially if one intends to express its degree with some kinds of numerical data. Only in the animal experiment changes in the vascular permeability can be demonstrated numerically as increases in the lymphatic flow rate or in the lymphatic protein concentration[3]. The protein washdown technique into lymph[4], which was used in this study may be one of most exact methods for assessing the reflection coefficient of microvascular endothelial barrier, because the confusing effects of dynamically changing vascular surface area or contamination of lymph on the estimation of reflection coefficient are offset.

On the other hand, the loss of microvascular endothelial integrity and the leakage of plasma components into the extravascular space make a tremendous volume substitution necessary in the treatment of burn patients. The infusion for burn patients tends to go excess easily by the fear that the vascular permeability in unburned body area will also increase following a widely involved burn. The purpose of this study is to know whether the microvascular permeability in the normal, not burned body area can really increase following a burn or not.

Methods

17 adult mongrel dogs weighing 10 to 18.5 kg were anesthetized with an intra-

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venous Ketamine chloride of 10 $mg \cdot kg^{-1}$. The Vasa femoralis of both sides were laid open. A 7-F balloon tipped pulmonary arterial catheter and a 16-G infusion catheter were placed through the femoral veins in the pulmonary artery and inferior caval vein. They were used for infusion and measurements of pulmonary arterial and capillary wedge pressures (PAP & PCWP). Through one of the femoral arteries, a 7-F pigtail catheter (Cordis) was introduced into the left atrium via the left ventricle[5] for monitoring of left atrial pressure (LAP). Via another artery, a catheter with a thermistor probe at the tip was placed in the descending aorta for measuring the systemic mean aortic pressure (MAP) and the cardiac output (CO). Cardiac output was determined with the thermodilution method by injecting 5 ml of cold saline into the left atrium (Kimray; Model 3500E Cardiac Output Computer).

The animals were tracheotomized with a metallic cannula. In order to avoid a leakage of air through the breach between tracheal wall and cannula, the trachea around the cannula was tightly ligated. Skin incisions of about 6 cm were made by the external jugular veins of both sides, and from a branch of the left external jugular vein, usually the cephalic vein, a 8-F Fogarty occlusion catheter (Edwards Laboratories) was introduced into the superior caval vein and the balloon was inflated slightly. This resulted in engorgement of the cervical veins and lymphatics and made it easy to identify the right lymphatic ampulla. The right lymphatic ampulla was ligated just cranial to the communication with the jugular vein and the balloon of the Fogarty occlusion catheter was deflated. A small tubing was placed in the right jugular vein through the right radial cutaneous vein and used for monitoring the cervical venous pressure (P_{EXJ}). The cervical lymphatics were traced from the ampulla to the cranial direction and one of the deep cervical lymphatics which were found just laterally to the carotid artery, was cannulated with a 21-G needle. This needle was connected with a polyethylene tubing of a inner diameter of 0.6 mm, and its distal end was fixed at the height of 10 cm beneath the sternal notch. Because the lymphatic flow rate (Q_L) was influenced by the height of the outflow cannula[6,7], Q_L was always determined with this drainage height. In order to facilitate the outflow of lymph, the neck of the dogs was distended periodically with a frequency of about 10 times per minute. Then the dogs were allowed to stabilize for 60 min under spontaneous respiration and at an interval of 15 min, three determinations of lymphatic flow rate, protein concentrations in the lymph and plasma and of the hemodynamic parameters were repeated. These values were used as the baseline values. The figure 1 illustrates the schema of the setting up of venous catheterization.

Here, dogs were divided into three groups. In the Control group, the jugular pressure was elevated up to 30 ± 2 mmHg by inflating the balloon of the Fogarty occlusion catheter in the superior caval vein. Hereafter, the same determinations were repeated every 15 min for 3 hr. After the inflation of the intracaval balloon, falls in the systemic aortic pressure were treated with the infusion of lactated Ringer solution. The volume of infusion was controlled by maintaining the left atrial pressure in the range of baseline ± 2 mmHg.

In the Histamine group, after the determination of the baseline value, the jugular venous pressure was elevated and the dogs were kept in that situation for 60 min. The same determination was repeated at the end of this 60 min and served as the control value. Then the histamine infusion, through a catheter placed in the right carotid artery, was started with a rate of 2 $mcg \cdot kg^{-1} \cdot min^{-1}$ and continued for 30 min. The determinations of lymphatic and hemodynamic parameters were repeated every 30 min for 60 min.

In the Burn group, after the determinations of the baseline and control values (60 min after the jugular venous pressure elevation), the dogs were allowed to breathe spontaneously from the tracheostomy cannula and forced to inhale the flame of the gas burner. The inhalation of flame was carried

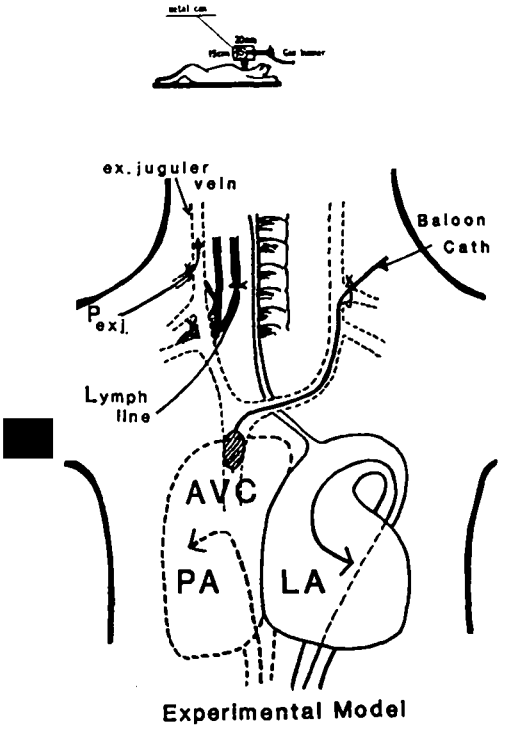

Fig. 1. Method of flame inhalation and cervical venous pressure elevation.

out as it is shown in figure 1. The free end of the cannula was inserted into a hole which was bored on the side of the bottom of a large tin can and the flame was blown into the can. By the blowing of flame into the can, dogs held respiration for about 30 sec and then started to inspire deeply several times. This hyperventilation lasted usually until bradycardia occurred. When the bradycardia was noted, the inhalation of flame was stopped and dogs were allowed to recover. This manoeuvres were repeated three times. After the flame inhalation, the dogs were ventilated mechanically again and the same determinations were repeated for three hours.

Measurements

The lymphatic fluid was collected in a small tube and the lymphatic flow rate (Q_L) was determined by weighing the tube and subtracting the tare weight every 15 min. The total protein concentrations in the lymph (C_L) and plasma (C_P) were determined with a spectrophotometric method using the biuret reaction. The lymph to plasma protein concentration ratio (C_L/C_P) was calculated.

Monitoring

ECG, mean aortic pressure (MAP), mean pulmonary arterial pressure (MPAP), pulmonary capillary wedge pressure (PCWP), mean left atrial pressure (LAP), central venous pressure (CVP) and right external jugular venous pressure (P_{EXJ}) were shown through the pressure transducers (HP-1290) on the multi-monitor (HP-78342A). The body temperature of the dog during the experiment was kept between 38–39°C. The blood gas measurements were repeated every 30 min.

Statistics

The means and standard deviations were calculated for each measured parameter during the experiment. Paired and unpaired t tests were applied where it was appropriate. A significant difference was indicated when P is smaller than 0.05.

Results

In the table 1, results of the Control group are presented. By the inflation of the intra-caval balloon, the right jugular pressure (P_{EXJ}) was maintained on the level of 30 mmHg. In the hemodynamic parameters, there were no remarkable changes except the falls in cardiac output 2 and 3 hr after the venous pressure elevation. Towards the end of the experiment, the difference between LAP and PCWP was enlarged. After the venous pressure elevation, the volume of infusion increased by about 10 times but it decreased gradually with time. The infusion volume needed, was about 0.5 $ml \cdot kg^{-1} \cdot min^{-1}$ 1 to 2 hr after the venous pressure elevation.

The profile of the lymphatic parameters is presented in figure 2. By the elevation of the jugular venous pressure, the vascular bed in the head and neck was recruited and the lymphatic flow rate (Q_L) increased by about 10 times. With the increase in Q_L, the protein concentration of the lymph (C_L) fell significantly. This was associated with a mild decrease in the plasma protein con-

Table 1. Control group (n = 6)

		baseline	30 min	60 min	120 min	180 min
CO	$ml \cdot kg^{-1} \cdot min^{-1}$	164±38	148±35	150±26	128±26*	130±35**
HR	$beats \cdot min^{-1}$	156±36	176±49	174±45	176±42	172±27
MAP	mmHg	134±15.6	140±18.8	136±18.7	135±13.6	134±12.8
MPAP	mmHg	17.7±0.8	18.6±2.6	20.8±5.8	19.5±3.1	18.3±2.4
PCWP	mmHg	6.2±2.8	6.8±3.3	7.0±2.2	7.7±2.9	8.2±3.4
LAP	mmHg	6.0±2.3	5.5±1.9	5.3±1.6	5.5±1.4	4.5±0.8
P_{EXJ}	mmHg	4.8±2.2	30.5±1.0**	30.0±0.6**	29.5±0.8**	30.0±0.6**
Hb	$g \cdot dl^{-1}$	13.4±1.7	12.8±1.6	12.8±1.7	13.0±1.7	13.3±2.3
Infusion	$ml \cdot kg^{-1} \cdot min^{-1}$	0.17±0	1.84±0.30**	0.64±0.14**	0.53±0.21**	0.35±0.56**
Pa_{O_2}	mmHg (FI_{O_2}=0.5)	225±25	217±28	214±14	221±24	213±15
Q_L	$mg \cdot kg^{-1} \cdot 15\ min^{-1}$	34±18	227±67**	316±55**	344±70**	374±75**
C_P	$g \cdot dl^{-1}$	4.70±0.87	4.11±0.37	4.12±0.27*	4.14±0.34	3.88±0.56**
C_L	$g \cdot dl^{-1}$	2.11±0.183	1.10±0.259**	0.84±0.073**	0.86±0.112**	0.81±0.132**
C_L/C_P		0.46±0.074	0.27±0.062**	0.21±0.026**	0.26±0.033**	0.21±0.038**

The values are the means ± standard deviation (n = 6).
*: significantly different from the baseline value, $P < 0.05$.
**: $P < 0.01$.

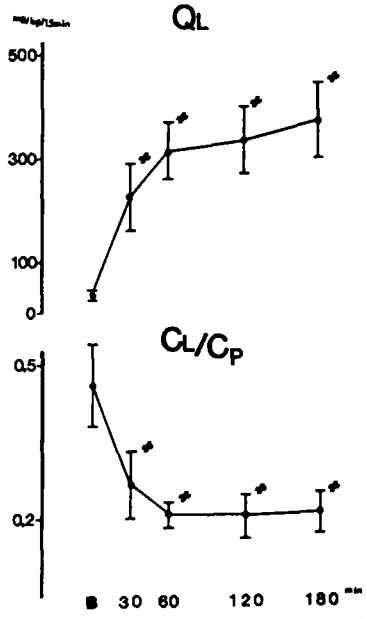

Fig. 2. Changes in lymph flow rate (Q_L) and protein concentration ratio between lymph and plasma (C_L/C_P) after venous pressure elevation.
Values are means ± SD. n = 6. B: baseline.
#: significantly different from the base line value with P smaller than 0.005.

centration (C_P). As it is seen in figure 2, after the venous pressure elevation the protein concentrations-ratio between lymph and plasma (C_L/C_P) decreased significantly in the first 60 min and made a plateau around the value of 0.2. A new steady state was established 45 min after the venous pressure elevation. These findings suggest that the reflection coefficient (σ) of the normal craniocervical vascular bed is about 0.8[8].

Table 2 shows the results of the Histamine group. The baseline and control values were almost the same as in the Control group. After the histamine infusion, the mean arterial pressure fell significantly but the cardiac output was kept unchanged. This reaction seemed due to the vasodilating effect of histamine on the systemic circulation. The cervical lymphatic flow rates increased after histamine but they were not significant compared with the control value. The most remarkable change associated with the histamine infusion, was the decrease in plasma protein concentration (C_P). The falls of C_Ps after histamine were significant not only against the control value but also against the C_Ps in the Control group of the same timing. Because the lymphatic protein concentration (C_L) remained without any marked changes, the calculated C_L/C_P increased significantly after histamine (fig. 3). The values of C_L/C_P after histamine were about 0.4 and signif-

Table 2. Histamine group (n = 6)

		baseline	Control (60 min)	90 min	120 min
CO	$ml \cdot kg^{-1} \cdot min^{-1}$	125 ± 25	134 ± 41	136 ± 47	139 ± 43
HR	$beats \cdot min^{-1}$	192 ± 24	190 ± 25	174 ± 39	178 ± 34
MAP	mmHg	142 ± 15.8	140 ± 17.1	78 ± 5.7*	93 ± 17.9*
MPAP	mmHg	16.3 ± 3.9	17.5 ± 4.3	15.8 ± 3.8	18.3 ± 4.1
PCWP	mmHg	7.2 ± 4.5	6.2 ± 4.2	5.7 ± 3.3	6.0 ± 3.3
LAP	mmHg	5.2 ± 1.7	5.0 ± 2.8	4.3 ± 2.9	5.0 ± 2.9
P_{EXJ}	mmHg	3.2 ± 1.5*	29.7 ± 0.5	30.5 ± 0.8	29.7 ± 0.7
Hb	$g \cdot dl^{-1}$	14.3 ± 1.9	13.0 ± 1.5	12.3 ± 2.0	12.6 ± 1.5
Infusion	$ml \cdot kg^{-1} \cdot min^{-1}$	0.17 ± 0*	0.44 ± 0.24	0.32 ± 0.57	0.30 ± 0.37
Pa_{O_2}	mmHg (FI_{O_2}=0.5)	241 ± 24	228 ± 35	202 ± 31	208 ± 34
Q_L	$mg \cdot kg^{-1} \cdot 15\ min^{-1}$	28 ± 17*	299 ± 111	366 ± 130	403 ± 143
C_P	$g \cdot dl^{-1}$	5.73 ± 0.68*	4.40 ± 0.24	3.16 ± 3.57*s	2.97 ± 0.37*s
C_L	$g \cdot dl^{-1}$	2.81 ± 0.626*	1.05 ± 0.215	1.28 ± 0.188s	1.16 ± 0.330
C_L/C_P		0.49 ± 0.072*	0.24 ± 0.043	0.41 ± 0.141*s	0.40 ± 0.125*s

The values are the means ± standard deviation (n = 6).
*: significantly different from the control value, $P < 0.05$.
s: significantly different from the same value in the Control group, $P < 0.05$.

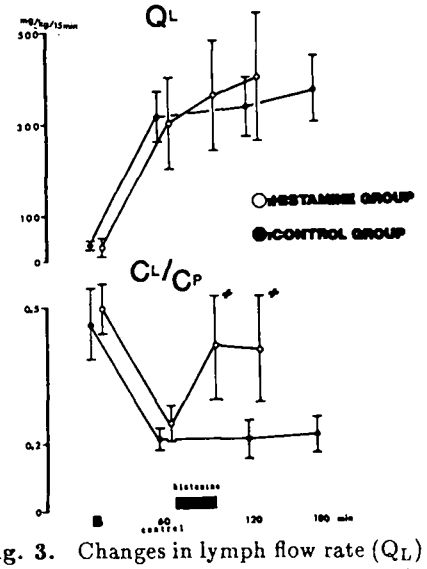

Fig. 3. Changes in lymph flow rate (Q_L) and protein concentration ratio between lymph and plasma (C_L/C_P) after venous pressure elevation and histamine infusion.

Values are means ± SD. n=6 in both groups.

B: baseline. 60 (control): after venous pressure elevation.

#: significantly different from the control value with P smaller than 0.01.

icantly different from the C_L/C_Ps in the Control group. This finding suggests a decrease in reflection coefficient (σ) by about 0.2 after the histamine infusion.

In table 3, the results of the Burn group are presented. In this group, the inhalation of flame was made just following the determination of the control values and the observation was continued for 3 hr after the flame inhalation. About one hour after the flame inhalation, a large volume of frothy fluid was noted in the trachea and the arterial oxygen tension (Pa_{O_2}) fell gradually. Two hours after the flame inhalation, Pa_{O_2} was significantly lower than the control value. This pulmonary edema continued until the end of the experiment. The lung removed at the end of the experiment was heavy and edematous and the epithelial surface of the trachea was burned black down to the bifurcation, but on the epithelium of the main bronchi no remarkable changes were noted under direct vision.

After the burn, the arterial blood pressure was maintained unchanged but the cardiac output decreased markedly. In the lymphatic parameters there were no significant changes either in the plasma- or in the lymphatic protein concentrations. Only the lymphatic flow rate increased significantly 2 hr after the burn but it decreased thereafter. It seems likely, if the cardiac output towards the end of the experiment were kept undecreased, the

Table 3. Burn group (n = 5)

		baseline	control (60 min)	90 min	120 min	180 min	240 min
CO	$ml \cdot kg^{-1} \cdot min^{-1}$	174±41	161±43	142±22	155±39	146±43	130±30
HR	$beats \cdot min^{-1}$	183±41	183±40	178±36	170±38	167±43	169±47
MAP	mmHg	144±16.3	139±19.8	137±16.1	141±17.3	140±15.2	136±21.6
MPAP	mmHg	16.4±5.0	18.0±8.8	17.4±9.1	17.6±8.8	21.2±8.6	19.4±4.0
PCWP	mmHg	6.4±2.6	6.0±2.6	6.6±2.1	6.2±1.3	6.6±1.7	7.0±2.6
LAP	mmHg	4.8±1.9	4.6±1.3	4.2±1.9	4.2±1.8	4.4±1.1	4.2±1.3
P_{EXJ}	mmHg	4.4±2.7*	39.6±0.6	30.2±1.3	29.6±1.5	29.0±0.7	29.8±0.8
Hb	$g \cdot dl^{-1}$	14.0±1.1	13.5±1.5	13.5±2.4	13.7±2.0	14.5±3.7	14.8±2.9
Infusion	$ml \cdot kg^{-1} \cdot min^{-1}$	0.17±0*	0.55±0.19	0.70±0.35	0.76±0.28	0.40±0.12	0.34±0.06*
Pa_{O_2}	mmHg (FI_{O_2}=0.5)	239±29	245±43	250±24	220±70	129±52*	82±6*
Q_L	$mg \cdot kg^{-1} \cdot 15\ min^{-1}$	37±10*	328±36	389±104	419±87	437±98*	364±44
C_P	$g \cdot dl^{-1}$	5.05±0.44	4.39±0.84	3.98±0.61	4.03±0.49	3.88±0.64	3.88±0.47
C_L	$g \cdot dl^{-1}$	1.71±0.410*	1.00±0.359	0.93±0.252	0.82±0.343	0.70±0.232	0.66±0.290
C_L/C_P		0.37±0.135	0.23±0.066	0.23±0.034	0.20±0.063	0.18±0.034	0.17±0.056

The values are the means ± standard deviation (n = 5).
*: significantly different from the control value, $P < 0.05$.
s: significantly different from the same value in the Control group, $P < 0.05$.

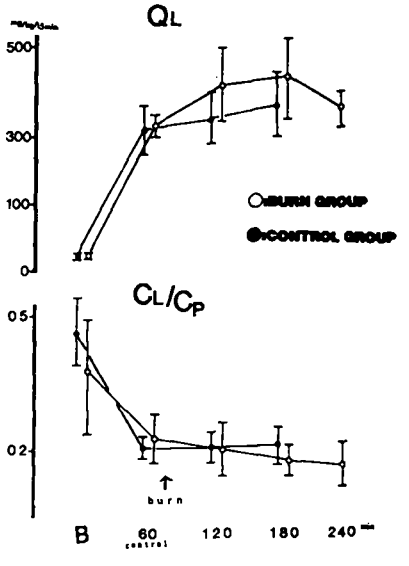

Fig. 4. Changes in lymph flow rate (Q_L) and protein concentration ratio between lymph and plasma (C_L/C_P) after venous pressure elevation and flame inhalation. Note, no values in the Burn group are significantly different from the Control group.

Values are means ± SD. n is 6 in the Control group and 5 in the Burn group.

B: baseline. 60 (control): after venous pressure elevation.

lymphatic flow rate should have increased much more. Therefore, the fact that the C_L/C_P in this group did not increase after the burn, should be emphasized (fig. 4). Here no evident decrease of σ was suggested.

Discussion

When a flame is inhaled, the penetration of thermal injury into the lung has been reported not deep[21]. Because the flame is cooled rapidly during the passage through airway, the injuries stay usually only in trachea. In our study, the visible lesions of the airway mucosa did not extend beyond the tracheal bifurcation. However, our intention for the flame inhalation is not to produce a thermal injury deeply in the lung, but to produce a burn lesion in the body area, from where humoral mediators released from the burned tissue, if any which can increase the vascular permeability in the unburned body area, can be distributed evenly over the whole body.

According to the Starling equation formulated by Kedem et al.[9], the net fluid filtration through the microvascular wall can be written as follows;

$$Qf = KS[(Pmv - Ppmv) - \sigma(\Pi mv - \Pi pmv)] \quad \ldots\ldots\ldots 1)$$

Where Qf is the net filtration rate of fluid, K is the fluid filtration coefficient of the microvascular wall, S is the microvascular surface area, σ is the reflection coefficient of the microvascular barrier, Pmv and Ppmv are the microvascular and interstitial hydrostatic pressures and Πmv and Πpmv are the microvascular and interstitial colloid osmotic pressures. The parallel equation for solute filtration is:

$$Qs = PS(\Pi mv - \Pi pmv) + (1 - \sigma)\,Cs \cdot Qf \quad \ldots\ldots\ldots\ldots 2)$$

Here, Qs is the net solute filtration rate, P is the diffusive permeability coefficient of the solute and Cs is the average solute concentration across the microvascular wall. If all the filtrate should be drained without any concentration or dilution into the lymph, the lymph flow rate must be equal to Qf and the solute concentration in lymph must be Qs/Sf[10,11].

$$C_L = Qs/Qf = PS(\Pi mv - \Pi pmv)/Qf + (1 - \sigma)\,Cs \quad \ldots\ldots\ldots\ldots 3)$$

When the vascular permeability increases, it causes a decrease in σ and increases in P and K and the result is increases in both Qs and Qf[3]. Therefore, in order to indicate an increase in vascular permeability, the changes in σ must be determined. On this account, we intended a maximal recruitment of the microvascular bed by elevating venous pressure. This caused an increase in Qf and a decrease of C_L on account of the increase in S and Pmv in equation 1. As it is clear from equation 3, if the increase in Qf is large enough, C_L approximates to $(1 - \sigma)$ Cs. Assumed $Cs = (C_L + C_P)/2$, σ can be written as follows[8,12,13];

$$\sigma = (1 - C_L/C_P)/(1 + C_L/C_P) \quad \ldots\ldots 4)$$

Therefore, the more the Qf increases and the more C_L/C_P decreases, the closer approximates the σ to $(1 - C_L/C_P)$[4,8]. This is the reason, why we estimated σ in the normal craniocervical vascular bed at about 0.8 from the plateau value of C_L/C_P of about 0.2, which was obtained in the Control group after the jugular venous pressure elevation.

By contrast, the C_L/C_P in the Histamine group increased by about 0.2 after the histamine infusion of 5 mcg·kg^{-1}·min^{-1} into the right carotid artery. Histamine is a potent vasodilator and it is widely believed that histamine increases vascular permeability. However, the effects of histamine on vascular permeability are not completely evident. In a canine model, Drake and his colleagues gave histamine of 3.6 to 8.3 mcg·kg^{-1}·min^{-1} intravenously but failed to prove any evidence of increased vascular permeability in the lung[14]. Rippe et al. reported no increases in vascular permeability following a bolus injection of histamine (2 to 4 mg) into the perfusate of a removed canine lung[15]. On the other hand, O'Neill and his colleagues have successfully proved an increased vascular permeability following an intra-arterial infusion of histamine of 16 mcg·kg^{-1}·min^{-1} in the lamb's hind leg[16]. Brigham et al. also reported an increase of vascular permeability after an infusion of histamine of 4 mcg·kg^{-1}·min^{-1} 4 hr long to the sheep[17]. In this study, the C_L/C_P from the area with fully recruited vascular bed, showed a significant increase after the intra-arterial histamine infusion. From these findings, we were convinced of the permeability increasing effect of histamine also in the canine peripheral vascular bed.

In this study, the Q_L and C_L/C_P in the Burn group showed no increases after the flame inhalation and only the Pa_{O_2} decreased significantly. Now it is believed that the vasodilation and endothelial damages due to heat cause a marked increase in vascular permeability, and a large volume of plasma proteins leaks out into the interstitial space with water[18,19]. It was also reported that the increase in vascular permeability in the thermally injured tissues reaches its maximum about 2 hr after the injury and continues 6 to 12 hr[20]. According to Demling and his colleagues, about 3/4 of the edema formed in the thermally injured tissues, occurs in the first 4 hr and reaches maximum 18 hr after the injury[2]. They also reported that lymphatic drainage from the injured tissues increases soon after

the burn and becomes maximum at 6 hr and stays increased for about 60 hr. Concerning the lymph from the lung with a thermal injury on the airway, similar results were reported[21]. The lymphatic flow rate from the injured lung continues to increase by about 6 hr after the injury and the C_L/C_P in it also increases with a maximum value at 4 hr after the injury. On the other hand, some studies suggest that edema formation in the thermally injured tissues is not only a result from the increased vascular permeability but from the transition of water into the interstitial space caused by the decreased plasma oncotic pressure[22]. Therefore we have no evident conclusions about the cause of edema formation following the burn.

The results in our Burn group did not suggest any increases in vascular permeability in the unburned tissues. If the changes in vascular permeability following a burn, especially in the uninjured tissues, should be referred to some neural[18] or humoral factors, for instance, to histamine[23], prostaglandins[24,25], or burn toxins, it must take time before vascular permeability changes. The time interval of 3 hr, during which we observed the changes in lymphatic parameters after the flame inhalation, can be too short for vascular permeability to increase. Although Demling reported immediate increases in lymphatic flow rates not only from the injured but also from the uninjured tissues after the burn, we could not find such prompt increase in lymphatic flow rate from the craniocervical region. This finding may also suggest that vascular permeability in the not directly burned tissues does not really increase following a burn. Anyway, so far as we could confirm through this study, vascular permeability in the unburned tissues did not increase at least in the first 3 hr after the burn.

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