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Donor Pretreatment With PAF Antagonist TCV－309 Enhances Lung Preservation

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background and purpose

Considerable efforts have been made to understand the physiological roles of PAF in organ transplantation and heart-lung and lung transplantation using several different PAF receptor antagonists. Experimentally pulmonary dysfunctions manifested as low oxygen tension, high pulmonary vascular resistance, decreased pulmonary compliance and lung edema following transplantation are similar to the pathophysiological manifestations of PAF.

methods

In the present study determination of the optimum time to administer PAF antagonist was elucidated for beneficial effects and also the function of the graft was assessed. Canine single lung allotransplantation was performed after 24-hour preservation of a donor lung.

The PAF antagonist TCV-309 was added to the Euro-Collins solution in all groups, and in Group 1 which served as control group, no other pharmacological intervantion was done. In Group 2 TCV-309 was adnministered to the recipient prior to reperfusion. In Group 3 TCV-309 was administered to the donor prior to organ harvesting and administered to the recipient prior to reperfusion.

results

Optimum posttransplant graft function and superior recipient's survival was obtained in Group 3. One hour after reperfusion, the PaO_2 in Group 3 was significantly higher than those in Group 1 and 2: 327±181 mm Hg versus 152±95.2 mm Hg and 151±143 mm Hg; ($p < 0.05$).

In every group posttransplant pulmonary function deteriorated until the 4th postoperative day though in Group 2 and 3 pulmonary venous oxygen tension, extravascular thermal volume and myeloperoxidase activity in the lung tissue was restored by the 14th postoperative day.

conclusions

It is a clue in achieving a great success of lung transplantation to administer the PAF antagonist TCV-309 to the donor, and TCV-309 shows considerable promise in improving the function of the 24 hour hypothermic preserved canine lung allografts after reperfusion.

Introduction

Reperfusion injury is defined as the organ damage which is sustained by an organ during ischemia and as a consequence of reestablishment of blood flow. Especially the generation of free oxygen radicals is presumed as a substantial pathogenetic principle in this injury. Reperfusion injury is attributed by a complex of various mechanisms, including leukocyte, activation of platelet, formation of oxygen free radical, activation of the complement, the generation of inflammatory mediators and arachidonic acid metabolites [1]. In ischemia reperfusion injury, PAF is known to have a consequential role in which the mechanism is complementary to that of oxygen free radicals.

PAF displays biological activities during an inflammatory reaction. PAF causes vasoconstriction, increases vascular permeability, and induces interstitial edema formation. Moreover, PAF recruites and activates platelets, neutrophils, and monocytes at the site of inflammatory reaction. These actions enhance the migration of inflammatory cells into the tissue. PAF causes the release of other humoral mediators, such as other autacoids, certain enzymes, and oxygen radicals, that contribute to tissue injury [2].

There are several known corroborations accounting PAF and its effect on the lung [3]. Using the isolated rat lung models, lung edema caused by intravenous infusin of PAF is secondary to leukotriene production. Stenmark and coworkers reported the presence of PAF in patients with bronchopulmonary dysplasia. PAF-like activity was found in the lavage fluid from whom premature baboons delivered by caesarian section at 140 days gestation and ventilated for 6 days with 100 % oxygen. These evidences indicate that PAF may be released by cells which are attracted to sites of lung injury and may exacerbate a pre-existing condition of lung injury. Platelet and leukocyte aggregation in the lung is a prelude to lung damage after ischemia and reperfusion.

TCV-309 was developed by Terashita [4][5][6] who first reported the PAF antagonist CV-3988 in 1985 which is more potent and selective than CV-3988. This PAF antagonistic action of TCV-309 is over 100 times more potent than

CV-3988. TCV-309 has a beneficial effect on endotoxin and anaphylactic shock in vitro and in vivo.

Tagawa et al.[7] demonstrated attenuation of reperfusion injury by using an isolated lung perfusion model when TCV-309 was added to perfusion medium or preservation solution in a canine 24 hour preserved lung. Our previous study[8] proved that the PAF antagonist TCV-309 was a beneficial agent when administered to the donor and the recipient and added to the Euro-Collins solution in a canine model of a single lung transplantation after 24 hr preservation.

There are several reports in lung or heart and lung transplantation using PAF antagonists[9,10], but the optimum timing of its administration has not yet been discussed.

It is undoubted that PAF and activated oxygen radicals play a major role in the phase of reperfusion[11] though the possibility that PAF may concern during organ harvest and preservation has not yet been proved. The result that TCV-309 in Euro-Collins solution enhanced lung preservation using isolated lung perfusion model by Tagawa offered the possible role of PAF in the phase of lung preservation. It is of interest that how the pulmonary function and edema after transplantation, not only immediately after transplantation but also during reimplantation response and stabilized phase which infection or rejection might interfere.

In this study canine single lung allotransplantation was performed after 24-hour preservation to determine the optimum time to administer PAF antagonist for beneficial effect and assess the function of the graft after transplantation.

The PAF antagonist, TCV-309, was added to the 500 mL of Euro-Collins solution in all groups at a dose of 375 μg and administered to recipient and donor or to recipient in order to find the difference between the groups. A unilateral pulmonary artery occlusion test was performed before organ harvesting and one hour after reperfusion, and it was done 4 or 14 days after transplantation in the surviving animals.

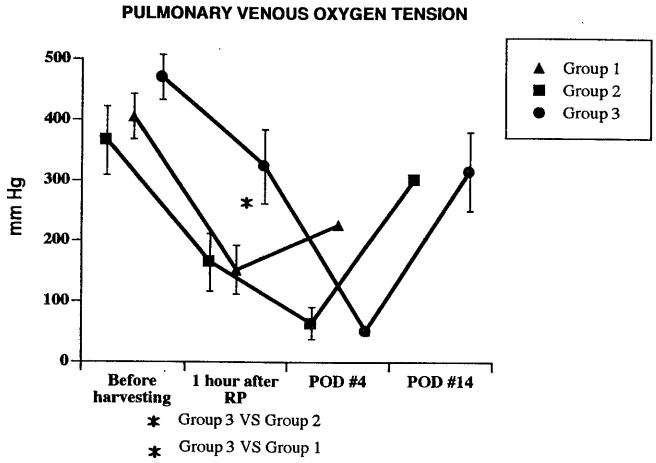

Fig. 1 Pulmonary venous oxygen tension before harvesting and after transplantation.

Definition of abbreviation: RP = reperfusion

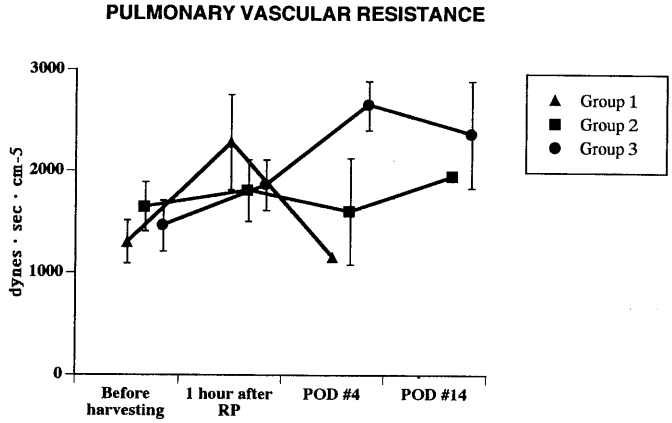

Fig. 2 Pulmonary vascular resistance before harvesting and after transplantation

Definition of abbreviation: RP = reperfusion

Materials and methods

TCV-309 was provided by Takeda Chemical Industries, Ltd. (Osaka, Japan), and was dissolved in normal saline at a dose of 0.1mg/ml.

Experimental design

Fourty-eight size-and weight-matched adult mongrel dogs weighing 10-12 kg were randomely devided into three groups.

Group 1 (n = 6): the donor lungs were flushed with 500 mL of the Euro-Collins solution containing 375 μg TCV-309.

Group 2 (n = 9): the donor lungs were flushed in the same way as Group 1. Recipient dogs were administered intravenously bolus of TCV-309 (100 μg/kg) followed by continuous infusion of TCV-309 (500 μg/kg/hr) for two hours.

Group 3 (n = 9): the donor dogs were pretreated with intravenous bolus of TCV-309 (100 μg/kg) and donor lungs were flushed in the same way as Group 1. Recipient dogs were treated in the same manner as Group 2.

Donor operation, organ harvest and preservation, recipient operation, transplant procedure

The donor dogs were anesthetized with pentobarbital 25 mg/kg intravenously, then endotracheally intubated, and were mechanically ventilated with a tidal volume of 35 mL/kg at a rate of 14 breaths/min with monitoring

airway pressure. An FiO_2 of 1.0 was maintained through out the experiment.

Other procedures, including donor preparation, unilateral pulmonary artery occlusion test, harvest and transplant procedures, were performed as dscribed in the previous publication[8].

The flushing time was defined as the time from the beginnig of flushing until the PA cannula was clamped.

The preparation time was defined as the time from the removal of heart and lung blocks from the cold storage until the anastomosis began.

The implantation time was defined as the time from the beginning of the atrial anastomosis until blood flow was established to the organ.

Posttransplant assessment

One hour after reperfusion, a unilateral pulmonary artery occlusion test was performed occluding right pulmonary artery (PA) and right mainstem bronchus for ten minutes to determine posttransplant graft function.

The surviving animals were sacrificed accordingly on either 4th or 14th postoperative day after the unilateral pulmonary artery occlusion test in supine position.

Histological assessment

One hour after reperfusion, four section from graft lower lobe were stained with hematoxylin and eosin and examined with a light microscope and assayed for MPO activity, lipid peroxide level and determined water content of the lung.

At the time of sacrifice transplanted lung biopsy was obtained from the upper lobe and treated as it was done one hour after reperfusion.

Interstitial and alveolar edema, atelectasis, vascular congestion, and red cell extravasation were graded as follows: 1 = minimal, 2 = moderate, and 3 = severe.

Scores were added, and a histological injury index was calculated for each specimen.

The samples for MPO and lipid peroxide level assay were frozen in liquid nitrogen and kept at −70℃.

Wet to dry weight ratio

Immediately wet weight was measured and then it was kept in a heating oven for 48 hours at 160℃ for dry weight. Water content was calculated as follows: Water content = Wet weight/Dry weight (W/D).

LPO, MPO assay

Measurement of lipid peroxide levels (LPO) and MPO activity in lung tissue were described in our previous study[8].

Immunosuppression

The chest was closed in a standard fashion after inserting a 20 Fr. chest tube. Each animal was treated with daily cyclosporin (10 mg/kg intramuscularly) and penicillin G (200.000 unit / body intramuscularly) for seven days.

No inotropic drugs or diuretics were given through the experiment and the chest tube was removed as soon as the animal awoke from anesthesia.

Animal care

Animals in this study were maintained in accordance with the guidelines of the Committee on Animals of the Nagasaki University School of Medicine.

Animal care was in compliance with the Principles of Laboratory Animal Care formulated by the National society for Medical Research and the Guide for the Care and Use of Laboratory Animals prepared by the Institute of Laboratory Animal Resources, National Academy of Science, and published by the National Institutes of Health (NIH Publication No. 86-23, revised in 1985).

Statistical analysis

Groups of data were evaluated by analysis of variance to indicate groups with significant differences. A P value less than 0.05 was considered significant. Results were presented as mean ± standard deviation. Data were analyzed by Macintosh II cx computer using Statview II statistical software package (Abacus Concepts, Inc., Berkeley, CA).

Result

Transplant results

All animals underwent successful lung transplantation after 24 hours of graft ischemia.

Survival

The survival rate at the 3rd postoperative day was superior in group 3 (77.8%). In contrast groups 1 and 2 showed the same survival rate 33.3%.

In group 1, only one recipient was sacrificed on the 4th postoperative day and another recipient died on the 5th postoperative day from bronchial anastomotic dehiscence. Remaining recipients died within 24 hours after transplantation because of pulmonary edema.

In Group 2, six of nine recipients died within postoperative 3rd day because of pulmonary edema. Other two recipients were sacrificed on the 3rd postoperative day and one recipients was sacrificed on the 10th postoperative day.

In Group 3, two recipients died within 24 hours after transplantation but other three recipients were sacrificed on the 3rd postoperative day four recipients were sacrificed on the 14th postoperative day.

Groups were similar with regard to animal weights, flushing time, preparation time, implantation time and total ischemic time (Table 1).

Pulmonary venous oxygen tension

All experimental groups demonstrated deterioration in pulmonary function after transplantation.

Before harvesting PaO_2 was identical among all groups (Table 2).

One hour after reperfusion PaO_2 in Group 3 was significantly higher than in Groups 1 and 2: 327 ± 181 mm Hg versus 152±95.2 mm Hg and 151±143 mm Hg ($p < 0.05$).

On the 4th postoperative day PaO_2 in Groups 2 and 3 were decreased similarly and recovered on the 14th post-

Table 1. Comparison of experimental groups

		Group 1	Group 2	Group 3
Donor weight	Kg	10.3±2.0	9.6±1.8	10.0±2.0
Recipient weight	Kg	10.8±2.1	10.8±1.6	10.2±1.9
Flushing time	sec	208.5±112.5	189.1±62.0	206.9±54.5
Preparation time	min	21.2±3.1	15.3±5.1	17.2±2.6
Implantation time	min	59.7±11.1	57.0±10.9	63.7±27.7
Total ischemic time	hr, min	25.0±37.7	26.0±7	26.0±7

No statistical significance was seen between groups.

Table 2. Data from donor animal before harvesting and recipient animal one hour after reperfusion

	Group 1		Group 2		Group 3	
	Before harvesting	1 hour after reperfusion	Before harvesting	1 hourafter reperfusion	Before harvesting	1 hour after reperfusion
PaO2 mmHg	405.5±92.2	152.1±95.2 *	352.8±169.8	150.9±142.6 §	474.0±108.9	326.7±180.8 * §
PaCO2 mmHg	23.2±4.7	29.3±8.8	34.3±17.7 §	36.0±17.0	21.3±3.9 §	26.9±5.8
PAP mmHg	24.1±7.5	31.1±8.9	26.8±6.2	29.1±9.9	24.0±7.0	28.0±4.6
PVR dynes.sec.cm-5	1299±514	2284±1150	1637±742	1804±914	1287±761	1685±749
C dyn ml/cmH2O	13.2±2.3	9.4±2.6	16.7±5.3	10.7±2.0	13.4±4.5	10.5±2.8
ETV ml/kg	3.74±1.05	10.05±4.07	3.82±1.72	10.39±5.37	4.22±2.52	8.92±4.52
W/D	5.39±0.17	8.01±1.35	5.38±0.24	8.50±1.29	5.54±0.27	8.11±2.01
LPO n mol MDA/mg protein	6.01±2.65 *	5.80±2.77 *	3.08±4.89	2.70±3.40	0.91±0.30 *	1.01±0.29 *
MPO unit	9.73±1.65	15.02±4.07	13.21±3.78	24.44±16.18	9.26±5.18	13.10±7.57

* $p < 0.05$ Group 3 VS Group 1

§ $p < 0.05$ Group 3 VS Group 2

Table 3. Data from recipient animal at the time of sacrifice

	Group 1	Group 2		Group 3	
	4 th POD	4 th POD	14 th POD	4 th POD	14 th POD
	(n = 1)	(n = 2)	(n = 1)	(n = 3)	(n = 4)
PaO2mmHg	226.8	51.1±37.2	287.5	54.7±11.4	318.5±131.2
PaCO2mmHg	42.8	49.9±21.3	43.2	43.0±17.1	36.3±14.3
PAPmmHg	24.6	30.8±10.7	39	37.4±6.4	30.0±7.3
PVR dynes.sec.cm-5	1155	1595±746	1942	2478±416	2193±1055
C dyn ml/cmH2O	14.2	7.27±4.35	3.16	4.6±0.7	10.0±6.8
ETV ml/kg	8.67	10.69±3.81	6.17	10.8±5.7	5.60±2.43
W/D	7.03	6.19±2.47	6.47	7.79±1.15	6.05±0.86
LPO n mol MDA/mg protein	4.93	0.77±0.54	0.93	0.85±0.20	2.5±2.60
MPO unit	19.72	55.69±15.38	28.62	23.92±31.67	16.01±13.92

Table 4. Lung injury score and cause of death after transplantation

Animals	1 hr after RP	At sacrifice	Day of death	Cause of death
Group 1				
No. 1	2		5	bronchial anastomotic dehiscence
No. 2	1		Day of operation	PE
No. 3	4		Day of operation	PE
No. 4	0	10	4	sacrificed
No. 5	7		Day of operation	PE
No. 6	7		Day of operation	PE
Group 2				
No. 1	6		Day of operation	PE
No. 2	6		Day of operation	PE and atelectasis
No. 3	1		1	PE
No. 4	1	4	4	sacrificed
No. 5	2		1	PE
No. 6	2	8	14	sacrificed
No. 7	9		1	PE
No. 8	1	6	4	sacrificed
No. 9	4		3	bronchial anastomotic dehiscence
Group 3				
No. 1	2	0	14	sacrificed
No. 2	3		Day of operation	PE
No. 3	1	2	14	sacrificed
No. 4	2	0	4	sacrificed
No. 5	2	7	4	sacrificed
No. 6	2	8	14	sacrificed
No. 7	0	6	13	sacrificed
No. 8	3		Day of operation	PE
No. 9	1	3	3	

Definition of abbreviation : RP = reperfusion PE = pulmonary edema

operative day (287.5 mm Hg and 318.5 ± 131 mm Hg for each) (Table 3).

In regard to $PaCO_2$ before harvesting Group 2 showed higher CO_2 tension than Group 3 ($p < 0.05$) (Table 2). Otherwise there was no significant difference in arterial $PaCO_2$ throughout the study.

PVR

All groups demonstrated elevation in pulmonary vascular resistance but one hour after reperfusion Groups 2 and 3 showed less elevation than Group 1 (1804 ± 914 dynes • sec • cm-5 and 1685 ± 750 dynes • sec • cm-5 vs. 2284 ± 1150 dynes • sec • cm-5) (Table 2).

On the 4th postoperative day PVR in Group 3 increased but PVR in other two groups decreased comparing one hour after reperfusion but Groups 2 and 3 showed same increase in PVR on the 14th postoperative day (1942 dynes • sec • cm-5 for Group 2 and 2193 ± 1055 dynes • sec • cm - 5 for Group 3) (Table 3).

Lung compliance

Dynamic lung compliance was similar in every group until the 4th postoperative day while it decreased after transplantation. One the 14th postoperative day lung compliance recovered in Group 3 while declined in Group 2 (10.0 ± 6.8 mL / cm H_2O for Group 3 and 3.2 mL/cm H_2O for group 2) (Table 3).

ETV

Extravascular thermal volume (ETV) was similar in all groups. (Table 1)

After transplantation ETV increased until the 4th postoperative day in Groups 2 and 3 and decreased on the 14th postoperative day, that is a slight higher than the before harvesting level (6.17 mL/kg in Group 2 and 5.60 ± 2.43 mL /kg in Group 3) (Table 3).

W/D

Wet to dry ratio was comparable to ETV in each group (Table 1). Water content in lung tissues increased after reperfusion and decreased in every group on the 4th postoperative day. On the 14th postoperative day in Groups 2 and 3 wet to dry ratios were slightly higher than those ratios before harvesting (Table 3).

LPO

LPO, measured as thiobarbituric acid reactive material, was significantly lower in Group 3 than Group 1 before harvesting and one hour after reperfusion: 0.91 ± 0.3 nmol MDA / mg protein versus 6.01 ± 2.65 nmol MDA / mg protein and 1.01 ± 0.29 nmol MDA / mg protein versus 5.8 ± 2.77 nmol MDA / protein ($p < 0.05$) (Table 1). In Group 2 LPO was lower than in Group 1 before harvesting and after reperfusion, although the difference was not statistically significant. On the 4th postoperative day LPO in Group 1 and 2 decreased while LPO in Group 3 showed slight increase and LPO in Group 2 and 3 showed further increase on the 14th postoperative day (Table 3).

MPO

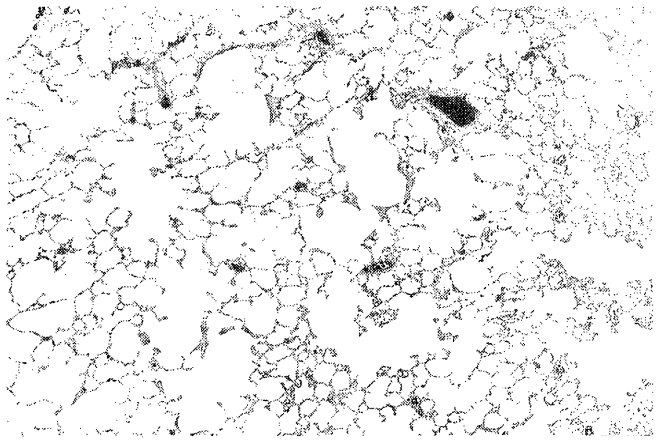

Fig. 3 Photomicrograph of the lung allograft in dog No. 4 in Group 3 before and one hour after reperfusion. Minimal congestion can be seen.

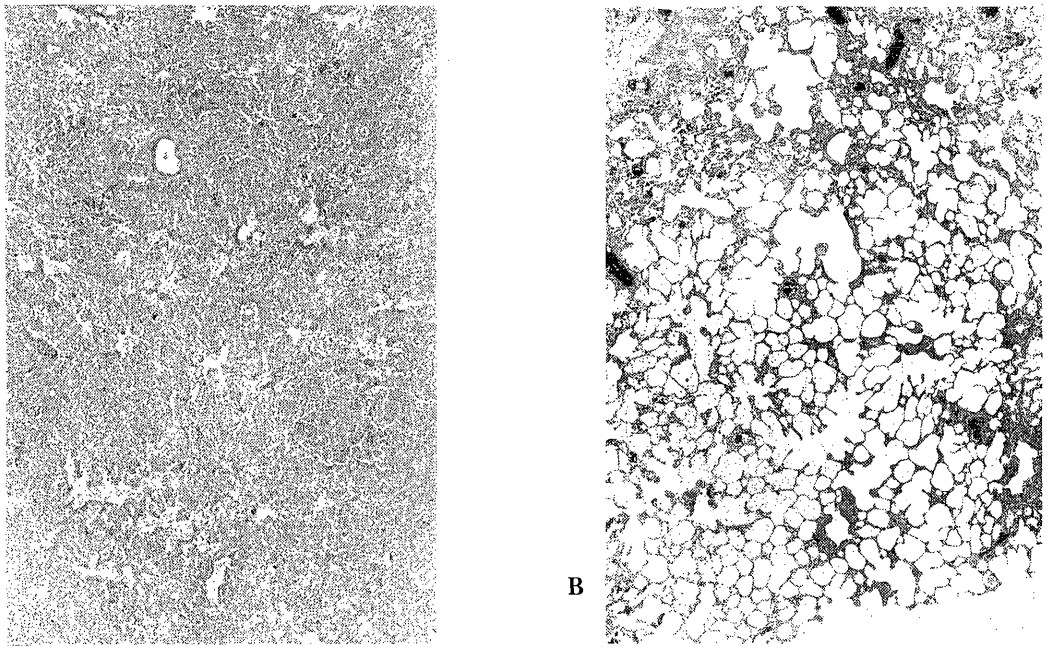

Fig. 4 A: Photomicrograph of the grafted lung (No. 6 in Group 2) 14 days after transplantation. Severe congetion and edema can be observed.
B: Photomicrograph of the grafted lung (No. 3 in Group 3) 14 days after transplantation. Pulmonary architecture is presrved and there is no evidence of rejection.

In each group MPO activity increased following reperfusion until the 4th postoperative day. In Group 3 MPO activity was smaller than in Groups 1 and 2 beginning from harvesting until the 4th postoperative day, but statistically not significant. On the 14th postoperative day MPO activity in Groups 2 and 3 decreased as that of one hour after reperfusion (Table 1 and 3).

Histopathology following lung transplantation

Histological injury indices one hour after reperfusion are depicted in Table 4. Alveolar structure were well preserved in Group 3, though statistical significance was not found (Fig. 3).

On the 4th postoperative day histological examination showed moderate to severe congestion and edema in every group. In Group 1 one recipient demonstrated acute bronchopneumonia.

On the 14th postoperative day only one recipient in Group 2 showed intraalveolar hemorrhage and congestion. In contrast, three of the four recipients in Group 3 showed normal pulmonary architecture without evidence of rejection (Fig. 4).

Discussion

As repoeted previously, the addition of TCV-309 to the Euro-Collins solution in vivo didn't prove beneficial effect on lung preservation. However, it attenuated ischemia reperfusion injury in an ex vivo canine isolated lung perfusion model after 24 hour preservation.

The applicating effect of BN 52021, which is classified as a natural product, to donor prior to harvest, to recipient prior to reperfusion and preservation solution was most efficient after 6 to 22 hour preservation in a canine model of single lung transplantation[9)10)11)]. In this study, the superior results were obtained in the lungs treated with intravenous bolus of TCV-309 prior to flushing with Euro-Collins solution. Conte and coworkers[9)] explained that the additional treatment of the donor may have caused less leukocyte and platelet adhesion to the vasculature during flushing of the lungs, and protected from both circulating leukocytes and alveolar macrophages. They also proved large numbers of polymorphonuclear leukocytes and twice as many macrophages in the aspirates obtained from the lungs during hypothermic storage. Considering the half life of TCV-309[5)], it is possible that antagonizing action of TCV-309 is able to prevent the activation of leukocytes, macrophages and endothelial cells during ischemic phase as well as reperfusion phase resulting in respiratory burst. Lambert and colleagues[13)] demonstrated that dimethyltiourea, a low molecular weight free radical scavenger in lung tissues at the time of ischemia was effective.

There are several evidences that factors to the donor are able to ameliorate and enhance lung preservation. Prostaglandin is a well-known agent of its potent property of vasodilator, and the importance of administration of Iloprost to donor was demonstrated by Novick[14)]. Another evidence is that donor pretreatment with PGE1 provided improved cellular preservation which decreased the extent of endothelial cell swelling on electron microscopy in a primate of heart-lung transplantation after a 6 hours duration of cold ischemia.[15)] Yokomise et al.[16)] proved administration before lung extraction was of a more benefit than verapamil infused only at reperfusion because prolonged ischemic necessitated verapamil with the beneficial action on preservation.

It is well known that organ preservation injury is composed of two components: damage induced during cold storage and damege resulting from reperfusion.
Moreover, organ damage during organ harvesting is postulated. In case of our heart-lung procurement, encircling main pulmonary artery and right pulmonary artery, manupilation of the heart and the lungs as well as warm ischemia might activate neutrophils and endothelial cells including platelets.

Southard and colleagues[17)] suggested the oxygen free radical generation in hypothermically preserved and transplanted organs be reponsible for injury to the organ in the 48-hour preserved rabbit liver by using isolated perfused model.
The oxygen free radicals are generated on reperfusion though the rate of its formation may be greater if oxidases are activayed during preservation and warm ischemia. Besides, as already proved, oxygen free radical generation was to be cytotoxic if the cellular antioxidant defense system were compromised. The present data clearly supports the tissue injury during organ harvest and preservation and speculate the role of oxygen free radicals and antagonizing action of TCV-309 which ameliorates ischemia reperfusion injury. Hypoperfusion and consecutive hypoperfusion of the graft by no-reflow phenomenon under reperfusion can occur if vasoactive metabolites are accumulated in the lung during cold storage and reoxygenation contributes to tissue damage through the formation of oxygen free radicals, the release of chemoattractant mediators such as TNF, IL-1 and LTB 4 and the activating leukocytes. The leukocytes, after upregulation of leukocytic (CD11/CD 18) and endothelial adhesion receptors (ICAM, GMP-140) adhere to endothelium which release chemoattractant and oxygen radicals resulting in organ damage.

Another cytoprotective possibility of PAF antagonist was forwarded by Bielenberg et al.[18)] using WEB 2086. They proved the cytoprotective action by apafant, as a result of interruption of multiple pathways triggered by PAF, mainly via a direct effect on brain tissue that has no major vascular component in a rat stroke model.

In this study total ischemic time was about 26 hours in every group. It might be vulnerable to the grafts considering severe pulmonary edemas occuring on the postopertive three to four days as expressed by most incresed lung water content and MPO activity in lung tissues, as a result recipients failed to survive. In contrast, a long ischemic time might revealed the substance of administration of TCV-309 to the donor. In consequence deterioration of lung function in each of the experimental groups was outstanding. Especially, the function in the lungs which were not treated with intravenous bolus of TCV-309 prior to flushing with preservation solution, were deteriorated remarkably and therefore animals died with histologically proved congestion and edema.

It is noteworthy that difference of the function between the lungs treated with TCV-309 prior to reperfusion and the lungs treated with TCV-309 prior to flushing was investigated, because there are so many evidences that suggest the major part of tissue injury occurs upon reperfusion and is mediated by activated neutrophils.[19)]

The present study was designed to determine the optimum time to administer PAF antagonist for beneficial effect and assess the function of the graft in a canine model of single lung allotransplantation after 24 hour

preservation. In this study it is a clue to administer the PAF antagonist TCV-309 to the donor which is consequently manifested by better posttransplant recipient's long term survival, oxygenation, lower pulmonary vascular resistance, less lipid peroxidation and less neutrophil sequestration. Posttransplant pulmonary function was deteriorated until the 4th postoperative day and their pulmonary venous oxygen tension, extravascular thermal volume and myeloperoxidase activity in lung tissue were restored by the 14 th postoperative day in the lungs which were transplanted to the recipients treated with TCV-309 before and after reperfusion.

In summary, it is a clue to administer the PAF antagonist TCV-309 to the donor and TCV-309 shows a considerable promise in improving the function of the 24-hour hypothermic preserved canine lung allografts after reperfusion.

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