Bronchial Blood Flow at Anastomosis of Allografts in Relation to Immunosuppresive Drugs

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ABSTRACT : The microflow in the bronchial mucosa was measured by means of electrochemically generated hydrogen on dogs, identifying close producibility of measurement. In general anesthsia, the microflow of tracheal bifurcation was 71.5± 13.23 ml/min/100 g that of right main bronchus, 65.6±10.84 and that of left main bronchus, 69.0±12.51 respectively. There was no significant difference in microflow between anastomically difeerent sites. Basic diffusion in the bronchial mucosa was estimated as many as 17.0±4.80 ml/min/100 g. The microflow at bronchial anasto-mosis in autografts increased on day 3 and hyperdynamic state continued on day 7 to 14. On the other hand, that in allografts treated with cyclosporine A (CyA) showed increased levels on day 5 although that treated with azathioprine demon-strated lower levels until on day 7, thereafter increased on day 10.

INTRODUCTION

Determination of microflow of the brain and digestive tract by means of electrochemically generated hydrogen has been applied in clinical use. However, little information in the field of study on microflow in the submucosa of the trachea is available[1, 2].

In this study, the availability of determina-tion of microflow of the trachea and its bifur-cation is tested on dogs in terms of the repro-ducibility of this measurement method and diffusion volume of electrochemically generated hydrogen. Furtheremore, wound healing at bronchial anastomosis was experimentally com-pared between lung allografts using immuno-suppressive drugs of azathioprine (Aza) and cyclosporine A (CyA) in terms of microflow in the submucosal layer of the trachea to define the influence of the immunosuppressive drugs on the sites of bronchial anastomosis of lung allografts.

I Preliminary Study

1 MATERIALS AND METHODS

Mongrel dogs weighed from 8.0 to 14.5 kg were anesthetized with 35 mg/kg of nembutal sodium and intratracheally intubated and con-nected with Harvard respirator with respirato-ry rate of 14/min and tidal volume of 25mg/kg. The counter electrode (plate type) was placed on the membranous layer of the mouth. Bron-chscopy (BF type 2 of Olympus) was also used and two electrode catheters (1.8mm outer dia-meter and 2.5mm insertion length, Fig. 1) were introduced from the channel hole. The place-ments of these electrodes were selected in bet-ween cartilaginous rings which was visible via bronchscopy and stable in setting. The flow meter (RBF-1 Biomedical Sci.) and analizer
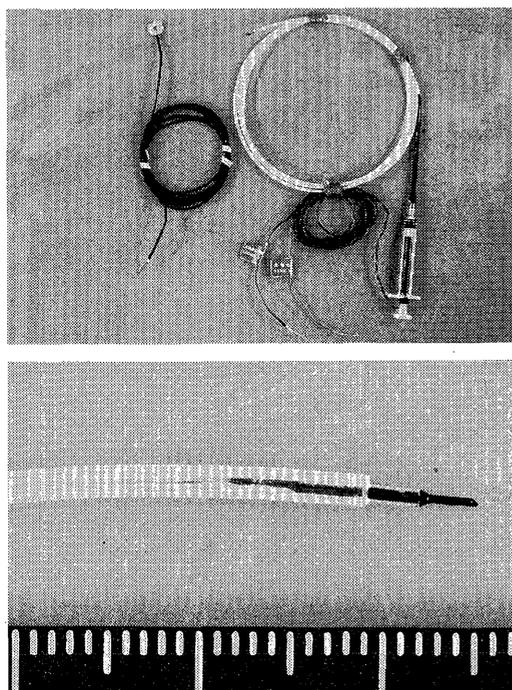
Fig. 1. Photograph showing two kinds of ele-
         ctrode, plate (left) and catheter (right)
         electrode ; upper and the tip of probe ;
         lower

(AD-1002 Biomedical Sci.) were used in this
study as shown in Fig. 1 and 2, on the condition
of biochemical current of 10 μA and its
time duration of 60 sec and polaro voltage of
600 mV respectively.

1. Evaluation of Reproducibility

The reproducibility of microflow values by
means of electrochemically generated hydrogen
was evaluated with double measurements at
the interval at least 5 minutes at 17 sites on
the same conditions.

2. Microflow Values among the Sites of the Tracheal Bifurcation, Left and Right Main Bronchi

The measurements by means of electro-
chemically generated hydrogen were made at
the anatomically different sites and its vari-
ation was also tested.
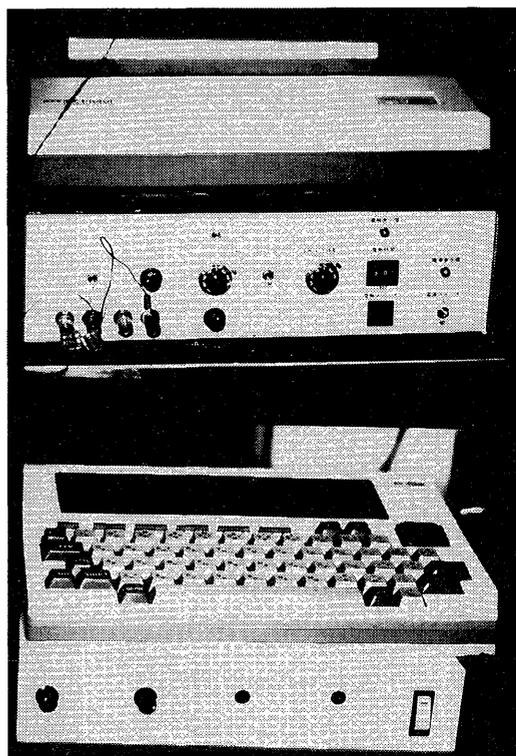
Fig. 2. Photograph showing a data analyzer,
         Model ; PC RP401, RBF-1, PC 8201, AD-
         1002.

3. Measurement of Basic Diffusion Volume

The changes in microflow on the tracheal
wall were assessed on the condition of cardiac
arrest during 60 minutes after instillation of
40 mEq KCL.

2 RESULTS

The relationship between time course and
measured voltage was shown in Fig. 3 in a dog
whose submucosal microflow of the trachea
was measured by means of electrochemically
generated hydrogen. It showed a plateu at 30
sec of the beginning of the measurement by the
limitter of a data analizer. Rapidly decresing
part on this graph contained the sites of diffu-
sion into the surrounding tissues which was
inadequate for the measurement. At the time
from 180 to 230 sec after the beginning of the
measurement value of 68.6 ml/min/100g was
obtained. The correlation rate between two

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  VOLTS                              LOG(V)
            -2        -1.5        -1       -0.5          0          0.5         1
          0I---------I---------I---------I---------I---------I---------I
  0.000    #                                        I          *
  1.865    I                                        I          *
  4.414    I                                        I                     *
  4.414    I                                        I                     *
  4.414   5I---------------------------------------+--------------*------I
  4.414    I                                        I                 *
  4.414    I                                        I                 *
  4.414    I                                        I                 *
  4.260    I                                        I              *
  2.788  10I---------------------------------------+-----------*-------I
  1.904    I                                     I          *
  1.357    I                                     I *
  1.011    I                                        *
  0.776    I                                  *  I
  0.615  15I-------------------------------*----+-----------------------I
  0.503    I                              *
  0.417    I                            *
  0.359    I                          *
  0.313    I                          *       I
  0.276  20I--------------------------*-----+-------------------------I
  0.244    I                        *         I
  0.222    I                       *          I
  0.203    I                      *           I
  0.188    I                      *           I
  0.173  25I--------------------*-----------+-------------------------I
  0.161    I                   *              I
        x 10sec
```
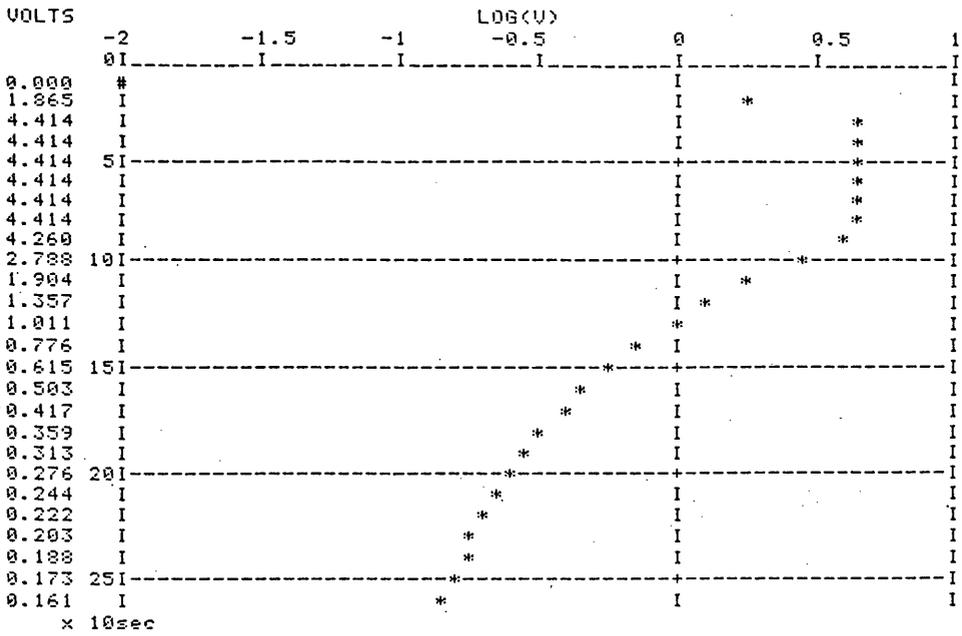
F= 68.6 [Ml/Min/100s] at interval between 18 and 23

Fig. 3.   Relationship between time course and measured voltages immediately after
measurement by means of electrochemically generated hydrogen.

values obtained by double measurements was 0.9799 with a revolving equation ($Y = 1.31222 + 0.987886X$, Fig. 4). In the sites of tracheal bifurcation ($F = 71.5 \pm 13.23$ ml/min/100 g), attachment of right main bronchus ($F = 65.6 \pm 10.84$ ml/min/100 g) and attachment of left
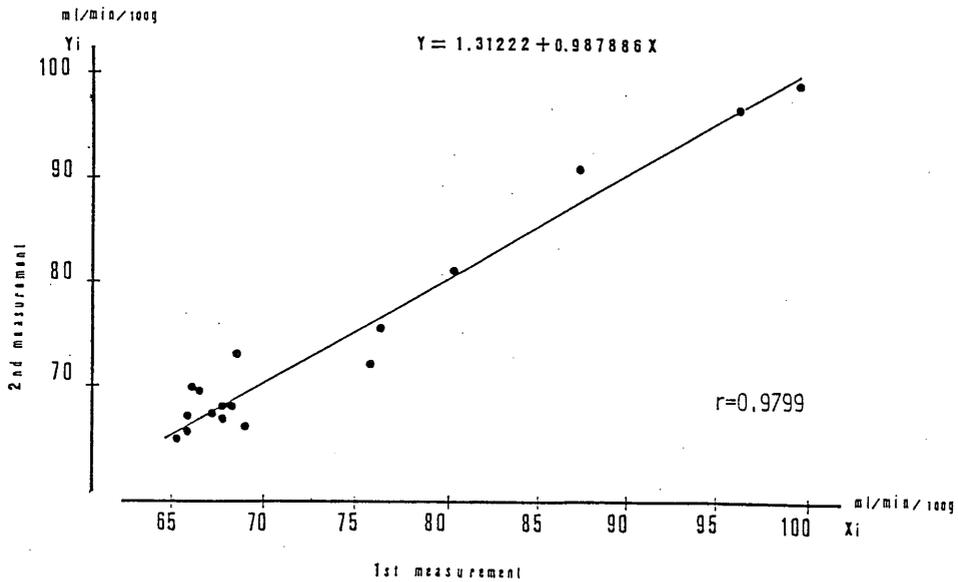
Fig. 4.   The corrllation between double values measured twice at the same site.
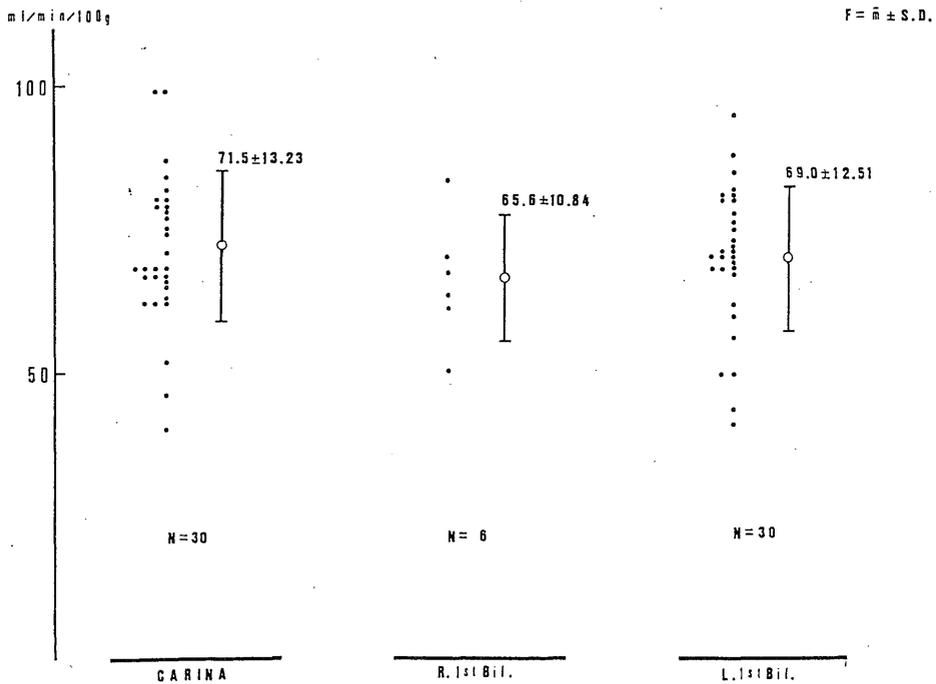
Fig. 5. Comparision among the values measured at the three sites, tracheal carina, attachment of left main and right main bronchi.

main bronchus (F=69.0±12.51 ml/min/100g), each equation was calculated without statistically significant difference (p<0.05) as shown in Fig. 5. The changes in microflow after arrest of the heart demonstrated a slow decrease and reached at 17.0±4.80 ml/min/100g at 60 minutes, showing a values as false diffusion volume which was shown in Fig. 6.

II   Changes in Microfow at Bronchial Anastomosis on Lung Allografts

1   MATERIALS AND METHODS

The microflow at bronchial anastomosis was assessed on dogs with auto- and allografts by means of electrochemically generated hydrogen. Lung transplantation was performed by left thoracotomy at the 5th intercostal space and operation steps of anastomosis were made in the following order, the left atrium, left pulmonary artery with continuous suture of 5-0 prolene and left main bronchus with continous
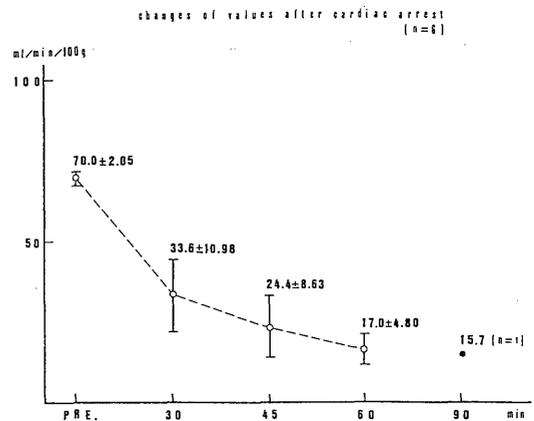
Fig. 6. Submucosal microflow measured by means of electrochemically generated hydrogen after induced cardiac arrest with KCL.

suture of 4-0 prolene. Antibiotics of sephem and/or aminoglucoside were used for prevention. of postoperative infection The dogs were supplied from the Animal Center of Nagasaki University School of Medicine and divided into three groups, Au group of autotansplantation

on 10 dogs, Az group of lung allotransplanta-tion with azathioprine 50mg/body on 9 dogs and Cy group of lung allotransplantation with cyclosporine A 20mg/kg on 8 dogs. The measure-ment was made with the same instruments as a preliminary study. On autografts the measure-ments of microflow were carried out at the four sites of the tracheal bifurcation, bronchial anastomosis, the distal site to bronchial ana-stomosis and left main bronchus at 3, 5, 7, 10, 14, 21 and 28th day after surgery. In allografts, the measurements were made at the sites of the tracheal bifurcation in a recipient preopeg ratively, attachment of the main bronchus postoperatively until on day 21. The dogs with loss of aeration on chest XP films and stenosis or ulcerative change at anastomosis were ex-cluded from this study. These values obtained were compared with the control of the tracheal bifurcation preoperatively and of attachment of left main bronchus postoperatively. Statist-ical comparioson between the post- and pre-operative values were performed using the Student's t-test for compared variable.

2 RESULTS

1 Lung Autografts (Table 1, Fig. 7. 1-4)

There was no significant difference between the values at tracheal bifrucation until on day 7. At the 10 and 14th days, these were increas-ee to 89.5 ± 3.58 ml/min/100g on day 10 and to 106.0 ± 5.43 ml/min/100g on day 14. At the pro-ximal sites to anastomosis, the tissue flow

were increased to 102.2 ± 27.13 ml/min/100g re-spectively. At the distal sites, these were reduced from 66.5 ± 11.65 to 33.4 ± 10.99 ml/min /100 g g and subsequently increased to 86.7 ± 21.23 on day 7, 97.8 ± 18.51 on day 10, 98.0 ± 14.91 ml/min/100 g and reduced to the normal. At attachment of the left main bronchus (in Fig. 7-4) the tissue flow was kept normal until on day 5 without significant reduction and these kept high flow of 87.9 ± 14.41 ml/min/100 g on day 7, 83.2 ± 8.11 on day 14, 79.4 ± 1.50 on day 28.

2. Lung Allografts with Azathioprine (Table 2, Fig. 8. 1-4)

At the tracheal bifurcation, tissue flow showed a high value of 88.8 ± 11.36 ml/min/100 g. At the sites proximal to broncheal anasto-mosis, it was decreased to 64.5 ± 6.59 ml/min/ 100 g on day 7. At the sites distal to bron-chial anastomosis (Fig. 8-3), it was reduced from 72.1 ± 4.96 to 30.0 ± 8.32 ml/min/100 g thereafter, it was still kept reduced to 46.5 ± 14.67 on day 3, 42.0 ± 8.39 on day 5, 55.8 ± 10.75 ml/min/100 g on day 7. Thereafter it gradually increased on day 10. Meanwhile, at the attach-ment of the main bronchus (Fig. 8-4) it was reduced to 58.9 ± 5.08 on day 5, thereafter in-creased on day 7 without statiscal difference.

3 Lung Allografts with Cyclosporine A (Table 3, Fig. 9. 1-4)

At the site of tracheal bifurcation, the tissue flow increased to 103.9 ± 26.59 ml/min/

Table 1. The submucosal microflow at the sites of tracheal carcine, left main bronchus proximal and diatal to anastomosis and its attachment according to time course after left long autotrans-plantation. $F = m \pm S. D.$: ml/min/100g

Au	pre ope	post ope	p. o. 3	p. o. 5	p. o. 7	p. o. 10	p. o. 14	p. o. 21	p. o. 28
Carina	72.9 ± 14.37	78.2 ± 9.99 (n=8)	78.4 ± 18.05 (n=6)	89.4 ± 13.85 (n=6)	85.9 ± 17.34 (n=6)	$89.5 \pm 3.58^{**}$ (n=6)	$106.0 \pm 5.43^{**}$ (n=7)	75.1 ± 4.88 (n=5)	79.0 ± 15.83 (n=3)
proximal site of ana.	(n=10)	72.1 ± 13.21 (n=7)	71.6 ± 17.21 (n=5)	68.2 ± 1.40 (n=5)	$102.0 \pm 27.13^{*}$ (n=5)	105.7 ± 30.02 (n=6)	81.8 ± 7.80 (n=5)	81.3 ± 19.50 (n=5)	89.2 ± 17.52 (n=4)
distal site of ana.	66.5 ± 11.65	$33.4 \pm 10.99^{**}$ (n=8)	57.1 ± 8.50 (n=5)	70.0 ± 24.84 (n=6)	$86.7 \pm 21.23^{*}$ (n=6)	$97.8 \pm 18.51^{**}$ (n=6)	$98.0 \pm 14.91^{**}$ (n=6)	79.6 ± 14.70 (n=5)	74.4 ± 9.03 (n=5)
left the 1st. bifu	(n=10)	62.6 ± 14.28 (n=10)	63.3 ± 6.74 (n=7)	67.5 ± 5.06 (n=6)	$87.9 \pm 14.41^{*}$ (n=5)	78.0 ± 9.75 (n=5)	$83.2 \pm 8.11^{*}$ (n=5)	68.8 ± 4.01 (n=5)	79.4 ± 1.50 (n=4)

(* $p < 0.05$, * * $p < 0.01$)
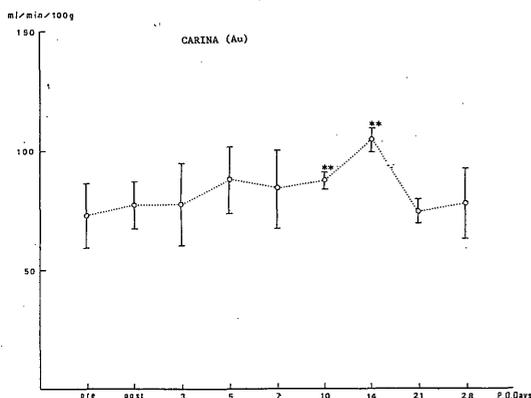
Fig. 7-1.   Changes in microflow of tracheal carine after left lung autotransplantation.
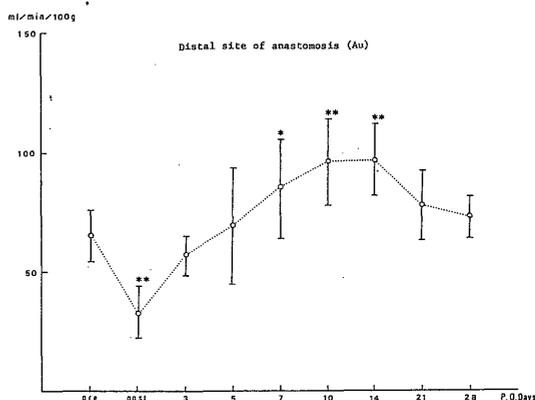
Fig. 7-3.   Changes in microflow in left main bronchus distal to anastomosis after lung autotransplantation.
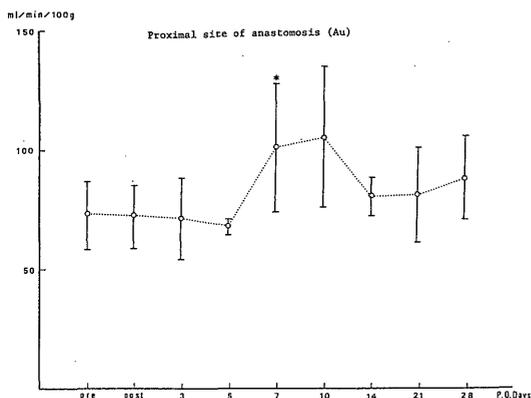
Fig. 7-2.   Changes in microflow in left main bronchus proximal to anastmosis after left lung autotransplantation.
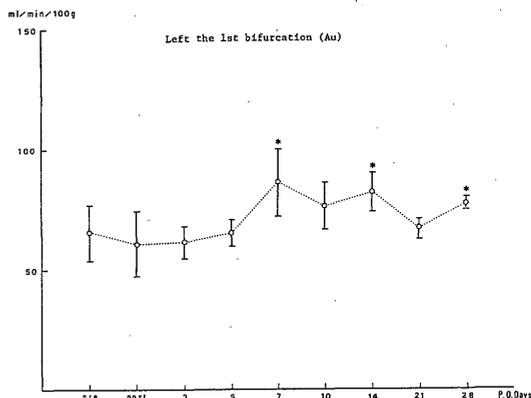
Fig. 7-4.   Changes in microflow of the attachment of left main bronchus after lung autotransplantation.

Table 2.   The submucosal microflow at the sites of tracheal carcine, left main bronchus proximal and diatal to anastomosis and its attachment according to time course after left long allotransplantation treated with Aza.

$F = m \pm S.\ D.\quad : ml/min/100\ g$

Au	pre ope	post ope	p. o. 3	p. o. 5	p. o. 7	p. o. 10	p. o. 14	p. o. 21
Carina	73.7± 7.42 (n=9)	75.2± 9.95 (n=9)	76.2±13.00 (n=7)	76.3±13.30 (n=7)	88.8±11.36** (n=7)	77.5±19.40 (n=6)	75.0±18.16 (n=6)	83.1± 5.92 (n=4)
proximal site of ana.		70.2± 9.39 (n=8)	86.3±17.33 (n=8)	64.5± 6.59 * (n=7)	69.5± 7.39 (n=6)	72.2± 5.45 (n=5)	80.6±14.40 (n=6)	92.3±18.00 (n=4)
distal site of ana.	42.1± 4.96 (n= 9)	30.0± 8.32** (n=8)	46.5±14.67** (n=8)	42.0± 8.39** (n=7)	55.8±10.75 * (n=6)	63.4±13.67 (n=6)	64.9±10.22 (n=6)	66.1±24.40 (n=4)
left the 1st. bifu		62.7± 6.01** (n=7)	69.1± 6.16 (n=8)	58.9± 5.08 (n=6)	77.7±10.83 (n=6)	66.6±14.44 (n=5)	73.2± 8.28 (n=6)	82.0±16.40 (n=4)

(* p<0.05, * * p<0.01)

ml/min/100g
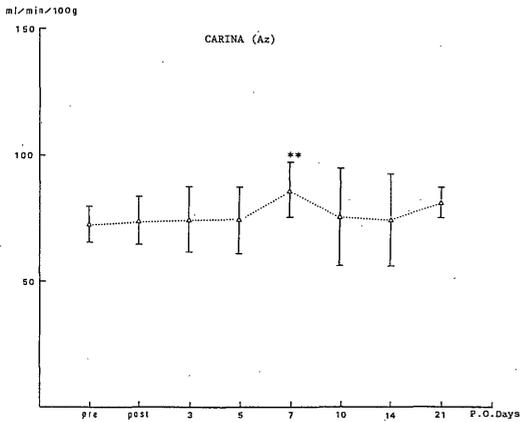
Fig. 8-1 Changes in microflow of tracheal carina after left lung allotransplantation treated with Aza.
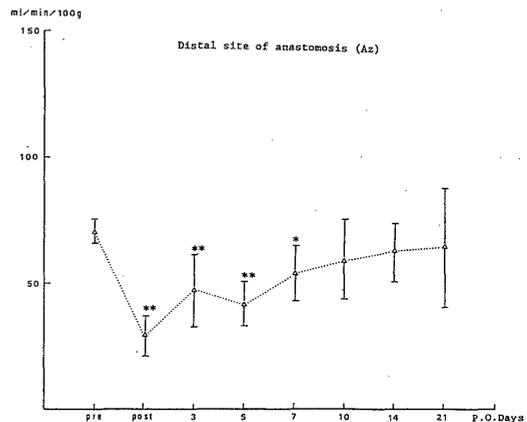
Fig. 8-2. Changes in microflow in left main bronchus proximal to anastomosis after left lung allotransplantation treated with Aza.

Fig. 8-3. Changes in microflow in left main bronchus distal to anastomosis after lung allotransplantation treated with Aza.
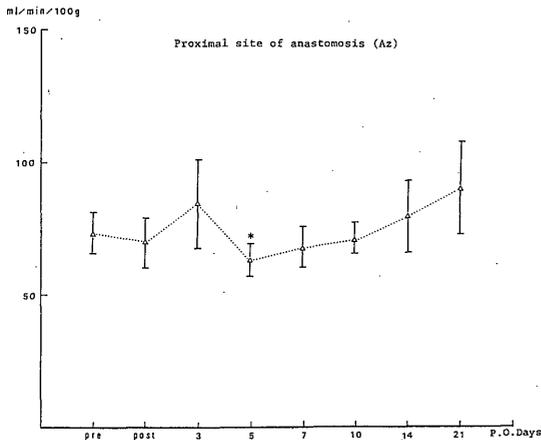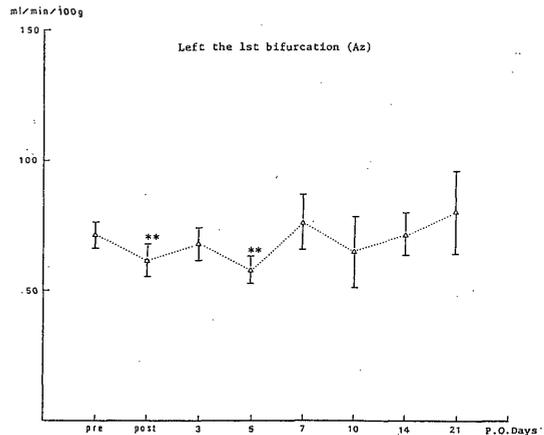
Fig. 8-4. Changes in microflow of the attachment of left main bronchus after lung allotransplantation treated with Aza.

Table 3. The submucosal microflow at the sites of tracheal carcine, left main bronchus proximal and diatal to anastomosis and its attachment according to time course after left long allotransplantation treated with CyA.

$F = m \pm S. D.$: ml/min/100g

Cy	pre ope	post ope	p. o. 3	p. o. 5	p. o. 7	p. o. 10	p. o. 14	p. o. 21
Carina	76.6± 9.59 (n=8)	77.0± 7.79 (n=8)	71.5±13.18 (n=8)	103.9±26.59 [*] (n=7)	83.8±11.85 (n=7)	78.5±10.43 (n=5)	71.6±10.65 (n=5)	87.1±18.22 (n=5)
proximal site of ana.	(n=8)	61.6±15.28 [*] (n=8)	62.9±10.81 [*] (n=8)	77.7±16.22 (n=7)	68.0± 9.08 (n=7)	77.9±10.72 (n=5)	80.6± 3.39 (n=5)	83.4±17.14 (n=5)
distal site of ana.	72.5±12.55 (n= 8)	35.4± 4.95 [**] (n=8)	49.9± 9.36 [**] (n=8)	68.4±11.72 (n=7)	63.6± 5.88 (n=7)	81.9±10.44 (n=5)	88.1± 7.58 [*] (n=5)	90.2±11.30 [*] (n=5)
left the 1st. bifu		65.6±13.94 (n=8)	72.7±16.33 (n=8)	67.3±10.40 (n=7)	69.0± 8.43 (n=7)	80.4±24.55 (n=5)	74.7±10.00 (n=5)	72.1± 8.41 (n=5)

(* p<0.05, * * p<0.01)
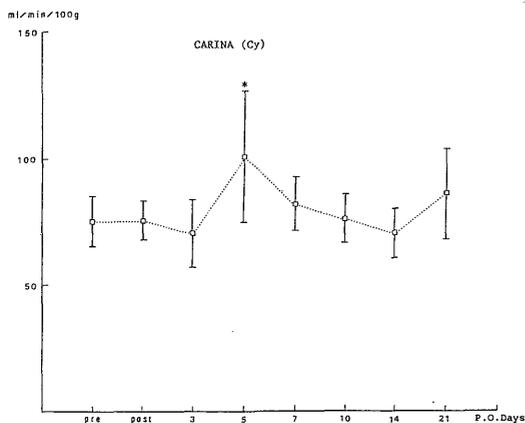
ml/min/100g

Fig. 9-1. Changes in microflow of tracheal car-
ine after left lung allotrasplantation
treated with CyA.
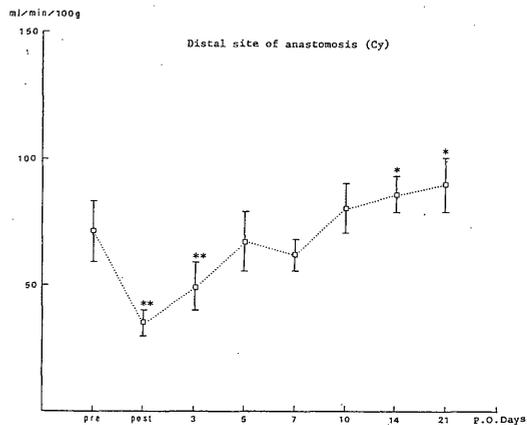
ml/min/100g

Fig. 9-2. Changes in microflow in left main
bronchus proximal to anastomosis
after left lung allotransplantation
treated with CyA.

ml/min/100g

Fig. 9-3. Changes in microflow in left main
bronchus distal to anastomosis after
lung allotransplantation treated with
CyA.

ml/min/100g
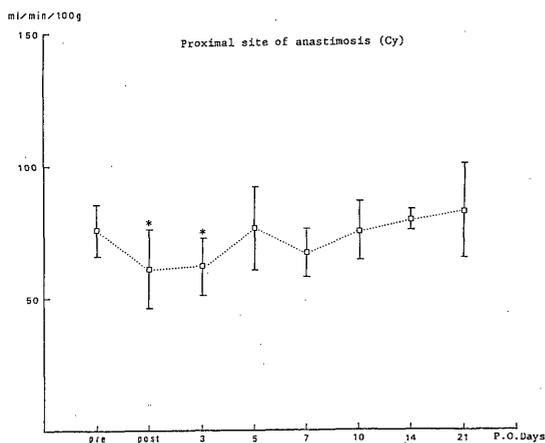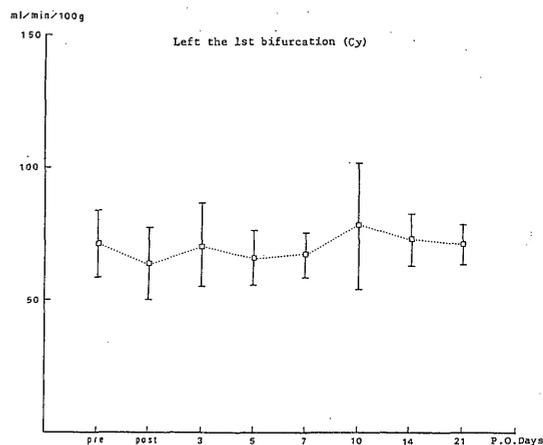
Fig. 9-4. Changes in microflow of the attach-
ment of left main bronchus after lung
allotransplantation treated with CyA.

100 g on day 5. At the sites proximal to ana-
stomosis (Fig. 9-2) it maintained a low value
of 61.6 ± 15.28 immediately after transplant-
ation and 62.9 ± 10.81 ml/min/100 g on day 5,
although it showed no significant change. At
the sites distal to anastomosis, it reduced
from 72.5/12.55 to 35.4/4.95 immediately after
transplantation and to 49.9 ± 9.36 on day 3,
thereafter it gradually increased to 88.1 ± 7.58
on day 14, 90.2 ± 11.30 ml/min/100 g on day 21.
At the sites of attachment of the left main
bronchus, there was no significant changes.

DISCUSSION

The measurement of local tissue flow has
been made with the aid of electrochemically
generated hydrogen by means of gas inhalation.
However, the main drawback to this method is
that there is a fear of fire and ill effects of
gas inhalation on the body, for example, suffo-
cation by gas in small animals and also it
takes considerably long time for hydrogen gas
to concentration on ischemic area, in addition,
the concentration of the intracheal hydrogen
may contribute to make an error to measure

the tissue flow because the measured sites is very close to the sites of gas inhalation by means of hydrogen gas clearance test.

However, the measurement of local tissue flow by means of electrochemically generated hydrogen is simple and transmission of inhalated hydrogen gas is not essential to repeated measurements.

This method by using locally generated hydrogen has been modified in additiont to improvement of Stosseck and Aukland' methods.[3] ~[5] Since Koshu[6] reported a close relationship between the values measured by Stosseck' method and inhalated hydrogen gas clearance method, this method has been prevalent in its use.[7]~[10] It is a major ploblem that tissue measured is locally limited around the introduced electrode and it is related to the inserted depth of the electrode. The electrode had a stopper at the depth of 2.5mm so that the electrode may not be introduced more than 2.5mm in depth. The electrode used to be obliquelly introduced to the mucosal layer. In this study, the sites of electrodes introduced were bronchoscopically confirmed to anchor the mucosa. It is ascertained that the lower the current and the shorter the time, the higher a reciprocal of half-life time has become and it means relative large volume of diffusion. Damage to the tissue is caused by heat, and production of heat is ruled by Joul's law. To minimize damage to the tissue, the measurement should be set on the condition of the current of 10 μ A and current time of 60 sec. There was no damage to the tissue by measuremet except for a little bleeding at the sites in which eletrodes were introduced. Repeated measurement ensured close producibility which represents an equation $(Y=1.31222+0.98786X)$ and correlation coefficient ($\gamma=0.9799$). Basic diffusion was confirmed on the condition of cardiac arrest[7] as a value of 24.1 ± 1.4ml/min/100 g in canine stomach, 25ml/min/100g in human stomach[8] and 14.0ml/min/100 g in human muscles.[10] Recently Fujino[1] reported a value of basic diffusion of 16.03 ± 4.91ml/min/100g in canine bronchus. In this study it was 17.0 ± 4.80ml/min/100 g with almost the s ame as him. There was no difference in the microflow of the trachea among three anatomi-

cally different sites. Kobayashi[2] reported that there was no difference in the microflow between the sites of bilateral main bronchi and attachment of bilateral diaphragmatic lobe bronchi.

Evaluation of Wound Healing at Bronchial Anastomosis in Terms of Local Microflow

1 Autotransplantaton

Restoration of bronchial blood flow at bronchial anastomosis was assessed by means of electrochemically generated hydrogen. It is known that the blood flow in which the bronchial artery was interrupted at bronchial anastomosis is compensated with pulmonary bronchial collateral circulation.[11] In lung transplantation, the bronchial bifurcation in lung grafts are well nourished as compared with those in the recipients, although microflow at distal site to anastomosis is significantly reduced. However, it was returned to the normal, accompanying a hyperdynamic state with an increase in the blood flow on day 7, 10 and 14. It is generally accepted that restoration of bronchial blood flow in lung grafts is established until on day 14.[11]~[13] However, blood flow in the submucosa is already increased on day 3 and is pronounced on day 14.

2 Lung Allotransplantation

Immunosuppressive drugs should be prescribed on lung allografts. CyA contributes to facilitation of wound healing at bronchial anastomosis and to electromicroscopic promotion of collagen fiber as compared with autografts.[14] Kawahara[13] confirmed that recanalization of the interrupted bronchial artery in allografts treated with CyA is completed until on day 14 in the same manner as that in autografts although that in allografts treated with Aza is retarded. In this study, it was defined that restoration of the interrupted bronchial artery in allografts treated with CyA started on day 5, although that treated with Aza began on day 10. It is known that CyA helps lung allografts to enhance proliferation of vessels and production of fibrin by chemical mediator produced by macrophages whose activity is not depressed.[15] [16] It is reported that Aza enables the count of monocytes and polynuclear

leucocytes to reduce by bone marrow depression, and overdose of Aza impairs wound healing. In this study it was evident that recanalization of the interrupted bronchial aryery was much more facilitated by using CyA rather than that by Aza and the use of CyA is superior to that of Aza in the respect of wound healing.

ACKNOWLEDGEMENT

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