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Predictive Value of Blood Flow in the Gastric Tube in Anastomotic Insufficiency after Thoracic Esophagectomy

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Abstract. Anastomotic insufficiency is considered to be one of the most serious complications associated with esophageal reconstruction. The purposes of this study were to identify (1) the relationship between anastomotic insufficiency and tissue blood flow (TBF) in the gastric tube in the perioperative period, and (2) the effects of intravenous prostaglandin E_1 (PGE_1) on TBF in the gastric tube. The study group consisted of 44 patients who were to undergo esophagectomy for esophageal cancer. Intraoperative and postoperative TBF on the serosal side of the gastric tube were measured by laser-Doppler tissue blood flowmetry. The TBF of the Leakage(+) group (n = 5) was poorer than that of the Leakage(−) group (n = 39) during the intraoperative and postoperative periods. There was a significant difference in TBF between the two groups at postoperative day (POD) 3. There was a tendency in the PGE_1(+) group (n = 18) to exhibit richer blood flow through the anastomosis than the PGE_1(−) group (n = 26), intraoperatively, but the difference was not significant. Two of five Leakage(+) cases were also in the PGE_1(+) group. There was no relationship between intraoperative medication with PGE_1 and incidence of leakage. The TBF of three-field lymph node dissection and reconstruction of the retrosternal route group (n = 21) was poorer than that of the two-field lymph-node dissection and reconstruction of the posterior mediastinal route group (n = 23). The TBF in the gastric tube after esophagectomy may be a predictor of anastomotic insufficiency. However, PGE_1 treatment in the intraoperative period alone is not effective in preventing anastomotic insufficiency.

Esophagectomy is performed in response to various benign and malignant esophageal diseases [1]. For patients with esophageal cancer, esophagectomy provides the best hope of cure, but it is a major undertaking. Recently, large studies have shown that aggressive extended radical lymphadenectomy combined with esophageal resection increases the survival rate of patients with thoracic esophageal carcinoma [2–5], but it also increases postoperative morbidity and mortality [6]. Two mainly postoperative complications are anastomotic leakage and pulmonary complications [7–10]. The prevention of such complications is essential, not only to improve the postoperative quality of life of these patients but also to reduce the rate of perioperative mortality [11–13]. Some of the factors responsible for anastomotic insufficiency have been reported, and one of the most important problems is thought to be ischemia of the gastric tube [14, 15]. Recently, laser-Doppler flowmetry has been used in several studies to evaluate blood flow during surgery [16, 17]. There are not yet, however, any reports concerning tissue blood flow (TBF) in the gastric tube during the period after esophagectomy. Because it is possible that changes in TBF may affect anastomotic insufficiency in the postoperative period rather than in the intraoperative period, we measured the TBF of the gastric tube at both of those times.

Prostaglandin E_1 (PGE_1) is a powerful pulmonary and systemic vasodilator that also inhibits platelet and leukocyte aggregation [18]. It is a prostanoid derived from arachidonic acid, and it has been used to treat patients undergoing extracorporeal surgery and those with severe liver disease. The purposes of this study were to evaluate (1) the relationship between anastomotic insufficiency and TBF in the perioperative period and (2) the effects of intravenous PGE_1 on TBF in the gastric tube.

Materials and Methods

Patients

The study group was made up of 44 patients who were to undergo esophagectomy for treatment of esophageal cancer between 1998 and 2000. The cohort included 41 men and 3 women aged 36 to 77 years (mean, 63.1 years). Written informed consent to participate in the study was obtained from each patient before surgery, according to the ethical guidelines of our university. All patients underwent a detailed preoperative risk assessment based on their clinical history, symptoms and signs of chronic lung or heart disease, chest radiograph, electrocardiogram, arterial blood gas analysis, pulmonary function tests, and biochemical and hematologic tests. Disturbances of organ function and postoperative complications were investigated according to the criteria of Kuwano et al. [13]. Patients who had little discharge and no signs of systemic infection, and who were diagnosed only at radiographic check were identified as having minor leakage. Signs of systemic infection were fever of higher than 39°C and a high value of C-reactive protein (CRP) and/or an extraordinaly high or low white blood cell count. Each patient was randomly assigned to

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either the $PGE_1(+)$ group ($n = 18$) or a control [$PGE_1(-)$] group ($n = 26$). Patients assigned to the $PGE_1(+)$ group were given PGE_1 intravenously at a rate of 0.02 μg/kg per minute throughout the operation.

Operative Technique

We performed surgery using one of two different techniques. Of the 44 patients, 21 underwent cervico-thoraco-abdominal three-field lymph node dissection through a right-sided thoracotomy, and reconstruction of the retrosternal route (3F). The remaining 23 patients underwent thoraco-abdominal two-field dissection through a right-sided thoracotomy, and reconstruction of the posterior mediastinal route (2F). 2F patients were selected according to the indication criteria for operation in our department. Our indications for this procedure were as follows. Briefly, a tumor located in the middle or lower thoracic esophagus and restricted within the esophageal submucosal layer was a primary indicator. No evidence of either neck lymphadenopathy or any prominent intramediastinal lymph node swelling based on the findings of a preoperative examination.

All anastomoses were completed with a circular stapling device [Premium-plus-Circular End to End Anastomosis stapler (PC-EEA), United States Surgical Corporation, Norwalk, CT, USA]. The diameter of the staples was 21 mm. The flat type anvil head was placed in the esophageal stump by pursestring suture, and the top of the body was inserted from the stump of the gastric tube and anastomosis was performed by way of esophageal end-to-gastric tube side. The stump of the gastric tube was closed with automatic linear cutter instruments [Gastro-Intestinal-Anastomosis (GIA), United States Surgical Corporation, Norwalk, CT, USA] and sutures were buried. Intrathoracic mechanical anastomosis was performed by end-to-side anastomosis with a stapler at the top of the upper thoracic esophagus in all 2F patients. Neck mechanical anastomosis was performed in the 3F cases. We reinforced the anastomosis with some external sutures when the anastomosis was incomplete. The mean operative time was somewhat shorter in the 2F group (435.7 ± 17.3 minutes) than in the 3F group (451.1 ± 19.5 minutes), but without any significant difference.

TBF Measurement

Intraoperative Blood Flow. Tissue blood flow was studied intraoperatively in 44 patients. The blood flow on the serosal side of the gastric tube was measured using a laser-Doppler tissue blood flowmeter (model ALF-21N, Advance Co. Tokyo, Japan) three times during surgery. Measurement time points were $t1$, when the left gastric artery and short gastric artery were ligated and cut, $t2$, when the construction of the gastric tube was completed, and $t3$, when the gastric tube was elevated and the anastomosis was complete. Measurements were taken at the level of both the anastomosis and the antrum. The blood flow ratio (BFR) was defined as the value of TBF at the anastomosis of the gastric tube divided by the value of TBF at the antrum.

Postoperative Blood Flow. The side-type probe (Advance Co, Tokyo, Japan) was fixed to the top of the gastric tube by a buried suture of 4-0 catgut. Measurement time points were immediately at end of the surgery (POD 0), 6 hours after (PO6h), and on days 1, 2, and 3 thereafter (POD 1, POD 2, and POD 3). The side-type probe was removed after we measured the flow volume at POD 3. We removed the probe carefully just like drains after we removed dermal fixed sutures. No complications occurred.

Because the measured blood flow value is affected by hematocrit, it was corrected using Oka's formula [19], the corrected value being considered as the blood flow volume (BFV):

$$BFV\ (blood\ flow\ volume) = \frac{100 \times measured\ TBF}{\{100 - (40 - hematocrit\ of\ the\ patient) \times 0.5\}} \quad (1)$$

Statistical Analysis

All values are expressed as the mean ± standard error of the mean (SEM). Statistical analysis was performed with the chi-squared test, Fisher's exact probability test, and the Mann-Whitney U test. The level of statistical significance was set at $p < 0.05$.

Results

Patient Characteristics

No patient died within 30 days of the operation. Eighteen of the 44 patients (40.9%) had some organ dysfunction (pulmonary dysfunction, cardiac dysfunction, diabetes mellitus) preoperatively and 16 (36.4%), developed postoperative complications (leakage, pulmonary dysfunction, cardiac dysfunction, ileus, recurrent nerve paresis, wound infection). Major leakage did not occur, but minor leakage occurred in 5 patients (the Leakage(+) group). There was no significant difference in age, gender, operating time, intraoperative blood loss, or operative technique between the Leakage(+) group and those who exhibited no leakage [Leakage(−) group]. Neither was there an association between preoperative organ dysfunction (pulmonary, cardiac dysfunction, or diabetes mellitus) and leakage. On the other hand, postoperative complication tended to occur more frequently in the Leakage(+) group than in the Leakage(−) group, but without any significant difference. The 18 patients who were assigned to the $PGE_1(+)$ group were given PGE_1 intravenously throughout the course of the operation. There was no significant difference in age, gender, operating time, intraoperative blood loss, operative technique, preoperative organ dysfunctions, and postoperative complications between the $PGE_1(+)$ group and the $PGE_1(-)$ group. No patient experienced complications with the infusion of PGE_1. Two of the 5 Leakage(+) patients were treated with PGE_1. There was no relationship between intraoperative medication with PGE_1 and leakage.

Correlation between Leakage and TBF

Intraoperative Blood Flow. The BFR of the Leakage(+) group was poorer than that of the Leakage(−) group. Although the difference between the two groups increased step by step at $t2$ and $t3$, the differences between time points were not significant (Fig. 1).

Postoperative Blood Flow. The mean corrected BFV value in the Leakage(−) group was stable, and ranged from 25 to 30 ml/

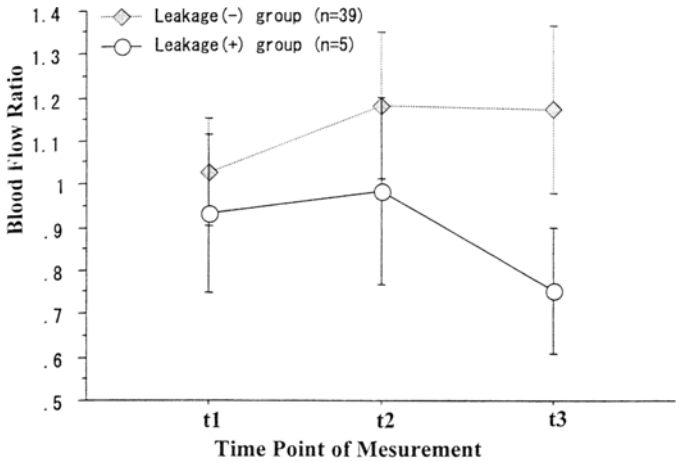

Fig. 1. Changes in the blood flow ratio (BFR) of the gastric tube during surgery. The time points of measurement are defined as follows: *t*1, when the left gastric artery and short gastric artery were ligated and cut; *t*2, when the construction of the gastric tube was completed; *t*3, when the gastric tube was elevated and the anastomosis was completed. Shaded squares, Leakage(−) group; open circles, leakage(+) group. Values are expressed as the mean ± SEM.

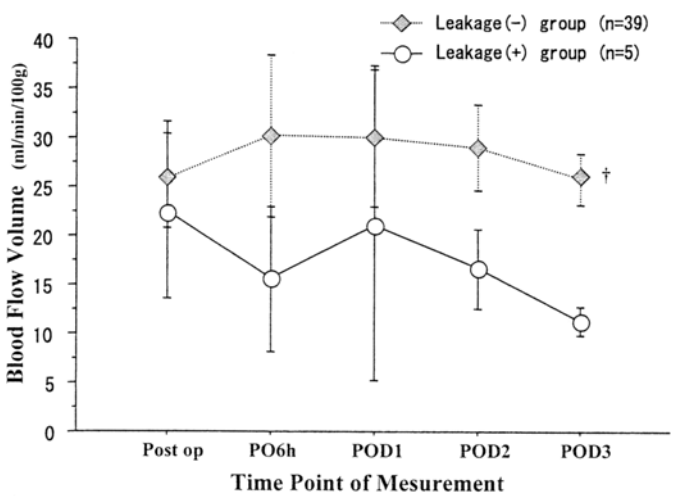

Fig. 2. Perioperative changes in the blood flow volume (BFV) of the gastric tube. The time points of measurement are defined as follows: Post op, the end of the operation; PO6h, 6 hours after surgery; POD1, the morning of the 1st postoperative day; POD2, the morning of the 2nd postoperative day; POD3, the morning of the 3rd postoperative day. Shaded squares, Leakage(−) group; open circles, Leakage(+) group. $^{\dagger}p < 0.05$ between the two groups. Values are expressed as the mean ± SEM.

minute per 100 g. However, BFV in the Leakage(+) group was lower than in the Leakage(−) group. There was a significant difference between the BFV in the Leakage(+) group and Leakage(−) group at POD 3 (Fig. 2).

Influence of PGE_1 on BFR

Intraoperative BFR at *t*2 was 1.01 ± 0.17 in the $PGE_1(-)$ group versus 1.25 ± 0.25 in the $PGE_1(+)$ group; BFR at *t*3 was 1.05 ± 0.17 ($PGE_1(-)$ group) vs 1.08 ± 0.25 ($PGE_1(+)$ group). There was a tendency in the $PGE_1(+)$ group toward a richer intraoperative BFR than in the $PGE_1(-)$ group, but the difference was not significant.

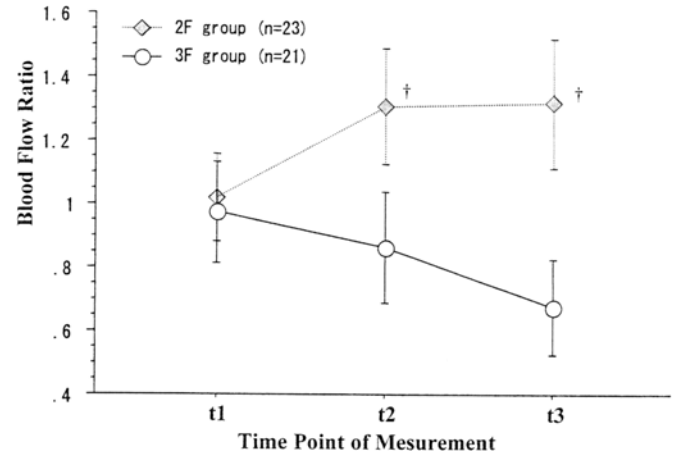

Fig. 3. Changes in the BFR of the gastric tube during surgery. The time points are the same as in Figure 1. Shaded squares, 3F group; open circles, 2F group. $^{\dagger}p < 0.05$ between the two groups. Values are expressed as the mean ± SEM.

Comparison of the 3F and 2F Groups

Intraoperative Blood Flow. The BFR of the 2F group was richer than that of the 3F group at *t*2 and *t*3. Although the BFR of the 2F group was increased, that of the 3F had decreased at *t*2 and *t*3. The difference in BFR between the 2F and 3F groups at *t*2 and *t*3 was significant (Fig. 3).

Postoperative Blood Flow. The BFV of the 2F group was richer than that of the 3F group during the measurement period. There were significant differences at the all time points after surgery (Fig. 4).

Laboratory examinations revealed that serum CRP levels in the 3F group were significantly higher than in the 2F group at PODs 1, 2, 3, and 5 ($p < 0.05$). There was no significant difference in WBC or serum total bilirubin between the two groups at any time (data not shown).

Discussion

It is difficult how to evaluate the blood flow of the gastrointestinal tract. Hydrogen clearance, microsphere, and laser-Doppler method have been reported as ways of estimating tissue blood flow directly [20–25]. The hydrogen clearance method is very popular, but it requires implantation of electrodes invasively. Moreover, it takes a lot of time because of the need for stabilization of electrodes, and so reproducibility of data is questionable [20, 21]. Microsphere is very valuable method for estimating the blood flow throughout the intestine, but it cannot measure tissue blood flow in isolated areas of the intestine [23]. Kvietys et al. investigated the estimation of laser-Doppler and hydrogen clearance and microsphere methods [26]. Laser-Doppler flowmeter measurements of blood flow correlated with measurements of the others. The laser-Doppler method is useful clinically because of quickness of measurement, low invasiveness, and high reproduc-

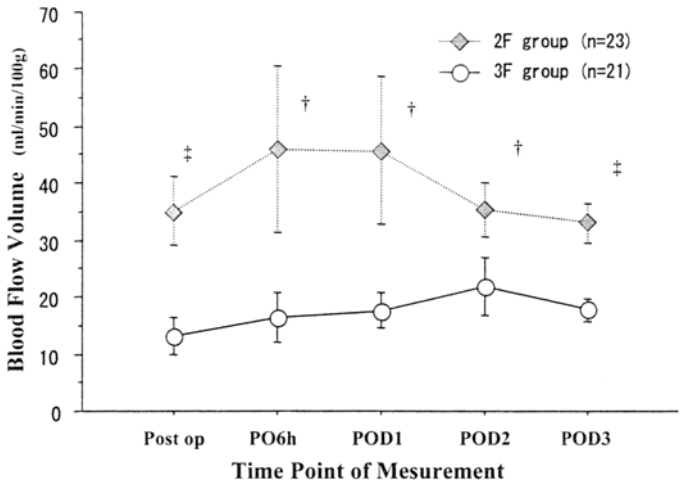

Fig. 4. Perioperative changes in the BFV of the gastric tube. The time points of measurement are the same as in Figure 2. Shaded squares, 2F group; open circles, 3F group. $^{\dagger}p < 0.05$; $^{\ddagger}p < 0.01$ between the two groups. Values are expressed as the mean ± SEM.

ibility. We selected this method for its advantage in making comparisons and because other laboratories have measured intestinal blood flow by this method.

Anastomotic insufficiency is considered to be one of the most serious complications associated with esophageal reconstruction [7, 9, 10]. The primary cause is thought to be inadequate blood supply to the tissues [14, 15]. Local infection, tension at the anastomosis site, and hypoproteinemia are other important factors [14, 15].

In this study, the BFR in cases of anastomotic insufficiency was reduced intraoperatively. This tendency persisted postoperatively. The difference increased gradually and reached significance at POD 3. Thus, we suspect that the decrease in TBF in the gastric tube after surgery may cause anastomotic insufficiency. Because the side-type probe was inserted with a drain, it was easy to remove, and the complication that can be caused by this probe did not occur. The TBF of the gastric tube may be a predictor of anastomotic insufficiency after esophagectomy. Furthermore, we think that a fall of BFR during the course of the operation may serve as a good index of whether to add an auxiliary vascular anastomosis.

PGE_1 is a powerful vasodilator. It is reported that during esophagectomy, the TBF in a reconstructed gastric tube increases as a result of intravenous infusion of PGE_1 [27]. In our study, there was a tendency for patients who received such an infusion of PGE_1 intraoperatively to have a richer intraoperative BFR than control patients. Matsuzaki et al. [27] have reported that when used intravenously at a dose that reduces the systolic blood pressure by 10%, PGE_1 produces a beneficial vasodilator effect, thereby increasing blood flow to the gastric tube. The infusion rate of PGE_1 that we used (0.02 μg/kg per minute) lies within the range employed in their study (0.02-0.03 μg/kg per minute).

The BFR of the $PGE_1(+)$ cases tended to be richer than that of the control cases. However, two of the five Leakage(+) cases were also in the $PGE_1(+)$ group. There was no relationship between intraoperative medication with PGE_1 and incidence of leakage. This discrepancy in our results may explain why the factors responsible for anastomotic insufficiency are not easy to establish. We believe that the effects of these factors on the anastomosis may be much greater than the benefits of PGE_1. This study was performed to study intraoperative medication with PGE_1. Postoperative treatment with PGE_1 may show another result.

The TBF in the 2F group was better than that of 3F throughout the postoperative period, beginning when construction of the gastric tube had been completed. We believe that this is so because of the length of the gastric tube and the route of its reconstruction. The gastric tube in 2F patients is shorter, and the blood flow richer than that in 3F patients. Furthermore, in the 3F patients, the gastric tube is pressed against the episternum because it passes behind the manubrium of the sternum in a retrosternal direction. We feel that from the viewpoint of TBF, reconstruction of the posterior mediastinal route is a better and more natural approach than the retrosternal route. Serum CRP in the 2F group was lower than in the 3F group. It was reported that from the viewpoint of postoperative quality of life, intrathoracic anastomosis is better in preventing for dysphagia [28]. Therefore, we believe that thoraco-abdominal, two-field dissection and reconstruction of the posterior mediastinal route is a good adaptation of the surgical protocol for poor-risk cases and for patients with early-stage cancer.

In conclusion, the TBF of patients with anastomotic insufficiency is reduced perioperatively, especially in the postoperative period. The TBF of the gastric tube may be a predictor of anastomotic insufficiency after esophagectomy. However, PGE_1 treatment in the intraoperative period alone is not effective in preventing anastomotic insufficiency.

Résumé. La fistule anastomotique après anastomose oesophagienne est une des complications les plus sévères. Les buts de cette étude ont été d'identifier: (1) dans la période postopératoire, les rapports entre la fistule anastomotique et le débit sanguin des tissus (DST) du tube gastrique, (2) les effets de la prostaglandine E_1 (PGE_1) administrée en intraveineux sur le DST du tube gastrique. Le groupe d'étude a comporté 44 patients ayant eu une œsophagectomie pour cancer de l'œsophage. Le DST a été mesuré au niveau de la séreuse du tube gastrique par une débitométrie sanguine au laser-Doppler en peropératoire et en postopératoire. Le DST mesuré en peropératoire et en postopératoire a été plus faible dans le groupe avec fistule (+) ($n = 5$) que dans le groupe sans fistule (−) ($n = 39$). Au jour postopératoire 3, la différence observée du DST des deux groupes a été significative. On a noté une tendance dans le groupe $PGE_1(+)$ ($n = 18$) à un débit plus élevé à travers l'anastomose que dans le groupe $PGE_1(-)$ ($n = 26$), en peropératoire, mais cette différence n'était pas significative. Deux des cinq cas de fistule (+) étaient dans le groupe $PGE_1(+)$. Il n'y avait aucun rapport entre la prise de PGE_1 peropératoire et l'incidence de fistule. Le DST après oesophagectomie par trois champs et reconstruction par voie rétrosternale ($n = 21$) était moins bon que celui de l'oesophagectomie par deux champs et reconstruction par voie médiastinale postérieure ($n = 23$). Le DST du tube gastrique après oesophagectomie pourrait être un facteur prédictif de fistule anastomotique. Cependant, le traitement par PGE_1 pendant la période peropératoire seul n'est pas efficace dans la prévention de fistule anastomotique.

Resumen. La complicación más grave de las reconstrucciones esofágicas es la insuficiencia o fuga anastomótica. Los objetivos de este trabajo fueron: (1) establecer las relaciones existentes, durante el periodo perioperatorio, entre la insuficiencia o fuga anastomótica y el flujo sanguíneo tisular (TBF) del tubo gástrico, (2) averiguar los efectos de la administración intravenosa de prostaglandina E1 (PGE_1) en el TBF del tubo gástrico. Estudiamos 44 pacientes esofagectomizados por cáncer. Utilizando un flujómetro sanguíneo textural tipo Laser-Doppler se midió, en el periodo tanto intra como postoperatorio, el TBF en la serosa del tubo gástrico. Durante estos periodos el TBF, en el grupo insuficiencia o fuga anastomótica (+) $n = 5$ fue menor que en el grupo sin insuficiencia

(−) $n = 39$. Se constató al tercer día del postoperatorio (POD) una diferencia muy significativa del TBF entre ambos grupos. Se registró en el grupo PGE_1 (+) ($n = 18$) en relación con el grupo PGE_1 (−) ($n = 26$) una tendencia no significativa por lo que a un mayor flujo sanguíneo textural, a través de la anastomosis, se refiere. Dos de las 5 insuficiencias anastomóticas se registraron en el grupo PGE_1 (+). No hubo relación alguna entre la administración intraoperatoria de PGE_1 y la frecuencia de la dehiscencia. El TBF en tres áreas ganglionares tras disección y reconstrucción retroesternal ($n = 21$) fue menor, que en dos áreas ganglionares tras disección y reconstrucción mediastínica posterior ($n = 23$). El TBF del tubo gástrico es un factor pronóstico válido de la dehiscencia o fuga anastomótica. El tratamiento intraoperatorio con PGE_1 no es eficaz en la prevención de la misma.

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