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# The effect of prostaglandin $E_1$ on the increase of serum lactate and plasma granulocyte elastase activity during radical surgery for esophageal cancer

TAKAE KAWAMURA, KAZUTOSHI OKADA, HIROSHI OKADA, JUNNE AKIYAMA, MIDORI ISHIDA, and REIJI WAKUSAWA

Department of Anesthesiology, Iwate Medical University, 19-1 Uchimaru, Morioka, Iwate, 020 Japan

**Abstract:** Serum lactate concentrations and the lactate/pyruvate (L/P) ratio were measured in two groups of patients undergoing radical esophagectomy, as an indicator of tissue hypoxia, and β-glucuronidase and granulocyte elastase as indicators of tissue damage. One group received prostaglandin $E_1$ ($PGE_1$) and the other group received nothing. Serum lactate concentrations and the L/P ratio increased significantly 30 min after starting thoracotomy in the patients who were not treated with $PGE_1$. On the contrary, intravenous drip infusion of $PGE_1$ (0.04 $\mu g \cdot kg^{-1} \cdot min^{-1}$) suppressed the increases in serum lactate concentratons and L/P ratios. Plasma granulocyte elastase activity increased significantly at the end of surgery in both groups. There was no change in serum β-glucuronidase activity in both groups. This study suggests that low doses of $PGE_1$ maintain organ blood flow without affecting blood pressure. However, these low doses of $PGE_1$ could not suppress granulocyte elastase release.

**Key words:** Lactate, Prostaglandin $E_1$, Esophageal cancer

## Introduction

Postoperative pulmonary complications associated with thoracotomy and mediastinal lymph node dissection for esophageal cancer have been reported [1,2]. These complications may progress to multiple organ failure (MOF). Pathogenic factors of MOF include organ ischemia related to circulatory insufficiency and the effect of humoral mediators, indicating the importance of maintaining blood flow during surgery [3–5]. Prostaglandin $E_1$ ($PGE_1$) is known to be a vasodilator and to increase organ blood flow, and has direct cytoprotective effects such as cellular membrane stabilization [6–8].

*Address correspondence to:* T. Kawamura
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In this study, the effect of $PGE_1$ therapy was assessed by measuring serum concentrations of lactate and pyruvate as an indicator of tissue hypoxia, and β-glucuronidase and granulocyte elastase (GEL) activity as indicators of tissue damage.

## Patients and methods

After institutional approval of the study protocol, informed consent was obtained from 30 patients. All underwent radical surgery for esophageal cancer. Preoperative medication consisted of atropine 0.01 $mg \cdot kg^{-1}$, hydroxyzine 1 $mg \cdot kg^{-1}$, and pethidine 1 $mg \cdot kg^{-1}$ was administered intramuscularly 1 h before arrival in the operating room.

ECG, a pulse oximeter (Datex, IMI), and a capnometer (Datex, Capnomac 873379-15, IMI) were monitored continuously. A radial arterial catheter was inserted after induction of anesthesia and direct arterial pressure was measured. After induction of anesthesia with thiamylal (5 $mg \cdot kg^{-1}$), the trachea was intubated with a double-lumen tube using succinylcholine chloride. Anesthesia was maintained with $N_2O$ in 50% $O_2$ and isoflurane (2%) and muscle relaxation was achieved with pancuronium (0.1 $mg \cdot kg^{-1}$). Supplementary fluid infusion was accomplished with intravenous drip infusion of 10 $ml \cdot kg^{-1} \cdot hr^{-1}$ Ringer's lactate solution and 5 units of fresh frozen plasma.

The patients were divided into two groups: one not receiving $PGE_1$ (group I) and the other receiving the drug (group II). $PGE_1$ (0.04 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was given by intravenous drip infusion throughout the surgery.

In each patient, four blood samples were drawn from the radial artery, one each at the time of inducing anesthesia, 30 and 60 min after starting thoracotomy, and at the end of the surgery. Serum lactate, pyruvate, β-glucuronidase and plasma GEL activity were measured in those blood samples.

Activity of the complex of polymorphonuclear (PMN) elastase with $\alpha_1$-protease inhibitor ($\alpha_1$-PI) was determined by the sandwich immunoassay method [9], and the results of this assay were used as GEL activity. β-glucuronidase was assayed by enzyme immunoassay. Serum lactate and pyruvate were measured by the enzymatic method.

The data was statistically analyzed by analysis of variance and Neuman-Keuls multiple comparison tests. The level of significance was defined as $P < 0.05$. All statistics are given as the mean ± standard deviation (SD).

## Results

There were no significant differences with regard to the patients' age, body weight, and duration of surgery between groups I and II (Table 1).

Mean arterial pressure increased significantly at 30 min after thoracotomy compared with the preoperative level in group I. There were no other changes in either group (Table 2).

Serum lactate levels increased significantly, compared with the values before surgery, from 30 min after thoracotomy up to the end of surgery in both groups. In group II, the increase of serum lactate concentration at the end of surgery was lower than that in group 1 ($P < 0.01$) (Table 2) (Fig. 1). In both groups, the L/P ratio increased significantly at the end of surgery ($P < 0.01$) (Table 2).

Plasma GEL activity increased significantly at the end of surgery compared with the value before surgery in each group ($P < 0.05$) (Table 2) (Fig. 2). Serum β-glucuronidase activity did not change significantly in either group (Table 2).

The volume of urine output during surgery was 2.6 ± 1.3 $ml \cdot kg^{-1} \cdot hr^{-1}$ in group II, much more than 1.5 ± 0.7 $ml \cdot kg^{-1} \cdot hr^{-1}$ in group I ($P < 0.01$).

## Discussion

Blood lactate concentration is a valuable indicator of the severity of surgical stress. Hyperlactacidemia appears in two situation. First, it occurs when the common metabolic pool for lactate and pyruvate increases; that is, no change in redox with a constant ratio of lactate to pyruvate. Second, it is caused by an elevated L/P ratio with a shift in redox to the direction of reduction. An elevated L/P ratio reflects a high NADH/NAD ratio, suggesting that NADH accumulates in the cytoplasm due to tissue hypoxia or impairment of the respiratory chain in mitochondria.

In this study, we observed the increase in serum lactate levels from 30 min after the start of thoracotomy during radical surgery for esophageal cancer. At the end of the surgery, the L/P ratio increased significantly,

**Table 1.** Patient's age, body weight, and duration of surgery (mean ± SD)

| | *n* | Age (years) | Body weight (kg) | Duration of surgery (min) |
|---|---|---|---|---|
| Group I | 15 | 63 ± 7.3 | 51 ± 5.6 | 373 ± 45.3 |
| Group II | 15 | 66 ± 8.5 | 51 ± 7.5 | 397 ± 64.3 |

**Table 2.** Value of serum lactate, lactate/pyruvate ratio (*L/P ratio*), ß-glucuronidase, plasma granulocyte elastase (*GEL*) activity, and mean arterial pressure (*MAP*) in each period (mean ± SD)

| | | Before surgery | 30 min after thoracotomy | 60 min after thoracotomy | End of surgery |
|---|---|---|---|---|---|
| Lactate (mg/dl) | group I | 11.2 ± 3 | 14.8 ± 3* | 15.9 ± 3** | 31.8 ± 5** |
| | group II | 12.2 ± 2 | 15.9 ± 2 | 17.6 ± 2* | 25.5 ± 6***# |
| L/P ratio | group I | 11.0 ± 1 | 11.9 ± 1 | 12.0 ± 1 | 15.2 ± 4* |
| | group II | 10.9 ± 1 | 12.1 ± 1 | 12.9 ± 1 | 13.2 ± 1.6* |
| GEL activity (μg/l) | group I | 232 ± 104 | 256 ± 105 | 271 ± 127 | 386 ± 148* |
| | group II | 160 ± 19 | 152 ± 24 | 161 ± 21 | 351 ± 106* |
| β-glucuronidase (μg/dl) | group I | 556 ± 174 | 590 ± 194 | 599 ± 190 | 654 ± 183 |
| | group II | 577 ± 102 | 662 ± 59 | 634 ± 219 | 747 ± 156 |
| MAP (mmHg) | group I | 80 ± 15 | 98 ± 7* | 92 ± 9 | 81 ± 14 |
| | group II | 78 ± 18 | 92 ± 13 | 90 ± 14 | 82 ± 10 |

* $P < 0.05$ compared with value before surgery; ** $P < 0.01$ compared with value before surgery; # $P < 0.01$ compared with value in group I.

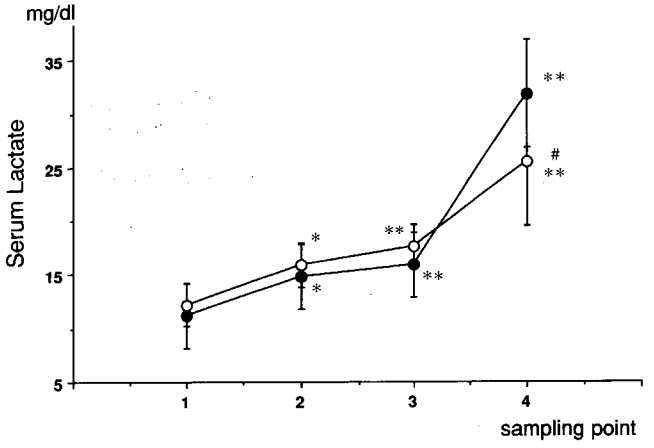


**Fig. 1.** Changes in serum lactate concentration (mean ± SD) for control (*closed circles*) and prostaglandin $E_1$ ($PGE_1$, *open circles*). $^*P < 0.05$ compared with value before surgery; $^{**}P < 0.01$ compared with value before surgery; $^{\#}P < 0.01$ compared with value in group I sampling points: 1, before surgery after induction of anesthesia; 2, 30 min after thoracotomy; 3, 60 min after thoracotomy; and 4, the end of surgery

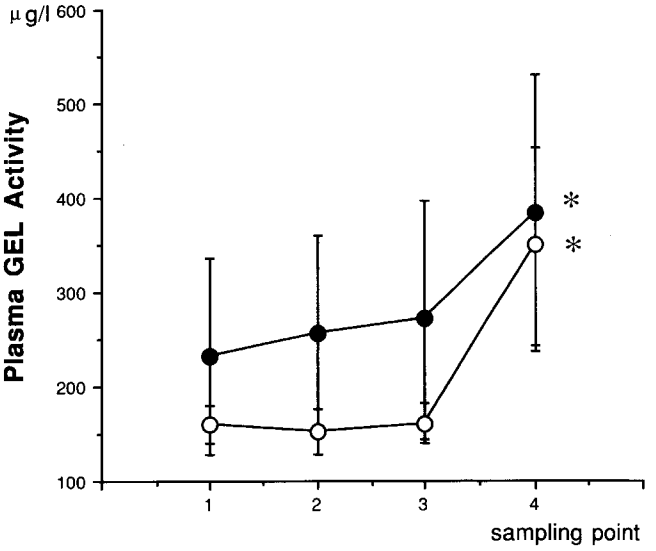


**Fig. 2.** The changes of plasma granulocyte elastase (*GEL*) activity (mean ± SD) for control (*closed circles*) and $PGE_1$ (*open circles*). $^*P < 0.05$ compared with value before surgery

These results suggest that prolonged massive surgical stress affects circulation in various organs due to excessive stimulation of the autonomic nerves [10], resulting in ischemia in the peripheral tissues. In hypoxia, oxidative phosphorylation of mitochondria is suppressed which leaves anaerobic glycolysis as the major source of ATP production, followed by a rise in pyruvate. In the reaction of pyruvate + NADN + $H^+ \rightarrow$ lactate + $NAD^+$ by lactate dehydrogenase (LDH), the lactate level is much higher than pyruvate at equilibrium, causing lactate to accumulate [11,12].

Normally, lactate is taken up in mitochondria where it is oxidized after entering the citric acid cycle following reaction with pyruvate dehydrogenase (PDH). In the liver and kidneys, however, it is consumed as the substrate for glyconeogenesis. When oxygen delivery to the tissues is impaired, lactate production increases, while lactate consumption simultaneously decreases due to impaired mitochondrial function. As a result, the serum lactate concentration increases significantly [12].

With tissue hypoxia, the liver, which is primarily responsible for metabolizing lactate, begins to produce it [13]. $PGE_1$ decreases blood pressure by its vasodilating effect on peripheral arteries, while it is reported to maintain blood flow and thus protect the heart, kidneys, liver, and brain [14–17]. When tissue perfusion is improved by decreased peripheral vascular resistance, the production of lactate in the peripheral tissues seems to be suppressed.

It has been reported that $PGE_1$ regulates the energy balance in hepatocytes and intracellular electrolyte balance by activating adenyl cyclase in hepatocytes, and thus by increasing cyclic AMP. Okabe et al. [18] reported that $PGI_2$ attenuates the reduction in oxidative phosphorylation of liver mitochondria due to ischemia [18]. In this study, the accumulation of lactate was inhibited by $PGE_1$. This seemed to be due to a synergistic effect between increased hepatic and renal blood flow and improved mitochondrial function in the liver and kidneys.

$PGE_1$ has been reported to increase renal plasma flow, urine output, and Na excretion [19–21]. The present results support previous findings that urine output was significantly higher in patients receiving $PGE_1$ than in those not receiving the drug.

Plasma GEL is one of the chemical mediators which cause postoperative pulmonary complications. In both groups, it increased significantly at the end of surgery. These results may be explained by the release of GEL following aggregation of polymorphonuclear cells associated with mechanical stimulation of the lungs during thoracotomy. GEL is one of the neutral proteases which lyse or destroy pulmonary components including collagen, elastin, and fibronectin, resulting in increased vascular permeability [22–25], and affect postoperative pulmonary complications.

Nuytinck et al. [26] studied multiple organ failure following trauma and suggested that GEL was the best

predictor of adult respiratory distress syndrome (ARDS) and MOF, and was related to the survival rate of those who developed these diseases. These results indicate the importance of intraoperative management to suppress the increase in GEL activity. We had expected that $PGE_1$ suppress GEL by stabilizing the membrane; however, it did not show this effect at the relatively low dose of 0.04 $\mu g \cdot kg^{-1} \cdot min^{-1}$ used in this study.

$PGE_1$ has been reported to maintain organ blood flow without affecting blood pressure, when given at low doses of 0.02–0.04 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The results of this study suggest that low doses of $PGE_1$ can be used safely without producing excessive hypotension. In conclusion, serum lactate concentration and the L/P ratio increased significantly during radical surgery for esophageal cancer. The treatment with $PGE_1$ inhibited the increase of serum lactate. It is suggested that $PGE_1$ maintains blood flow in the vital organs. However, low doses of $PGE_1$ could not suppress the increase in granulocyte elastase.

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