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EFFECT OF PHOSPHODIESTERASE III INHIBITOR (OLPRINONE) ON THORACIC DUCT LYMPH FLOW IN ANESTHETIZED SHEEP WITH EXPERIMENTALLY INDUCED HEART FAILURE BY ENDOTHELIN-1

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ABSTRACT

We investigated the short-term effects of a phosphodiesterase III Inhibitor (Olprinone) on hemodynamics and thoracic duct lymph flow in anesthetized open-chest sheep with heart failure induced by endothelin-1 (cardiogenic shock). Ultrasound transit-time flow probes were attached to the thoracic duct, the ascending aorta and the renal artery. Arterial, pulmonary and central venous pressures were monitored. Endothelin-1 was infused intravenously at a dosage that reduced cardiac output to 50% or more of baseline (n=11). The effects of Olprinone were examined (n=5) by intravenous infusion after endothelin-1 administration. Other sheep (n=6) were used as controls. Olprinone significantly increased cardiac output that had been decreased by endothelin-1 and further increased thoracic duct flow that had been increased by endothelin-1. Increased arterial and pulmonary pressures induced by endothelin-1 administration were rapidly decreased by Olprinone. Renal arterial flow and central venous pressure were, however, unchanged by Olprinone. Overall, Olprinone acutely improved experimental cardiogenic shock (heart failure) induced by endothelin-1, and maintained thoracic duct lymph flow at a high level after endothelin-1 administration.

Endothelin-1 (ET-1) is a peptide implicated in various pathological states (1) including heart failure (2). During heart failure, systemic and pulmonary edema are induced if both the right and left ventricles fail to contract optimally. With decreased blood flow from lowered cardiac output, edema worsens systemic organ and pulmonary function by decreased tissue oxygenation. Therefore, improvement of edema (both pulmonary and systemic) in heart failure is desirable to interrupt this vicious cycle.

Lymph flow plays an important drainage role in both systemic and pulmonary edema. It has been our goal to improve edema in heart failure by augmenting lymph transport, and especially flow in the thoracic duct, the major pathway returning lymph to the central venous circulation. We have recently investigated lymph flow dynamics in the thoracic duct (3-5) and now applied these techniques to the treatment of fluid imbalances in experimental heart failure.

To augment lymph flow, we chose to study a phosphodiesterase III (PDE III) inhibitor, namely Olprinone or OLP. A PDE III inhibitor has both cardiotonic and potent vasodilating effects (6,7) by increasing the intracellular concentration of cyclic adenosine monophosphate (8,9) and has been used for

the treatment of acute heart failure (7,10). These hemodynamic responses to a PDE III inhibitor suggested to us that Olprinone might act to improve lymph flow dynamics including thoracic duct contraction. Accordingly, in the following experiments, we induced acute depression of cardiac output in sheep by administrating ET-1 and then examined the short-term effects of OLP on blood and lymph dynamics before, during, and after recovery of acute heart failure.

MATERIALS AND METHODS

Anesthetized Sheep Preparation

This study was approved by the University Committee on Animal Resources and conformed to the guiding principles of our institution in the care and use of animals.

Eleven mongrel sheep of either sex, with a mean weight of 49±2 kg, were used. Anesthesia was initiated with intramuscular injection of ketamine hydrochloride (10 mg/kg) and atropine sulfate (0.5 mg). After intravenous injection of thiopental sodium (5 mg/kg), an endotracheal tube was introduced. Respiration was controlled by a ventilator (Harvard pump Model No.607, Mass) under muscle relaxation using pancuronium bromide (0.05mg/kg/hr). Halothane (0.5-1.5%) was delivered from a calibrated vaporizer using a mixture of oxygen and room air. A tracheostomy was then performed and the long endotracheal tube was exchanged with a short tracheostomy tube to minimize tube complications. A catheter was inserted into the right common carotid artery and connected to a pressure transducer (MPU-0.5A, Nihon Kohden, Tokyo, Japan) for monitoring arterial blood pressure (ABP). A Swan-Ganz catheter was inserted via the right external jugular vein and connected to a low-pressure transducer (LPU-0.1A, Nihon Kohden) for measurement of central venous pressure (CVP) and pulmonary arterial pressure (PAP). Pressure data were recorded using a multi-channel polygraph system (RM-6000, Nihon Kohden). With the sheep in the left lateral decubitus position, a right 7th intercostal thoracotomy was performed and an ultrasound transit-time flow probe (Model H2SB, Transonic Systems Inc., Ithaca, NY) was attached to the thoracic duct for measurement of thoracic duct lymph flow (TDF). A right 4th intercostal thoracotomy was then performed, and an ultrasound transit-time flow probe (Model 20SS, Transonic Systems Inc.) was attached to the root of the ascending aorta for measurement of cardiac output (CO). An ultrasound transit-time flow probe (Model H2.5SB, Transonic Systems Inc.) was also attached to the right renal artery using a retroperitoneal approach for measurement of renal blood flow (RBF). Each probe was connected to an ultrasound transit-time flow meter (Model H207 or H102, Transonic Systems Inc.). A computer (Model 2411 Kit-P95, IBM) and polygraph system recorded the flow parameters. Flow data were analyzed by using software (Flowtrace, Transonic Systems Inc.) and the average flow for each minute was calculated.

Heart Failure Induced by ET-1

In preliminary experiments, we defined heart failure as that condition in which CO had decreased to at least 50% of the baseline value. We also tested the effect of ET-1 on CO in anesthetized sheep using different amounts of ET-1 and different methods of ET-1 administration. These techniques included slow administration of ET-1 for 3 minutes or bolus administration for 1 second with 20, 200 or 400 pmol/kg body weight. These experiments showed the effect of ET-1 on CO was most intense after 200 pmol/kg of bolus administration or 400pmol/kg of slow administration with the maximum decrease in CO occurring after the latter dosage and rate (11). Only slow administration of 400 pmol/kg of ET-1 produced a CO decrease of less than 50% of the baseline value with a maximum effect after ~4-5 minutes from the

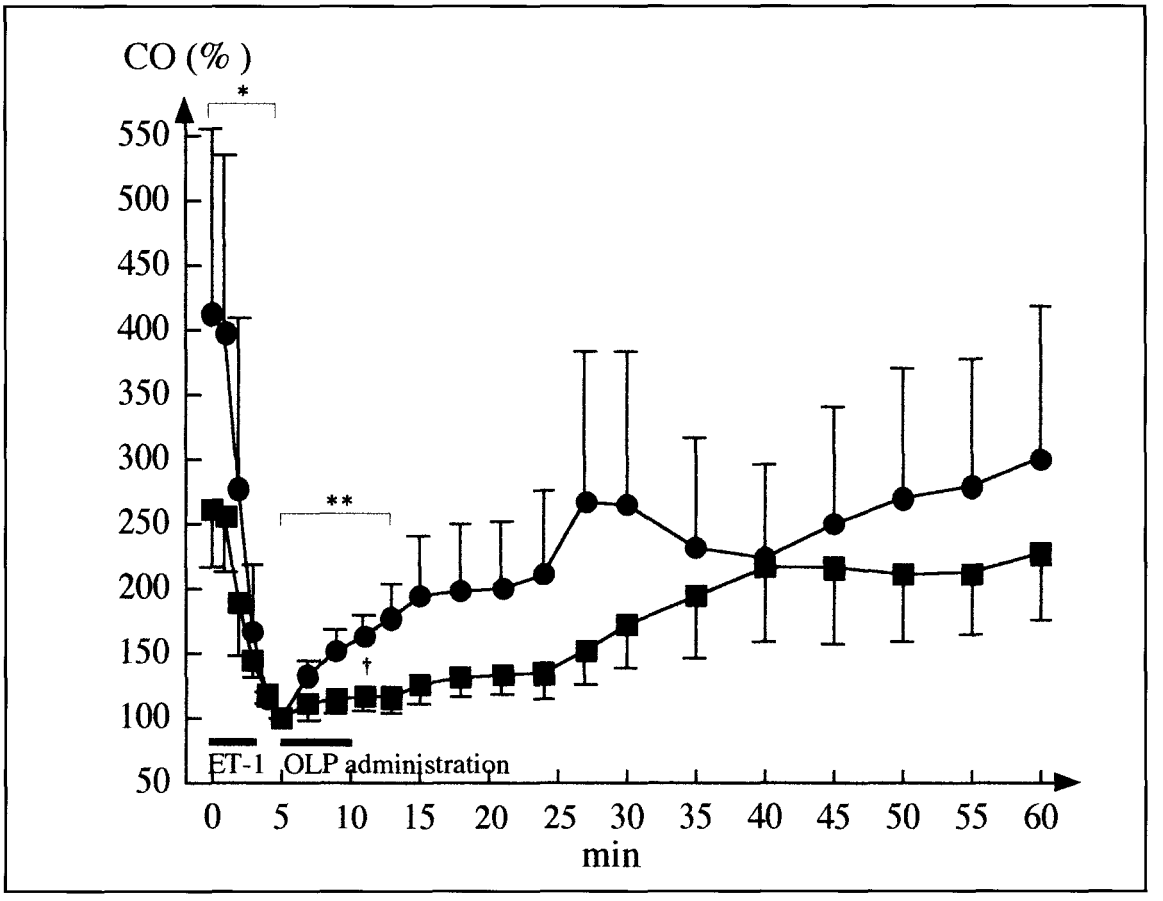

*Fig. 1: Time course of the changes of cardiac output (CO). Endothelin-1 (ET-1) was administrated only to the control group (■, n=6). OLP (30μg/kg for 5 min) was administrated after ET-1 administration in treatment group (●, n=5). To clarify the effect of OLP, data are presented by % of the value at the starting period of OLP administration and expressed by mean ± standard error. CO decreased significantly after ET-1 administration (400 pmol/kg for 3 min) (*p <0.01). On the other hand, CO increased significantly during and 3 min after OLP administration (**p <0.05). The maximum difference appeared at 11 min (†p <0.05).*

initiating slow ET-1 administration. Accordingly, for purposes of this study, we induced experimental heart failure by slow administration of 400 pmol/kg of ET-1 for 3 minutes ("endothelin-cardiogenic shock").

Drugs and Experimental Protocols

After hemodynamic and flow parameters stabilized, baseline values were measured for 5 minutes and the sheep were divided into two groups. One received only ET-1 (400 pmol/kg in 10ml saline) over 3 minutes after baseline measurements (control group, n=6). The second group received OLP (30μg/kg in 10ml saline) intravenously for 5 minutes after ET-1 administration with a 2 minute interval (OLP treatment group, n=5).

Data and Statistical Analysis

To determine the short term hemodynamic and lymphodynamic effects of ET-1 and OLP, data were presented as % of the value (mean ± SEM) at baseline before ET-1 and as % of the value of a second baseline

just before starting OLP administration.

Formulas for hemodynamic calculations are shown below (12).

1) Mean ABP (mABP, in mmHg) = (systolic ABP + diastolic ABP×2) /3

2) Systemic vascular resistance (SVR, in dynes•sec•cm^{-5}) = (60×mABP/CO)×1,332

3) Total pulmonary vascular resistance (TPR, in dynes•sec•cm^{-5}) = (60×mPAP/CO)×1,332

The significance of the difference between the two groups was analyzed by repeated measures of analysis of variance (ANOVA). The significance of the difference between the two groups at each interval and the significance of the difference between baseline value and each interval in the same group was analyzed by one-way ANOVA with Fisher's protected least significant difference test. Each p value was calculated using software (Stat-View 4.5, SAS Institute Inc., North Carolina).

RESULTS

Slow administration of 400 pmol/kg of ET-1 induced experimental heart failure or endothelin-1 cardiogenic shock.

Before ET-1 administration, CO was similar: 1.60±0.15 in the control group and 2.00±0.26 L/min in the latter OLP treatment group (N.S.). CO decreased significantly after ET-1 administration in the control group (0.73±0.15 L/min, p =0.0013), similar to the significant CO decrease after ET-1 administration in the later to be treated OLP group (0.73±0.22 L/min, p =0.0099). After OLP administration, CO increased significantly (p =0.0152) in an early stage (from 5 to 13 min after the start of ET-1 administration) compared with the control group *(Fig. 1)*. The maximum difference between the two groups was at 11 minutes after the start of ET-1 administration (121±13% in the control group and 162±16% in the OLP treatment group, p =0.0427) *(Fig. 1)*.

Before ET-1 administration, renal blood flow (RBF) was 104.9±36.2 ml/min in the control group and 88.0±20.2 ml/min in the OLP treatment group (N.S.). RBF decreased significantly after ET-1 administration (15.9±8.9 ml/min in the control group, p =0.0056 and 14.3_4.4 ml/min in the OLP treatment group, p =0.0026). After OLP administration, RBF showed no statistical difference between the two groups.

Before ET-1 administration TDF was 2.31±0.26 ml/min in the control group and 3.19±0.48 ml/min in the OLP treatment group (N.S.). TDF increased significantly after ET-1 administration (3.46±0.46 ml/min in the control group, p =0.0351 and 4.53±0.87 ml/min in the OLP treatment group, p =0.0462). After OLP administration, TDF increased significantly in the treatment group (p =0.0252) in an early stage (from 5 to 18 min after the start of ET-1 administration) compared with the control group. The maximum difference between the two groups was at 11 minutes after the start of ET-1 administration (88±7% in the control group and 125±8% in the OLP treatment group, p =0.0079) *(Fig. 2)*.

Before ET-1 administration SVR was 4248.9±641.4 dynes•s•cm^{-5} in the control group and 4172.3±757.1 dynes•s•cm^{-5} in the OLP treatment group (N.S.). SVR increased significantly after ET-1 administration (14833.0±4354.7 dynes•s•cm^{-5} in the control group, p=0.001) and 20839.5±10738.9 dynes•s•cm^{-5} in the OLP treatment group, p =0.001). After OLP administration, SVR decreased significantly in the treatment group (p =0.0473) at a relatively early stage (from 5 to 24 min after the start of ET-1 administration) compared with the control group. The maximum difference between the two groups was at 24 minutes after the start of ET-1 administration (76.2±7.0% in the control group and 49.6±8.6% in the OLP treatment group, p =0.0384) *(Fig. 3)*.

Before ET-1 administration TPR was 1453.5±154.4 dynes•s•cm^{-5} in the control group and 1110.9±174.4 dynes•s•cm^{-5} in the OLP treatment group (N.S.). TPR increased significantly after ET-1 administration (6247.3±1903.2 dynes•s•cm^{-5} in the control

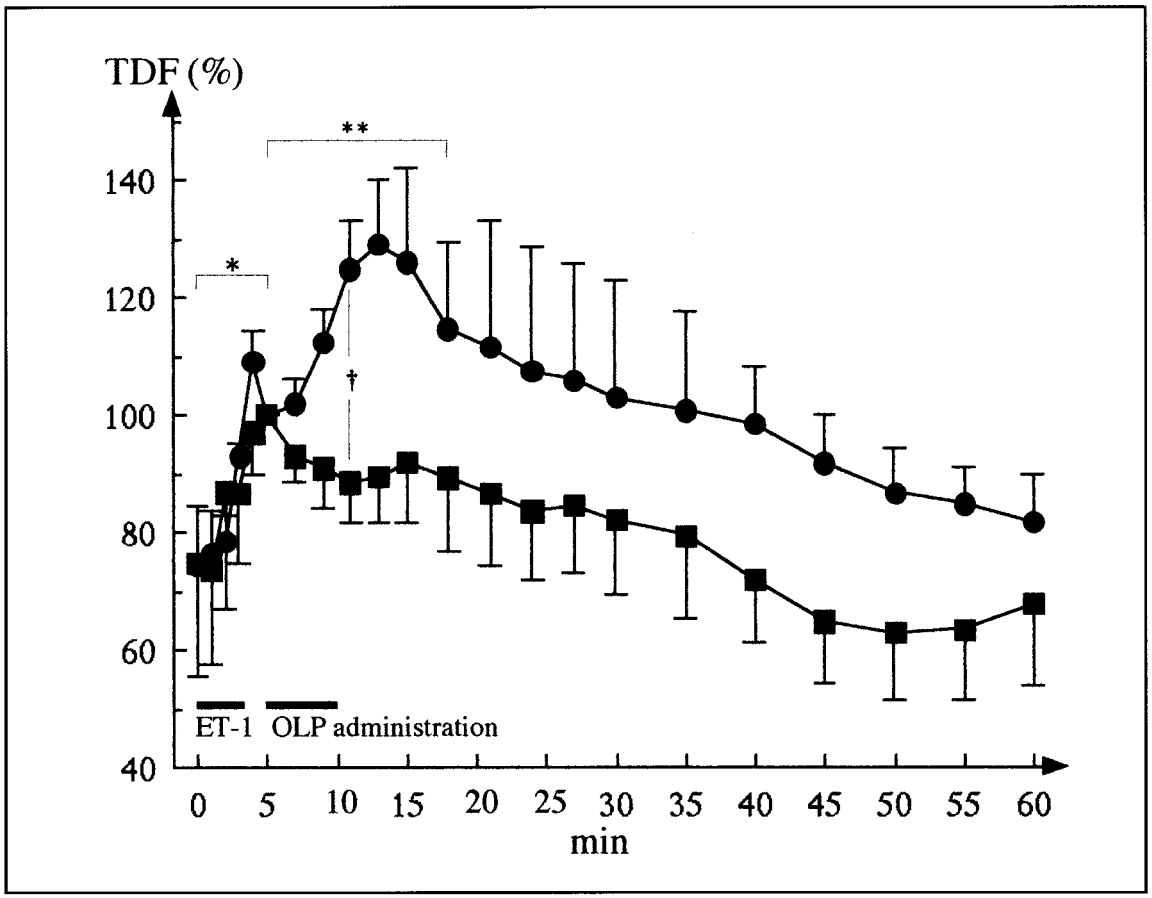

*Fig. 2: Time course of the changes of thoracic duct lymph flow (TDF). Endothelin-1 (ET-1) was administrated only to the control group (■, n=6). OLP (30μg/kg for 5 min) was administrated after ET-1 administration in treatment group (●, n=5). To clarify the effect of OLP, data are presented by % of the value at the starting period of OLP administration and expressed by mean ± standard error. TDF increased significantly after ET-1 administration (400 pmol/kg for 3 min) (*p <0.01). Furthermore, TDF increased significantly during and 8 min after OLP administration (**p <0.05). The maximum difference appeared at 11 min (†p <0.01).*

group, p =0.001) and 8096.5±3679.6 dynes • s • cm^{-5} in the OLP treatment group, p =0.001). TPR decreased significantly in the treatment group (p =0.0309) at a relatively early stage (from 5 to 21 min after the start of ET-1 administration) compared with the control group. The maximum difference between the two groups was at 13 minutes after the start of ET-1 administration (74.3±9.4% in the control group and 40.6±6.5% in the OLP treatment group, p =0.0202) *(Fig. 3)*.

Before ET-1 administration CVP was 9.9±1.0 mmHg in the control group and 9.3±0.6 mmHg in the OLP treatment group (N.S.). CVP did not change after ET-1 administration or after OLP administration.

DISCUSSION

ET-1 is a potent vasoconstrictor peptide (13) that produces myocardial ischemia by constricting coronary arteries and thereby induces acute heart failure (14). We succeeded in creating acute heart failure or ET-1 cardiogenic shock in sheep by

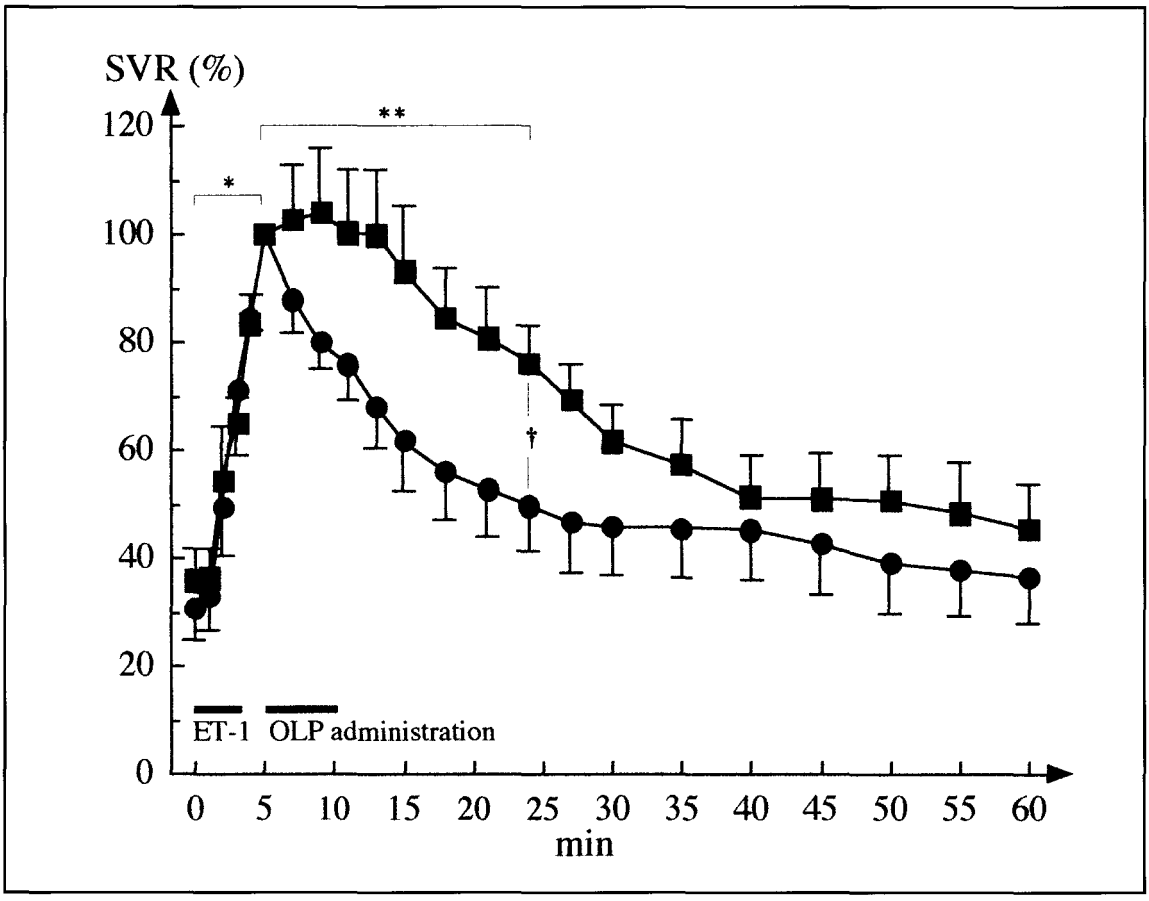

*Fig. 3: Time course of the changes of systemic vascular resistance (SVR). Endothelin-1 (ET-1) was administrated only to the control group (■, n=6). OLP (30μg/kg for 5 min) was administrated after ET-1 administration in treatment group (•, n=5). To clarify the effect of OLP, data are presented by % of the value at the starting period of OLP administration and expressed by mean ± standard error. SVR increased significantly after ET-1 administration (400 pmol/kg for 3 min) (*p <0.01). SVR decreased significantly during and 14 min after OLP administration (**p <0.05). The maximum difference appeared at 24 min (†p <0.05).*

administering 400 pmol/kg of ET-1 over 3 min. To determine the optimal amount of ET-1 and the method of administration, we relied on a report that showed that the EC_{50} value of ET-1 that produced coronary artery constriction was 5 nM (15) and another study showing that intravenously administrated ET-1 was absorbed in the pulmonary circulation with a half life of just a few minutes (16). Whereas the amount of ET-1 in the plasma of normal sheep is <8 pM (17), two other reports (15,16) suggested intense coronary artery constriction could be produced by an ET-1 dose of 400 pmol/kg for 3 min. In fact, in preliminary experiments, we demonstrated that CO decreased to less than 50% by administering this dosage.

There are probably two major reasons for the decrease in CO by the administration of ET-1 *(see Fig. 1)*. One is left ventricular dysfunction generated by myocardial ischemia from induced constriction of the coronary arteries (18,19). Another is increased ventricular afterload from constriction of the arteriolar resistance vessels (20). The latter was demonstrated in our experiments that

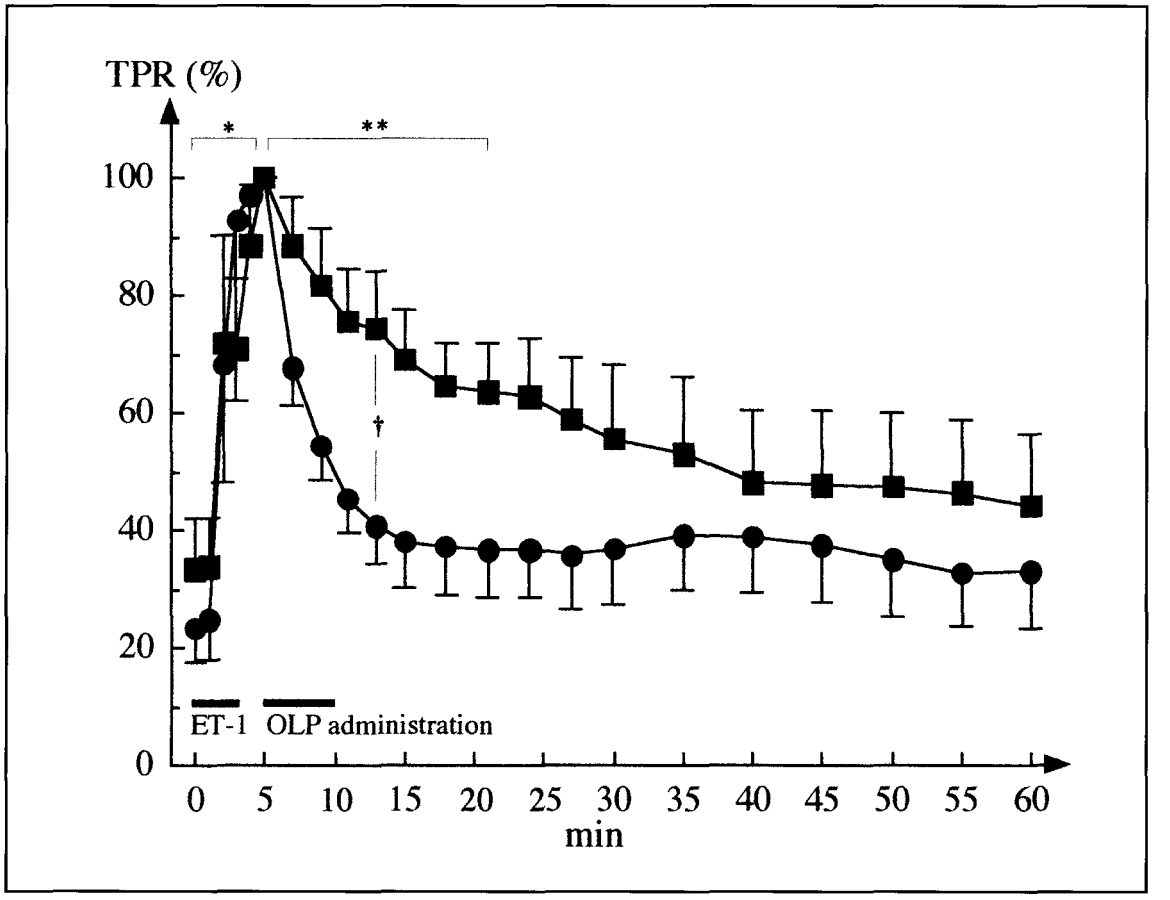

*Fig. 4: Time course of the changes of total pulmonary vascular resistance (TPR). Endothelin-1 (ET-1) was administrated only to the control group (■, n=6). OLP (30μg/kg for 5 min) was administrated after ET-1 administration in treatment group (●, n=5). To clarify the effect of OLP, data are presented by % of the value at the starting period of OLP administration and expressed by mean ± standard error. TPR increased significantly after ET-1 administration (400 pmol/kg for 3 min) (*p <0.01). TPR decreased significantly during and 11 min after OLP administration (**p <0.05). The maximum difference appeared at 13 min (†p <0.05).*

showed a significant rise in the SVR *(see Fig. 3)*. OLP, on the other hand, exerts a potent inotropic effect on cardiac contractility (21) and also a vasodilating response, favoring ventricular afterload reduction (9). In our experiments, CO, which was sharply decreased by ET-1 administration, was acutely reversed by these two main actions of OLP *(see Fig. 1)*.

SVR, which was increased by ET-1, was sharply decreased acutely by OLP administration *(see Fig. 3)*, primarily because of its vasodilating activity (9,22). This viewpoint is supported by a single report that *in vitro* constriction of human internal mammary arterial rings induced by ET-1 were fully relaxed by another PDE III inhibitor, namely milrinone (23).

In our experiments, after ET-1 administration, a decline in RBF occurred with the fall in CO and vasoconstriction of the renal arteries (24,25). OLP administration did not alter the decreased RBF, although another report showed that a different phosphodiesterase III inhibitor, namely amrinone increased RBF significantly in

anesthetized dogs (26), suggesting organ or species response differences to different phosphodiesterase III inhibitors.

In our experiments, a significant increase in TPR occurred after ET-1 administration *(see Fig. 4)*. These findings are consistent with others showing that ET-1 increased TPR (27,28). TPR acutely decreased after continuous infusion of OLP (30 µg/kg) *(see Fig. 4)*.

We previously demonstrated that an intravenous infusion of ET-1 significantly increased TDF (11). We suggested two reasons to explain the response. ET-1 either increases production of lymph in peripheral tissues by increasing systemic and pulmonary microvascular pressure, and/or that ET-1 has a direct vasomodulating effect on the thoracic duct. Reeder et al described that ET-1 is a potent endothelium-derived vasoconstrictor of lymphatic vessels (29). Sakai et al reported that stimulation of ET(A) receptors elicits a positive chronotropic effect on spontaneous contractions, and stimulation of ET(B) receptors induces a release of nitric oxide (NO), which decreases the frequency and amplitude of spontaneous contractions in isolated bovine mesenteric lymph vessels (30). Consistent with these data, TDF showed a maximum flow after ~1-2 min after ET-1 infusion and then gradually decreased *(see Fig. 2)*. OLP administration, however, further increased TDF *(see Fig. 2)*. Three possible pathomechanisms account for the effect of OLP on TDF. One is that OLP increased lymph production by increasing hepatosplanchnic blood flow and thereby heightened the surface area for microvascular exchange and greater plasma capillary filtration (31,32). Another is that OLP reduces resistance to lymph flow by relaxing the smooth muscles (10) of peripheral lymphatic collectors while increasing the propulsive activity of the thoracic duct (3-5) similar to OLP's positive inotropic pumping action on the heart (9).

In summary, acute experimental heart failure (cardiogenic shock) was induced in anesthetized sheep by slow administration of ET-1. Systemic and pulmonary fluid imbalances occur with decreased CO and are the direct consequence of ET-1. An infusion of OLP transiently improved cardiac and peripheral hemodynamics in the early stage of heart failure. ET-1 administration increased TDF, and this increase was further augmented by OLP.

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