Effects of catecholamines on the pulmonary circulation in the ovine fetus

S. JAILLARD, V. HOUFFLIN-DEBARGE, Y. RIOU, T. RAKZA, S. KLOSOWSKI, P. LEQUIEN, AND L. STORME. Effects of catecholamines on the pulmonary circulation in the ovine fetus. *Am J Physiol Regulatory Integrative Comp Physiol* 281: R607–R614, 2001.—High levels of circulating catecholamines are found in the fetus, and fetal stress and birth induce a marked surge in catecholamine secretion. Little is known about the role of catecholamines on the fetal pulmonary circulation. To determine the effects of catecholamines on the pulmonary vascular tone, we tested the hemodynamic response to norepinephrine and dopamine infusion in chronically prepared late-gestation fetal lambs. We found that norepinephrine infusion (0.5 μg·kg⁻¹·min⁻¹) increased pulmonary artery pressure (PAP) by 10 ± 1% (*P* < 0.01), left pulmonary artery blood flow by 73 ± 14% (*P* < 0.01), and decreased pulmonary vascular resistance (PVR) by 33 ± 6% (*P* < 0.01). The pulmonary vasodilator effect of norepinephrine was abolished after nitric oxide synthase inhibition. Dopamine infusion at 5 μg·kg⁻¹·min⁻¹ did not significantly change PVR. Conversely, dopamine infusion at 10 μg·kg⁻¹·min⁻¹ increased PAP (*P* < 0.01) and progressively increased PVR by 30 ± 14% (*P* < 0.01). These results indicate that catecholamines may modulate basal pulmonary vascular tone in the ovine fetus. We speculate that catecholamines may play a significant role in the maintenance of the fetal pulmonary circulation and in mediating changes in the transitional pulmonary circulation.

norepinephrine; dopamine; nitric oxide

The fetal pulmonary circulation is characterized by high pulmonary vascular resistance (PVR) and low blood flow. Despite high pulmonary artery pressure (PAP), lung is perfused with <10% of combined ventricular output during late gestation. Because of high PVR in the fetus, most of the right ventricular output crosses the ductus arteriosus into the descending aorta, thereby increasing umbilical-placental flow and gas exchange. Mechanisms that maintain high PVR in utero are incompletely understood but may include low fetal PO₂, lack of a gas-liquid interface, and production of vasoconstrictor mediators.

Little is known about the role of catecholamines on the fetal pulmonary vascular tone under basal conditions or at birth. Catecholamine levels are higher in fetal than in maternal plasma (11, 27) and increase at the end of gestation (27). These data provide some indirect evidence that endogenous catecholamines may play a significant role in the fetus and the newborn. Norepinephrine and dopamine represent the main catecholamines found in the fetal circulating blood. Fetal stress (hypoxia, invasive procedures) induces a marked surge in catecholamine secretion (13, 33). An increase in plasma catecholamine concentration during fetal hypoxic stress is considered as one of the mechanisms of circulation redistribution toward the brain, heart, and adrenal glands (14). Abman and co-workers (3) have proposed that prolonged but not brief intratracheal hypoxia stimulates catecholamine release, which may contribute to persistent pulmonary vasoconstriction through activation of α-adrenergic receptors and altered vasoreactivity. High levels of circulating catecholamines have also been measured at birth (4). Increased catecholamines at delivery contribute clearly to lung fluid reabsorption, surfactant release, and systemic hemodynamic adaptations (25, 34). However, the effects of such a catecholamine release surge at birth on the pulmonary circulation are not known.

Conflicting results exist on the vascular effects of catecholamines. Although catecholamines are known as vasopressor agents, reports suggest that catecholamines may have some pulmonary vasodilator effects during the fetal life. Elevation of intracranial pressure in fetal goats results in a fall of PVR through activation of β-adrenergic receptors (16). In vitro studies have reported that norepinephrine dilates some systemic (24) and pulmonary (39) vessels in newborn animals. Activation of specific dopaminergic receptors mediates relaxation of pulmonary vessels (29, 30). Thus circulating catecholamines may play a significant role in the maintenance of the fetal pulmonary circulation and during transitional circulation at birth.

We therefore hypothesized that catecholamines modulate pulmonary vascular tone during fetal life. To test this hypothesis, we studied the pulmonary vascular


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response to norepinephrine and dopamine infusion in chronically prepared late-gestation fetal lambs.

MODEL AND METHODS

Animal Preparation

All animal procedures and protocols used in this study were reviewed and approved by the French “Ministère de l’Agriculture, de la Pêche et de l’Alimentation” before the studies were conducted. Nine mixed-breed (Columbia-Rambouillet) pregnant ewes between 126 and 128 days gestation (term = 145 days) were fasted for 48 h before surgery. Ewes were sedated with intravenous pentobarbital sodium (total dose 2–4 g) and anesthetized with 1% bupivicaine hydrochloride (4 mg) by lumbar puncture. Ewes were kept sedated but breathed spontaneously throughout the surgery. Under sterile conditions, the fetal lamb’s left forelimb was delivered through a uterine incision. A skin incision was made under the left forelimb after local infiltration with lidocaine (2 ml, 1% solution). Polyvinyl catheters (20 gauge) were advanced into the ascending aorta and the superior vena cava after insertion in the axillary artery and vein. A left thoracotomy exposed the heart and great vessels. Catheters were inserted into the left pulmonary artery (LPA; 22 gauge), main pulmonary artery (20 gauge), and left atrium (20 gauge) by direct puncture through purse-string sutures and secured as described (2). An ultrasonic flow transducer (size 6; Transonic Systems, Ithaca, NY) was placed around the LPA to measure blood flow. The uteroplacental circulation was kept intact, and the fetus was gently replaced in the uterus. An additional catheter was placed in the amniotic cavity to measure pressure. Ampicillin (500 mg) was added to the amniotic cavity before closure of the hysterotomy. The flow transducer and catheters were exteriorized through a subcutaneous tunnel to an external flank pouch. The ewes recovered rapidly from surgery, generally standing in their pens within 6 h. Food and water were provided ad libitum. Catheters were maintained by daily infusions of 2 ml of heparinized saline (1% solution). Polyvinyl catheters (20 gauge) were advanced into the left pulmonary artery (LPA; 22 gauge), main pulmonary artery catheter was flushed with normal saline at a constant rate of 6 ml/h during the 20 min before starting the norepinephrine infusion. 

Physiological Measurements

The flow transducer cable was connected to an internally calibrated flowmeter (T201; Transonic Systems) for continuous measurements of LPA blood flow. The output filter of the calibrated flowmeter (T201; Transonic Systems) for continuous measurement of pulmonary artery (LPA) blood flow value immediately before the beginning of the infusion. PVR in the left lung was calculated as the difference between mean pulmonary arterial pressure and the left atrial pressure (LAP). The output from a mercury column manometer. Heart rate was determined from the phasic pulmonary blood flow signal. PVR in the left lung was calculated as the difference between mean pulmonary arterial pressure and left atrial pressure (LAP). Pressure and flow signals were continuously recorded and processed on a computer (Pentium III, 450 Mz) using an analog-to-digital converter system (LabView, National Instrument, Woerden, The Netherlands). Data were sampled at a rate of 50 samples/s. Pressures were referenced to the amniotic cavity pressure. Calibration of the pressure transducers was performed with a mercury column manometer. Heart rate was determined from the phasic pulmonary blood flow signal. PVR in the left lung was calculated as the difference between mean pulmonary arterial pressure and left atrial pressure (LAP). Blood samples from the main pulmonary artery catheter were used for blood-gas analysis and oxygen saturation measurements (OSM 3 hemoximeter and ABL 520; Radiometer, Copenhagen, Denmark).

Drug Preparation

Norepinephrine (Aguettant, Lyon, France) was dissolved in normal saline to a concentration of 15 μg/ml. Dopamine (Pierre Favre, Boulogne, France) was dissolved in normal saline to two different concentrations: 150 and 300 μg/ml. The drugs were infused in the superior vena cava at a rate of 6 ml/h. l-Nitro-arginine (l-NA; Sigma Chemical, St. Louis, MO) solution was freshly prepared just before infusion. l-NA (30 mg) was dissolved in a few drops of 1 M HCl. Then, 1 ml of normal saline was added. One molar NaOH was added to titrate the pH to 7.40.

Experimental Design

Two different experimental protocols were included in this study: 1) pulmonary hemodynamic response to norepinephrine and dopamine infusion and 2) pulmonary hemodynamic response to norepinephrine after nitric oxide (NO) synthase (NOS) inhibition. The infusion protocols were randomized. A minimum recovery period of 24 h was required between each protocol. To ensure that complete recovery was achieved before starting a protocol, we checked that the measured parameters and arterial blood gases returned to the baseline values.

Protocol 1: hemodynamic response to catecholamines infusion. To investigate the effects of catecholamines on fetal pulmonary circulation, we studied the hemodynamic response to infusion of norepinephrine at 1.5 μg/min (~0.5 μg·kg⁻¹·min⁻¹), dopamine at 15 μg/min (~5 μg·kg⁻¹·min⁻¹), and dopamine at 30 μg/min (~10 μg·kg⁻¹·min⁻¹). All study drugs, including saline, were infused into the venous catheter (superior vena cava). Duration of each experiment was at least 240 min. Saline (6 ml/h) was first infused for at least 30 min. After 30 min of stable baseline measurements, the drugs were infused for 120 min (from 30 to 150 min). Then, the catheter was flushed with saline (6 ml/h) for 30 min (from 150 to 180 min). Mean PAP, LAP, mean aortic pressure (AoP), amniotic pressure, left pulmonary blood flow, and heart rate were recorded at 10-min intervals, starting at the beginning of the infusion. PVR in the left lung was calculated.

Protocol 2: hemodynamic response to norepinephrine after NOS inhibition. To investigate the effects of NOS inhibition on the hemodynamic response to norepinephrine, protocol 1 was repeated after l-NA infusion. l-NA (30 mg over 10 min) was infused into the LPA (from 30 to 40 min). This dose was selected from past studies that have demonstrated effective blockade of NOS activity during acetylcholine and flow-induced vasodilation for at least 4 h (9). Then the pulmonary artery catheter was flushed with normal saline at a constant rate of 6 ml/h during the 20 min before starting the norepinephrine infusion (from 60 to 180 min).

Data Analysis

The results are presented as means ± SE. The data were analyzed using repeated-measures and factorial ANOVA. Intergroup differences were analyzed with the Fisher’s, Scheffe’s, and Bonferroni/Dunn’s least-significant test because of multiple comparison (Stat View for PC; Abacus Concepts, Berkeley, CA). A P < 0.05 was considered statistically significant.
RESULTS

Protocol 1: Pulmonary Hemodynamic Response to Catecholamines Infusion

Norepinephrine infusion at 1.5 μg/min (~0.5 μg·kg⁻¹·min⁻¹; n = 9). Norepinephrine infusion increased mean pulmonary artery pressure (PAP), left pulmonary artery blood flow (Flow), and decreased mean pulmonary vascular resistance (PVR). Values returned to baseline after the end of drug infusion. Values are expressed as means ± SE.

**Table 1. Blood gas during baseline, after 60 min of drug infusion, and at 30 min of the recovery period**

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| Values are means ± SE. EB, excess base; L-NA, L-nitro arginine. *P < 0.05. Values are means ± SE.
LAP before infusion was 2 ± 1 mmHg and did not change during the study period. Heart rate did not change during the infusion. Mean PAP, LPA blood flow, mean PVR, and mean AoP progressively returned to baseline values after the end of drug infusion. Pulmonary arterial PO₂ did not change significantly during the study period (Table 1).

Dopamine infusion at 30 μg/min (≈10 μg·kg⁻¹·min⁻¹; n = 7). Dopamine infusion rapidly increased mean PAP by 20 ± 5% (from 55 ± 2 to 66 ± 3 mmHg; P < 0.0001). After an initial increase by 19 ± 8% (from 113 ± 6 to 134 ± 10 ml/min), left artery pulmonary blood flow returned to baseline after 30 min of dopamine infusion. Mean PVR progressively increased by 30 ± 14% (from 0.54 ± 0.03 to 0.70 ± 0.08 mmHg·ml⁻¹·min⁻¹) after 50 min of drug infusion (P < 0.01; Fig. 3). Mean AoP increased by 20 ±
7% (from 51 ± 2 to 61 ± 4 mmHg) after 20 min of drug infusion ($P < 0.0001$). Mean LAP before infusion was 2 ± 1 mmHg and did not change during the study period. Heart rate progressively increased during drug infusion by 40 ± 2% (from 162 ± 8 to 226 ± 5 beats/min; $P < 0.01$). Mean PAP, left mean PVR, and mean AoP remained elevated 30 min after the end of drug infusion (initial saline infusion/after drug infusion: $P < 0.01$). Arterial blood PO2 did not change significantly during the study period (Table 1).

**Protocol: Pulmonary Hemodynamic Response to Norepinephrine Infusion After NOS Inhibition**

($n = 6$)

1-NA infusion did not increase significantly mean PAP or mean AoP and did not decrease significantly pulmonary artery blood flow. However, mean PVR increased significantly by 20% (from 0.49 ± 2 to 0.59 ± 0.01 mmHg·ml⁻¹·min⁻¹; $P < 0.01$) after 1-NA infusion. Then, mean PVR did not change with norepinephrine infusion (Fig. 4).

**DISCUSSION**

In this in vivo study, we tested the hypothesis that catecholamines modulate pulmonary vascular tone and reactivity during perinatal life. We studied the pulmonary vascular response to norepinephrine and dopamine infusion in near-term fetal lambs. We demonstrated that norepinephrine (0.5 µg·kg⁻¹·min⁻¹) decreased and dopamine (10 µg·kg⁻¹·min⁻¹) increased PVR. The pulmonary vasodilator effect of norepinephrine was abolished by NOS blockade. Conversely, no significant pulmonary vascular response was found with a lower dose (5 µg·kg⁻¹·min⁻¹) of dopamine infusion. These results support the hypothesis that catecholamines may alter pulmonary basal tone during the perinatal period. Moreover, the data suggest that norepinephrine-induced pulmonary vasodilation is related to NO release.

This study provides information regarding the pulmonary hemodynamic effects of circulating catecholamines during fetal life. High levels of circulating catecholamines are found in the fetus (27). Concentrations of catecholamines increase with the gestational age and peak at delivery (11, 27). Moreover, the lungs contribute largely to postnatal catecholamine kinetics (34). Indeed, the lungs are a major site of norepinephrine release into the circulation just after birth, contributing about one-third of norepinephrine total body spillover (35). The lungs are also directly involved in catecholamine clearance, especially at high pulmonary blood flow (35). However, although the local pulmonary synthesis of catecholamines suggests that catecholamines may mediate, at least in part, pulmonary adjustments at birth, the effects of catecholamines on the fetal pulmonary vascular tone under basal conditions and at birth are not clear. It is likely that fetal basal production of catecholamines has little influence on the basal pulmonary vascular tone. Bilateral thoracic sympathectomy causes only subtle falls in resistance (8). Phentolamine, an α-adrenergic blocker, has little effect on fetal pulmonary blood flow (2). However, although catecholamines may not contribute to basal PVR in the fetus, the ability to respond to adrenergic stimuli exists early in maturation and may modulate pulmonary vascular tone during stress. Indeed, findings suggest that hypoxia may augment PVR through activation of α-adrenergic receptors. Prolonged (but not brief) intrapartum hypoxia results in sustained pulmonary vasoconstriction despite the return of fetal PO2 to normal values (3). Intrapulmonary infusion of phentolamine rapidly lowers PVR to baseline values during recovery after prolonged hypoxia. Furthermore, pulmonary vasoreactivity remains impaired during recovery after prolonged hypoxia, as reflected by decreased va-
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sodilation to increases in $P_{O_2}$ (3). Thus prolonged hypoxia stimulates catecholamine release, which may contribute to persistent pulmonary vasoconstriction and altered vasoreactivity to oxygen. Furthermore, activation of $\alpha_1$-adrenergic receptors in fetal goats, induced by increased intracranial pressure, results in a drop in PVR (14). Our study supports the hypothesis that catecholamines may modulate fetal pulmonary vascular tone.

Norepinephrine is a vasopressor agent that activates both $\alpha_1$- and $\alpha_2$- and $\beta_1$-adrenoceptors. $\alpha_1$-Adrenoceptors participate in the sympathetically mediated vasoconstriction of human vessels (26). Previous in vitro and in vivo studies showed pulmonary vasoconstrictor effects of norepinephrine (19, 20). However, conflicting results were reported. Norepinephrine infusion decreased PVR in a canine model of pulmonary embolism with pulmonary hypertension (17). A pulmonary vasodilator response to norepinephrine was observed after acute hypoxia in isolated perfused cat lung (10). Norepinephrine induces vasorelaxation in isolated intrapulmonary arteries of neonatal and adult pigs (37, 39). Similar relaxant effects of norepinephrine have also been found in rat isolated cerebral arteries (15) and in neonatal rat femoral arteries (24). Two conditions were required to obtain norepinephrine-induced pulmonary and systemic vasodilation in these studies: 1) preconstriction of the pulmonary vessels and 2) intact endothelium (15, 24, 37, 39). Thus norepinephrine could exhibit a pulmonary vasodilator effect in vivo at elevated pulmonary vascular tone. Our results support the hypothesis that norepinephrine may have pulmonary vasodilator properties. Mechanisms of norepinephrine-induced fetal pulmonary vasodilation remain speculative. In our study, the pulmonary dilator response to norepinephrine was abolished by NOS inhibition, suggesting that the pulmonary vasorelaxation is NO mediated. Further evidence demonstrates that norepinephrine induces endothelial NO release in systemic and pulmonary arteries from fetal to adult experimental models (15, 24, 28, 37, 39) and that NOS inhibition modulates the norepinephrine vascular response. Norepinephrine-induced NO-release mechanisms are uncertain but may include activation of $\alpha_2$- and/or $\beta$-adrenoceptors. $\alpha_2$-Adrenoceptor antagonists inhibit norepinephrine-mediated relaxation of pulmonary (37, 39) or systemic arteries (24) or enhance norepinephrine-mediated pulmonary vasoconstrictive response (20, 22). $\beta$-Adrenoceptor may also be involved in norepinephrine-induced, NO-dependent vasorelaxation as suggested in the pulmonary vessels of rats (31). Because $\alpha_1$-adrenoceptor agonists raise pulmonary vascular tone (20), pulmonary vascular response to norepinephrine may result from the balance between activation of $\alpha_1$-adrenoceptor-induced vasoconstriction and endothelial $\alpha_2$- and $\beta$-adrenoceptor-mediated NO release and vasodilation (20, 22, 28). Thus the vascular response to norepinephrine may depend on the ratio of $\alpha_1$- to $\alpha_2$- and $\beta$-adrenoceptors at the surface of the endothelium or of the smooth muscle cells (40). Maturational change in pulmonary arterial adrenergic receptors previously described may explain conflicting results regarding the vascular response to norepinephrine (3, 23, 30).

It has been widely established that dopamine plays an important role in cardiovascular, renal, hormonal, and central nervous system regulation through activation of $\alpha$- and $\beta$-adrenergic and dopaminergic receptors (38). Dopamine stimulates specific dopamine receptors at low concentration causing vasodilation, $\beta_1$-adrenoceptors at medium concentration, and $\alpha_1$-adrenoceptors at high concentration (12). Evidence demonstrates that dopamine receptor activation may induce pulmonary vascular relaxation in various experimental models (23, 29, 30). However, our study fails to demonstrate any vasorelaxant effect at low-dose dopamine infusion in fetal pulmonary circulation. Although a lack of dopamine-mediated pulmonary vasodilation has also been observed even at low dose by other investigators (6, 7), age-related changes in the pulmonary vascular response to dopamine may explain this result. Indeed, lower responsiveness of pulmonary vascular dopamine receptors has been demonstrated in newborn compared with older animals (23, 30). However, we cannot rule out the hypothesis that, at the dose of 15 $\mu$g/min ($\approx 5 \mu$g kg$^{-1}$ min$^{-1}$), dopamine may have also started to stimulate $\alpha_1$- and $\beta_1$-adrenoceptors. A high dose of dopamine-mediated increase in pulmonary vascular tone was found in isolated canine lungs (21). Our results support the hypothesis that high doses of dopamine may induce a pulmonary vasoconstriction. A striking difference can be observed between the pulmonary vascular response to low vs. high dose of dopamine (trend to a decrease in PVR at low dose, potent increase in PVR at high dose). This observation provides more evidence that dopamine may mediate two opposite responses depending on its concentration.

There are three potential limitations in our study. First, norepinephrine infusion may have caused changes in ductus arteriosus tone. As ductus arteriosus compression may induce pulmonary vasodilation (1), norepinephrine-mediated pulmonary vasodilation may result from ductus arteriosus constriction. However, this hypothesis is unlikely, because gradient pressure between the pulmonary artery and aorta did not change during norepinephrine infusion and after L-NA infusion, suggesting a lack of significant effect on basal tone of the ductus arteriosus. Second, we cannot rule out that the pulmonary vasodilation observed during norepinephrine infusion may result from systemic or centrally mediated reflex events. Indeed, norepinephrine infusion increases both pulmonary and systemic artery pressure. Because an increase in PAP elevates pulmonary artery blood flow (1), norepinephrine-induced vasodilation may be caused by the mechanical increase in shear stress. Furthermore, shear stress-mediated pulmonary vasodilation is also NO dependent. However, norepinephrine-mediated increase in PAP was lower (mean PAP increase = 6 mmHg) than the increase in PAP required to induce pulmonary vasodilation (usually 15 mmHg) (1). Furthermore, an
increase in PAP results in a brief decrease in PVR, whereas norepinephrine infusion induces a sustained pulmonary vasodilation (1). Thus it is unlikely that the pulmonary vasodilation found during norepinephrine infusion may be exclusively related to increases in PAP. Third, plasma catecholamine concentrations were not measured in our study. The norepinephrine infusion rate was chosen for consistency with earlier studies on norepinephrine effects or concentrations in the late-gestation fetal lamb. Especially, Hooper et al. (18) found that plasma norepinephrine concentrations increase to 6,800 ± 1,000 pg/ml after 2 h of a 1 μg·kg⁻¹·min⁻¹ norepinephrine infusion in fetal lamb. These data suggest that plasma norepinephrine concentrations obtained in our study at a rate of 0.5 μg·kg⁻¹·min⁻¹ might be in the same range as those observed at birth (2,200 ± 400 pg/ml) (11) or during fetal hypoxemia (4,100 ± 500 pg/ml) (36) and, therefore, might be of physiological relevance. To our knowledge, plasma catecholamine concentrations were not evaluated during dopamine infusion in fetal lambs. However, effects of low-dose dopamine infusion on plasma catecholamine levels were studied in preterm newborn infants (32). Plasma dopamine concentrations measured during 4 μg·kg⁻¹·min⁻¹ dopamine infusions in preterm neonates are clearly higher than those measured at birth in lambs (90,000 ± 25,000 pg/ml vs. 140 ± 20 pg/ml), suggesting that the pulmonary hemodynamic responses observed during dopamine infusion (5 and 10 μg·kg⁻¹·min⁻¹) in our study are pharmacological responses and are not of physiological significance.

Perspectives

We found that catecholamines may modulate pulmonary basal tone in the ovine fetus. Especially, norepinephrine induces a potent pulmonary vasorelaxant response related to NO release. As a surge of norepinephrine exists at birth with plasma norepinephrine concentrations in the same range as those obtained in our study, we speculate that norepinephrine may play a significant role in pulmonary vasodilation at birth. The birth-related surge in norepinephrine is explained, at least in part, by an increase in sympathoadrenal activity. Interestingly, Smolich et al. (35) reported that the lungs contribute about two-fifths of the total body norepinephrine spillover into the circulation. The contribution of norepinephrine release from the lungs in the pulmonary vascular adjustments that occur during the transitional circulation is yet to be fully elucidated.

Persistent pulmonary hypertension of the newborn (PPHN) is a clinical syndrome characterized by sustained elevation of PVR, structural changes in the pulmonary vascular bed, and abnormal pulmonary vasoreactivity. High PVR can cause right-to-left shunting of blood flow across the ductus arteriosus or foramen ovale, leading to severe hypoxemia. Dopamine infusion has been proposed in newborn infants with myocardial dysfunction or systemic hypotension. Because high-dose dopamine infusion (10 μg·kg⁻¹·min⁻¹) may increase PVR, special care should be taken when using dopamine in PPHN. Whether or not the pulmonary vasodilator effects of norepinephrine infusion exist in PPHN is presently unknown and remains to be studied in an experimental model.

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