Autonomic Control of Cardiovascular Functions during Neonatal Development and in Adult Sheep

J.R. Woods, Jr., A. Dandavino, K. Murayama, C.R. Brinkman, III, and N.S. Assali

SUMMARY We studied the autonomic control of resting heart rate and of systemic and pulmonary vascular blood pressures (BP) in chronically instrumented neonatal lambs 1-8 weeks of age. The maximum response to ganglionic blockade and sympathetic and parasympathetic antagonists was taken as an index of the magnitude of the total neural, adrenergic, and cholinergic tones. The reactivity of the circulatory parameters to adrenergic and cholinergic agonists also was investigated. All findings were compared with those in adult nonpregnant sheep studied concomitantly and with data previously obtained from term fetal lambs. The results of our studies show: (1) resting heart rate declines spontaneously throughout the 8 weeks of neonatal life approaching that of adult sheep; (2) the progressive bradycardia is not related to changes in the parasympathetic or sympathetic tone; (3) resting systemic BP is under strong neurohumoral control during the first two to three weeks of neonatal life; the control decreases progressively, becoming similar to that of adult sheep; (4) resting pulmonary artery pressure of neonatal and adult sheep has no neurohumoral control; (5) the systemic BP response of the neonate to autonomic agonists is greater than that of the term fetus and is similar to that of the adult; (6) in neonatal and adult sheep, compared to the term fetus, the pressor response to norepinephrine is accompanied by a baroreceptor-mediated bradycardia, and acetylcholine-induced systemic hypertension is accompanied by a "paradoxical" tachycardia mediated through β-adrenergic stimulation; (7) in contrast to our finding for the fetus, the pulmonary vascular pressure of neonatal and adult sheep is unresponsive to autonomic agonists.

PREVIOUS studies on fetal lambs between 60 days and term gestation (fetal weight, 300-5,000 g) have shown that (1) the sympathetic control of the cardiovascular functions begins earlier during fetal development than the parasympathetic control; (2) the influence of both systems on the fetal circulation increases with fetal growth until term; and (3) the fetal cardiovascular response to autonomic agonists increases during intrauterine development mainly because of maturation of the effector system.1-3

The present report deals with data that compare the changes in the neurohumoral control of the heart rate, systemic arterial pressure, and pulmonary vascular pressure of the neonatal lamb (3-60 days of age) with changes in the adult nonpregnant sheep.

Methods

Near-term ewes of mixed breed with well dated gestation were allowed to deliver spontaneously in our animal facilities; hence, the exact age of each lamb was known. The lambs were housed with their mothers so that normal lactation could be accomplished until they were able to eat the same alfalfa diet given to the ewes and drink on their own during the period of observation. Each lamb was allowed a 2- to 3-day period of neonatal adjustment before it was subjected to surgery. Chronic instrumenta-

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conditions by techniques used previously in adult pregnant and nonpregnant ewes.1-3 Under local infiltration anesthesia, polyvinyl catheters were implanted in the carotid artery and jugular vein as well as in the main pulmonary artery (prograde catheterization through the femoral vein). The animals were given 500 mg of ampicillin twice a day for 5 days prophylactically.

A postoperative recovery period of 24-48 hours was allowed before the onset of the studies. The lamb's activities, feeding habits, respiration, muscle tone and weight were checked daily while hemoglobin, hematocrit, blood respiratory gases and pH were analyzed at frequent intervals. The same lamb was studied from the 1st through the 8th week of neonatal life.

Autonomic agonists and antagonists used in these experiments, including the dosage, site of action, and number of tests are listed in Table 1. The autonomic agonists were given in progressively increasing doses to establish a dose-response relationship starting with doses smaller than those used in the fetus.2 An adequate interval was allowed between subsequent tests for the circulatory parameters to return to control values.

The autonomic blocking agents were administered in doses that were tested against the effects of their agonists; the dose of phenoxycbenzamine used blocked the effects of norepinephrine, 0.5 µg/kg; the atropine dose blocked the effects of acetylcholine, 0.5 µg/kg, and propranolol blocked the effects of isoproterenol, 0.5 µg/kg.

The experimental protocol comprised the following periods: (1) A control period of 30-40 minutes during which heart rate and pressures were recorded continuously, while the animal (lamb or adult sheep) stood quietly in its cage; the lamb was prevented from sitting or moving by a sling support that allowed full weight-bearing on all four extremities. (2) A testing period during which the agent
selected for assessing a given autonomic activity was administered through the jugular vein in the selected doses listed in Table 1; all agents except trimethaphan were administered as single bolus intravenous injections; trimethaphan was given by constant infusion as previously.1-4

(3) A recovery period until all parameters had returned to control values. During the testing and recovery periods, phasic and integrated pressure signals were recorded continuously on an Offner Dynograph; heart rate was obtained from the pulsatile pressure signal through a cardiotachometer; blood respiratory gases and pH were analyzed at frequent intervals.

A weekly study schedule was established for each lamb in terms of the type of agent to be used. No more than one autonomic agonist or antagonist was administered on a given day. This schedule permitted collection of data on the effects of all of the agents listed in Table 1 from the same animal every week.

We gauged the autonomic activities of the neonatal lamb in terms of adult response by performing the same tests on the mother (at least 3 weeks after delivery) or on other nonpregnant sheep available in our laboratories. No difference was observed in the response of the puerperal and nonpregnant adult ewe.

Blood pressures, heart rates, blood respiratory gases, pH, hemoglobins, and hematocrits were measured by techniques in current use in our laboratories.1-3,4 For statistical treatment of the data each animal was used as its own control. The response to a given agent and the percentage changes were related to the average of all the readings obtained during the 30- to 40-minute control period prior to each test. The data obtained from all the animals during a given week were averaged and compared to those observed in the previous week. Probability values were calculated by using the t-test for significance of differences in means for both paired and unpaired values.

Results

GENERAL CONDITIONS OF THE INSTRUMENTED SHEEP

Five lambs remained healthy throughout the study as judged by analysis of their blood respiratory gases, hemoglobin, hematocrits, daily activities, weight gain, and feeding habits. One lamb died suddenly at 3 weeks of age, following a rapid injection of saline solution into the carotid catheter. The six adult ewes that were studied remained equally healthy during the period of observation.

CHANGES IN THE RESTING HEART RATE AND SYSTEMIC ARTERIAL AND PULMONARY Pressures DURING NEONATAL DEVELOPMENT

In Figure 1 are plotted the weekly average values (± 1 se) for the resting heart rate and systemic arterial pressure of the lambs studied during the neonatal period; the average values for the near-term fetuses obtained from other series of unanesthetized lambs1-3 and for adult nonpregnant sheep are presented for comparison. Each heart rate and blood pressure datum represents the average of 60-70 recordings per week; the adult values represent the average of 80 readings.

The resting heart rate of the 1-week-old neonate was significantly higher than that of the near-term fetus (P < 0.01). During the 2nd and 3rd weeks the heart rate decreased significantly (P < 0.01); from the 3rd to the 4th weeks the changes were not significant; but after the 4th week a consistent and significant decline in heart rate occurred. By the 6th to 8th weeks of neonatal development, the heart rate had approached, but remained significantly higher (P < 0.001) than adult levels (Fig. 1).

The resting mean systemic arterial pressure of the neonate averaged about 80 mm Hg during the 1st week; it did not change appreciably during subsequent weeks and was not significantly different from the adult nonpregnant values (Fig. 1). The neonatal arterial pressure was, however, significantly higher (P < 0.001) than that of the term fetus (Fig. 1).

The mean pulmonary arterial pressure averaged 16 mm

<table>
<thead>
<tr>
<th>Table 1 Autonomic Antagonists and Agonists Used in the Neonatal Lambs (Including Dosage and Total Number of Tests)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agent</strong></td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Trimethaphan</td>
</tr>
<tr>
<td>Atropine</td>
</tr>
<tr>
<td>Propranolol</td>
</tr>
<tr>
<td>Phenoxybenzamine</td>
</tr>
<tr>
<td>Norepinephrine</td>
</tr>
<tr>
<td>Acetylcholine</td>
</tr>
<tr>
<td>Isoproterenol</td>
</tr>
</tbody>
</table>

*100 µg/kg per min.
Hg during the 1st week and remained at about that level during the 8 weeks of neonatal studies.

EFFECTS OF VARIOUS FORMS OF AUTONOMIC BLOCKADE

The tone exerted by the sympathetic nervous system on the resting heart rate, systemic arterial pressure, and pulmonary arterial pressure of the neonatal and adult sheep was assessed through the responses to propranolol and phenoxybenzamine. The parasympathetic tone was assessed through the response to atropine. Blockade of both β-adrenergic and cholinergic receptors at the same time was accomplished by simultaneous administration of propranolol and atropine. The maximum changes observed within 90 minutes after administration of the antagonist were taken as the response to that type of blockade.

Figure 2 presents the average heart rate changes from control values observed each week after cholinergic and β-adrenergic blockade; included in this figure, for comparison, are the responses of the term fetus and the adult sheep to the same procedures.

After cholinergic blockade with atropine, the resting heart rate increased by an average of 28% during the 1st postnatal week; these values were significantly higher than those of the term fetus \( (P < 0.001) \). During subsequent neonatal weeks the changes in heart rate after cholinergic blockade ranged from 40% to 50%; these values were significantly higher than those observed in the 1st week and in the term fetus \( (P < 0.01) \) but were not materially different from each other (Fig. 2).

β-Adrenergic blockade with propranolol did not alter the neonatal resting heart rate by more than 5-10%. These changes were the same throughout the 8 weeks of observations and were not materially different from those of the term fetus or the adult sheep (Fig. 2).

Simultaneous cholinergic and β-adrenergic blockades produced changes in the neonatal heart rate that were similar to those observed after cholinergic blockade alone.

In Figure 3 are presented data on the average weekly changes in the mean systemic arterial pressure observed after ganglionic and α-adrenergic blockades. The effects produced by the same procedures in the term fetus and adult sheep are presented for comparison.

The mean arterial blood pressure decreased by an average of 20% during the ganglionic blockade in the 1st neonatal week; these values were not significantly different from those observed in the term fetus. During the subsequent weeks of neonatal life, as well as in the adult sheep, the average blood pressure fall produced by the same dose of ganglionic blockade ranged from 8% to 12%; these values were significantly different from those observed in the 1st week and in the term fetus \( (P < 0.01) \) but were not materially different from each other (Fig. 3).

If we compare the effects of ganglionic blockade observed at the age of 6–8 weeks and in the adult to those observed in the 1st postnatal week, the difference is highly significant \( (P < 0.001) \).

α-Adrenergic blockade with phenoxybenzamine during the first 3 weeks of neonatal life elicited an average blood pressure fall of 17–21%; these values were significantly smaller \( (P < 0.01) \) than those observed in the term fetus (30%). After the 3rd week, however, the hypotensive effects of α-adrenergic blockade decreased significantly; the average changes observed between the 4th and 8th weeks ranged from 10% to 12%. These values were significantly lower than those observed during the first 3 weeks and in the term fetus \( (P < 0.001) \). In the adult nonpregnant sheep, the same dose of phenoxybenzamine produced no changes in the systemic arterial pressure (Fig. 3).

RESPONSES TO AUTONOMIC AGONISTS

Norepinephrine

In Figure 4 the average weekly changes in the mean arterial pressure and heart rate of the neonate to injections of norepinephrine, 0.2 µg/kg, are presented. For comparison, the response of the adult sheep to the same dose is illustrated, along with that produced in the term fetus by a larger dose (1 µg/kg).

In the neonate the magnitude of the systemic hyperten-
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-20
-40

1-2 wk
3-4 wk
5-8 wk

Term fetus
Neonate
Adult

Changes (±1 SE) in the systemic arterial pressure (MAP) and heart rate (HR) produced by norepinephrine (values for neonates are average of 10-12 tests per week; adult values are average of 22 tests).

FIGURE 4

Changes (±1 SE) in the systemic arterial pressure (MAP) and heart rate (HR) produced by norepinephrine (values for neonates are average of 10-12 tests per week; adult values are average of 22 tests).

FIGURE 5

Comparison of the systemic arterial pressure (MAP) dose-response curves of norepinephrine in the early neonate and the term fetus. Each datum represents mean ± 1 SE of six to eight tests in the neonates.

The tachycardia and hypotension produced by a given dose of isoproterenol were of about the same magnitude throughout the 8 weeks of neonatal life and were not significantly different from those observed in the adult sheep (P > 0.05). In contrast, both blood pressure and heart rate changes produced by isoproterenol were much smaller in the term fetus (P < 0.001) even when doses 5 times larger were used.2

Intravenous injections of isoproterenol had insignificant effects on the pulmonary arterial pressure (Table 2).

Acetylcholine

Figure 7 presents the average weekly neonatal changes in heart rate and systemic arterial pressure produced by the injection of acetylcholine, 0.4 μg/kg. The average changes produced by the same dose in the adult sheep, as well as those produced by 1 μg/kg in the term fetuses2 are given for comparison.

In the neonatal and adult sheep acetylcholine produced

Intravenous administration of norepinephrine in doses of 0.2-0.4 μg/kg had no appreciable effects on the pulmonary arterial pressure (Table 2).

Isoproterenol

Figure 6 presents the average weekly changes in heart rate and mean systemic arterial pressure produced by single injections of isoproterenol, 0.2 μg/kg; the average adult response to the same dose, as well as that of the term fetus to the dose of 1 μg/kg,2 is given for comparison.

In the neonatal and adult sheep acetylcholine produced

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose (μg/kg)</th>
<th>n</th>
<th>Control (mm Hg)</th>
<th>Maximum response (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine</td>
<td>0.4</td>
<td>23</td>
<td>16 ± 1</td>
<td>17 ± 1</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>0.4</td>
<td>24</td>
<td>16 ± 1</td>
<td>16 ± 1</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>0.4</td>
<td>19</td>
<td>16 ± 1</td>
<td>15 ± 1</td>
</tr>
</tbody>
</table>

Values represent average control and maximum response ± 1 SE; n = number of tests.

In the neonatal and adult sheep acetylcholine produced
a consistent tachycardia averaging 40–60% over control values; the systemic arterial pressure decreased by an average of 20–30%; the differences between the values observed during the various neonatal weeks and for the adult were not statistically significant ($P > 0.05$). Pulmonary artery pressure was not altered appreciably by acetylcholine (Table 2). Although the response in a given neonatal age was dose-related, the magnitude of the changes produced by a given dose was the same throughout the 8 weeks of neonatal life.

In contrast, in the fetus, acetylcholine produced a consistent bradycardia and a systemic hypotension; this latter response, however, was largely secondary to the pulmonary hypotension, since it was attenuated considerably when the ductus was closed.\(^2\)

**Discussion**

The present data obtained from the same group of unanesthetized lambs studied during the first 8 weeks of neonatal life indicate that radical changes occur in cardiovascular function and its neurohumoral control after birth.

**THE RESTING HEART RATE AND ITS CONTROL**

It is clear from these observations that the resting heart rate of the neonatal lamb undergoes a progressive and spontaneous decline beginning during the 1st week after birth and reaching levels close to those of the adult non-pregnant sheep by the 8th week.

There is very little information in the literature on the spontaneous changes in the resting heart rate during the neonatal period. Vappaavouri and his co-workers\(^5\) recorded the heart rate of five neonatal lambs between 2 and 21 days of age before and after autonomic blockade. Their control resting values for the same group of lambs, as listed in two different tables, were 193 and 168 beats/min. Unfortunately, the neonatal ages for these two different sets of values were not given and their observations were made with the lambs lying on their side, whereas our lambs were standing. Hence, comparison of their data with ours is difficult.

Our studies further indicate that the progressive and spontaneous decline in the resting heart rate with advancing neonatal age does not seem to be related to an increase in the cholinergic tone or to a decrease in the adrenergic tone, since the ratio between the two remained constant during the neonatal period and was similar to that for the adult sheep. We must therefore conclude that the mechanisms of the spontaneous neonatal cardiac deceleration is not related to neurohumoral factors but rather to alterations in the intrinsic properties of the heart. This hypothesis receives support from various reports which indicate that the fetal heart of various animal species begins its rhythmic activities before full development of cardiac innervation and that its rate throughout intrauterine life does not depend on the maturation patterns of either division of the autonomic nervous system; 1 to 6 such an independence seems to continue after birth and until the adult rate is reached.

Other reports have shown that the intrinsic properties of the fetal neonatal, and adult heart differ considerably whether these are investigated in vivo or in vitro. 10–12

Langer and his associates\(^11\) have observed marked alterations in the responses of the neonatal rat heart to increased frequencies of stimulation; they further showed that the duration of the ventricular action potential decreases strikingly from the 1st day after birth until the adult state. These changes corresponded with the progressive and spontaneous postnatal increase in the heart rate of the rat. Since, in the lamb, the resting heart rate follows an opposite course to that of the neonatal rat, it is possible that the action potential of the lamb myocardium lengthens during neonatal growth, resulting in a spontaneous deceleration.

Although our studies show that the spontaneous changes in the resting heart rate do not depend on the pattern of alterations in the activities of the autonomic nervous system, the present data show that the parasympathetic system far outweighs its adrenergic counterpart in the tone exerted on the heart rate at any given week after birth and in the adult state. Such a cholinergic predominance is in contrast to the adrenergic predominance in the fetus. Parasympathetic predominance in heart rate tone has been shown by other investigators in other animal species studied under a variety of experimental conditions and simulated with mathematical models. 15–16

**THE RESTING SYSTEMIC ARTERIAL AND PULMONARY ARTERIAL Pressures and THEIR NEURAL CONTROL**

The present studies confirm several other reports that in anesthetized and unanesthetized animals the resting systemic arterial pressure rises immediately after birth and remains at adult levels thereafter. 4, 5, 8, 17 We have previously demonstrated in the experimental animal and by mathematical simulation that the arterial pressure rise is related to (1) elimination of the low resistance system of the placental vascular bed, and (2) closure of the various vascular shunts. 17 The autonomic nervous system does not seem to play a significant role in the pressure increase since complete ganglionic blockade prior to umbilical cord interruption and onset of respiration did not diminish the
magnitude of the changes in the neonatal systemic pressure.4

Our present data, however, show that on the basis of the arterial pressure response to autonomic antagonists, the systemic circulation of the newborn lamb is under a neurohumoral control, the magnitude of which decreases progressively with neonatal growth. During the 1st week of neonatal life the systemic hypotension that followed ganglionic blockade was of the same magnitude as that observed in the full-term fetus. This fact suggests that (1) the ability of the autonomic ganglia to transmit neural impulses to the vascular beds probably reaches full maturity by the time birth becomes imminent, and (2) the vascular systems of both the term fetus and the early newborn lamb have a relatively high neurogenic tone similar in many ways to that existing in neurogenic hypertension or in normotensive pregnant sheep and women.15-17

The progressive decline in the hypotensive effects of ganglionic blockade with neonatal growth and the similarity of the responses of the 6- to 8-week-old lamb and the adult nonpregnant sheep are consistent with the observations in animals and human subjects of the lesser importance of the neural tone in the maintenance of the arterial blood pressure in the normotensive state.18-21

On the other hand, the systemic hypotensive effects produced by α-adrenergic blockade with phenoxybenzamine were much greater in the term fetus than in the neonatal lamb. Since this α-adrenergic antagonist inhibits the circulating catecholamines more effectively than it inhibits those released at the nerve ending,21 the greater response of the term fetus probably is related to an overall hyperactivity of its adrenal glands. A surge in adrenal function has been shown to occur as the fetus approaches maturity and such a surge is involved in lung maturation, as well as in initiation of labor, particularly in the sheep.22-24 The increased activity of the adrenal glands probably involves both the cortical and medullary hormones.

The decline in the hypotensive response to α-adrenergic blockade after the 3rd neonatal week is probably related to a decrease in the circulating catecholamines as well as to a fall in the adrenergic tone of the systemic vascular beds. The absence of any hypotensive response in the adult normotensive sheep to α-adrenergic blockade is consistent with findings in other animal species, including man.24

With respect to the pulmonary circulation, once the ductus arteriosus is closed and the lung ventilation is fully established, the resting pulmonary pressure falls to near-adult levels. Judging from the absence of any significant response to any form of autonomic blockade, this vascular bed does not seem to possess any neurohumoral tone in the neonatal or adult sheep.

**REACTIVITY TO AUTONOMIC AGONISTS**

The present data show clearly that the cardiac response, as well as the systemic and pulmonary vascular reactivity to autonomic agonists in the neonate, are quantitatively and qualitatively different from those of the fetus.

In the neonate, regardless of the age, the cardiovascular effects of a given dose of α- and β-adrenergic agonists were much greater than those in the term fetus and were similar to those in the adult sheep. Furthermore, norepinephrine administration to both the neonatal and adult sheep elicited consistent bradycardia and arrhythmias (with large doses), whereas tachycardia was the usual response in the fetus except when large doses were given.2

Two hypotheses could be advanced to explain the greater sensitivity of the neonatal cardiovascular system to adrenergic agonists. The first is related to the possibility of further maturation of the adrenoreceptors during the neonatal period. This hypothesis seems unlikely, however, because our dose-response curves obtained from the fetal lambs at different periods of pregnancy2 suggest that the receptors had reached full maturity at term gestation; the dose-response curve of the neonate does not contradict that finding. Furthermore, it is doubtful that the receptors would suddenly show a surge of maturation, reaching adult status within the first few days after birth.

The second hypothesis is that the increased reactivity of the neonatal cardiovascular system to autonomic agonists is related to the elimination of the umbilical-placental circulation and to closure of the various vascular shunts. During fetal life the placental circulation represents a low resistance system with a relatively high rate of blood flow grafted in parallel with the other fetal vascular beds.17 The overwhelming opinion is that this vascular bed has no neural control even though its vessels may contract in response to catecholamines in vitro.8,17,24 Thus, the umbilical-placental circulation and the various vascular shunts tend to dampen the circulatory effects of vasoactive agents. Such a dampening effect vanishes after birth when the umbilical cord is interrupted and the shunts are closed.

The bradycardia that occurred during the norepinephrine-induced hypertension in the neonate and the adult sheep is related to baroreceptor response, since it can be abolished by atropine. The predominance of the parasympathetic system in both the neonate and the adult sheep probably overshadows the β-adrenergic-stimulating effects of norepinephrine, leading to baroreceptor-mediated vagal stimulation during the rise in pressure. In contrast, in the term fetus, the adrenergic system is more predominant and is more susceptible to the action of norepinephrine. Therefore, when this agent is administered to the fetus, it stimulates both the α- and β-adrenergic receptors, leading to hypertension and tachycardia.2 This hypothesis is supported by the fact that when a specific β-adrenergic stimulant that has no pressor effect, such as isoproterenol, was given to the neonate, tachycardia did in fact always appear.

The effects of the cholinergic neurotransmitter acetylcholine in the neonate were entirely different from those observed in the fetus. In the latter, acetylcholine produced a profound pulmonary and systemic hypotension and bradycardia.2 The systemic hypotension was considerably blunted when the ductus arteriosus was closed, indicating that it was secondary to the pulmonary vasoconstriction;2 the bradycardia was abolished by atropine.

In the neonate and the adult sheep, acetylcholine produced a blood pressure fall accompanied by tachycardia which could be blunted by propranolol. Such "paradoxi-
cal" cardioaccelerating effect has been observed by various investigators during vagal stimulation at specific frequencies as well as during acetylcholine infusion. The mechanisms of the positive chronotropic action are complex and they involve liberation of adrenergic neurotransmitters, direct stimulation of adrenergic receptors, and possibly baroreceptor effects.

In contrast to its profound pulmonary vasodilator action in the fetus, acetylcholine failed to alter the pulmonary vascular pressure in the neonate and the adult sheep. Similar negative effects on the neonatal and adult pulmonary circulation have been observed in the sheep and dog with other vasodilating agents. The absence of response is probably related to the status of the pulmonary vascular bed in the resting state. When this bed is maximally dilated, as in the neonate and adult, it is difficult to produce further vasodilation; but when it is maximally constricted, as in the fetus, vasodilation is possible. This concept is supported by observations made in our laboratory (to be published) which showed that acetylcholine produces pulmonary vasodilation and hypertension when the pulmonary vascular resistance of the neonatal lamb is raised by hypoxia.

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