Physiol. Res. 44: 135 – 137, 1995

RAPID COMMUNICATION

Effect of Prenatal Hypoxia on Contractile Performance and Responsiveness to Ca^{2+} in the Isolated Perinatal Rat Heart

I. OŠŤÁDALOVÁ, B. OŠŤÁDAL, F. KOLÁŘ

Institute of Physiology, Academy of Sciences of the Czech Republic, Prague, Czech Republic

Received March 17, 1995
Accepted March 21, 1995

Summary

The effect of prenatal hypoxic stress on the cardiac contractile function and responsiveness to calcium was studied in rats during the perinatal period. Pregnant rats were exposed to intermittent high altitude hypoxia from day 14 to 18 of pregnancy. Foetal hearts (prenatal day 22) and the hearts of offsprings (days 1, 4 and 7) were isolated and perfused in the Langendorff mode. Developed force of contraction (DF) as well as the rate of force development and fall were measured a) at the Ca^{2+} concentration of 1.25 mmol.l^{-1}, b) under increasing Ca^{2+} concentration (from 0.6 to 10.0 mmol.l^{-1}). Body and heart weights were significantly smaller in hypoxic than in matched control rats starting from day 1. The contractile performance of hypoxic hearts did not differ from controls. Their inotropic response to increasing Ca^{2+} concentrations was, however, significantly reduced on prenatal day 22 and postnatal day 7. Our results suggest that prenatal maternal hypoxia affects the cardiac inotropic responsiveness to Ca^{2+} even postnatally.

Key words

Prenatal hypoxia – Cardiac contractility – Ontogenetic development – Calcium

We have shown previously that the early postnatal development of cardiac contractile function and its regulation at the level of Ca^{2+} transport is not linear and changes dramatically during the first week of life (Ošťádalová *et al.* 1993, 1995). These experimental data were obtained in healthy individuals. Such approach differs, however, from the clinical situation where the pathogenetic factors acting during the prenatal period (e.g. stress, hypoxia, toxic effects of drugs) may have serious consequences for further maturation (Benedetti 1986, Driscoll 1987, Ošťádal *et al.* 1989, Pexieder *et al.* 1995). The aim of the present study was, therefore, to evaluate the cardiac contractile function in rats exposed prenatally to hypoxic stress.

A total of 20 pregnant rats were used throughout this study. The beginning of pregnancy was determined by means of vaginal smears; the day when sperm was observed represented day 0. Experimental pregnant rats were exposed to intermittent high altitude (IHA) hypoxia simulated in a barochamber from day 14 to 18 of pregnancy; the altitude was 4000 m on day 1 and 5000 m on days 2 to 5; daily exposure lasted 8 h. The control pregnant rats were kept under normoxic conditions. All pregnant rats had free access to water and a standard laboratory diet. The foetuses were investigated on day 22 of pregnancy and the offsprings on days 1, 4 and 7 of postnatal life. Foetuses were removed from pregnant rats under thiopenthal anaesthesia. All experimental animals were weighed and killed by cervical dislocation. The hearts were quickly removed, isolated and perfused in the Langendorff mode under constant pressure with Tyrode solution saturated by O_2 at 37 °C as described previously (Ošťádalová *et al.* 1993). The hearts were electrically stimulated (120 beats.min^{-1} for foetuses, 180 beats.min^{-1} for offsprings). The resting force was gradually increased by means of a micromanipulator to the level at which the developed force was approximately 80 % of the maximum force attained at an optimum preload. The contractile force (DF, g), rate of contraction [$(+dF/dt)_{max}$, g.s^{-1}] and relaxation [$(-dF/dt)_{max}$ g.s^{-1}] were measured by means of an isometric force transducer and evaluated automatically using an on-line computer. After perfusion the hearts were weighed.

Table 1
The effect of prenatal intermittent high altitude hypoxia on the body weight, heart weight and cardiac contractile parameters of the heart during perinatal period of the rat.

Age (days)	n	Body Weight (g)	Heart Weight (mg)	Contractile parameters DF (g)	$(+dF/dt)_{max}$ $(g.s^{-1})$	$(-dF/dt)_{max}$ $(g.s^{-1})$
CONTROL						
Prenatal						
22	8	4.6±0.1	15.9±0.6	0.30±0.05	3.76±0.61	2.61±0.32
Postnatal						
1	6	7.4±0.2	37.3±2.2	0.57±0.06	8.69±0.84	6.70±0.68
4	8	11.3±0.3	59.7±1.6	1.01±0.13	14.80±1.81	11.65±1.41
7	6	16.1±0.1	68.1±2.9	1.90±0.10	27.97±1.37	20.53±0.77
EXPERIMENTAL						
Prenatal						
22	8	4.0±0.3	16.6±1.0	0.25±0.03	2.99±0.43	1.78±0.25
Postnatal						
1	7	5.7±0.1*	27.4±0.5*	0.75±0.09	10.21±1.20	7.48±0.96
4	7	9.2±0.4*	47.0±2.1*	1.26±0.16	18.80±2.56	13.35±2.03
7	7	12.5±0.7*	58.7±3.3*	2.20±0.28	31.64±4.10	23.73±3.42

*Values are means ± S.E.M. * significantly different ($p<0.05$) from corresponding control values.*

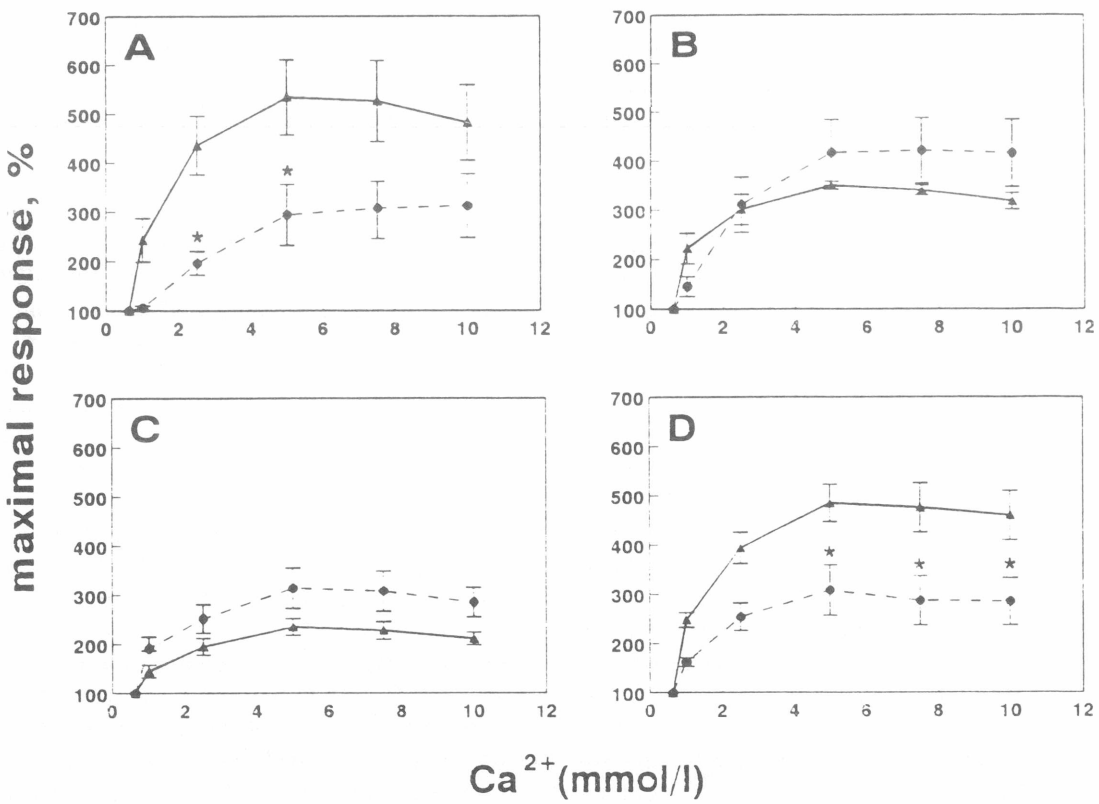

Fig. 1
Inotropic response to increasing Ca^{2+} concentrations (expressed as a percentage of the lowest value) of DF (developed force) in the control (full dots) and experimental hearts (circles) on prenatal day 22 (A), on postnatal day 1 (B), day 4 (C) and day 7 (D).

To estimate the inotropic responsiveness to Ca^{2+} the hearts were initially perfused with 1.25 mmol.l^{-1} Ca^{2+}. After stabilization, the Ca^{2+} concentration was decreased to 0.6 mmol.l^{-1} and thereafter again gradually increased up to 10 mmol.l^{-1}. The effect of each concentration was evaluated after reaching the peak value (about 4 min) and expressed as a percentage of the value corresponding to the lowest concentration of Ca^{2+}. Student's t-test was used for statistical evaluation.

The weight parameters are summarized in Table 1. Body and heart weights were significantly less in experimental rats as compared with the controls starting from day 1. Contractile parameters [DF, $(+dF/dt)_{max}$ and $(-dF/dt)_{max}$] measured at the concentration of 1.25 mmol.l^{-1} Ca^{2+} are shown in Table 1. Despite the significantly lower weight the experimental hearts exhibited similar values as the controls. The inotropic responsiveness to increasing concentration of Ca^{2+} is illustrated in Fig. 1. On prenatal day 22 (Fig. 1A) and postnatal day 7 (Fig. 1D), the response of DF (expressed as percentage of the minimum value) was significantly lower in experimental animals than in the controls. On the other hand, the difference was not significant on days 1 (Fig. 1B) and 4 (Fig. 1C).

Our results have shown that prenatal maternal hypoxia influenced body and heart growth of offsprings as well as cardiac inotropic responsiveness to extracellular Ca^{2+} even 12 days after the last exposure to IHA hypoxia. This may suggest that the development of Ca^{2+} handling could be altered. The above changes may be induced by at least three different factors: undernutrition, stress-induced catecholamines and maternal hypoxia *per se*. On the basis of our results it is, however, not possible to determine the most relevant cause. It seems interesting to mention that even a short period of perinatal hypoxia was able to induce permanent changes in the rat pulmonary vasculature (Heymann and Hoffmann 1984, Hampl and Herget 1990). Furthermore, Okubo and Mortola (1988) found increased lung ventilation in adult rats born in hypoxia. The possibility that prenatal hypoxia alters different physiological processes, which are activated by the lack of oxygen, must also be taken into consideration.

Acknowledgements

This work was supported by Grant No. Z129-4 from the Grant Agency of the Ministry of Health of the Czech Republic.

References

BENEDETTI T. J.: Life-threatening complications of betamimetic therapy for pre-term labor inhibition. *Clin. Perinatol.* **13:** 843–852, 1986.

DRISCOLL D.J.: Use of inotropic and chronotropic agents in neonates. *Clin. Perinatol.* **14:** 931–948, 1987.

HAMPL V., HERGET J.: Perinatal hypoxia increases hypoxic pulmonary vasoconstriction in adult rats recovering from chronic exposure to hypoxia. *Am. Rev. Resp. Dis.* **142:** 619–624, 1990.

HEYMANN M.A., HOFFMAN J.I.E.: Persistent pulmonary hypertension syndromes in the newborn. In: *Pulmonary Hypertension.* WEIR E.K., REEVES J.T. (eds), Futura Press, Mount Kisco, N.Y., 1984, pp. 45–71.

OKUBO S., MORTOLA J.P.: Long-term respiratory effect of neonatal hypoxia in the rat. *J. Appl. Physiol.* **64:** 952–958, 1988.

OŠŤÁDAL B., BEAMISH R.E., BARWINSKI J., DHALLA N.S.: Ontogenetic development of cardiac sensitivity to catecholamines. *J. Appl. Cardiol.* **4:** 467–486, 1989.

OŠŤÁDALOVÁ I., KOLÁŘ F., OŠŤÁDAL B., ROHLÍČEK V., ROHLÍČEK J., PROCHÁZKA J.: Early postnatal development of contractile performance and responsiveness to Ca^{2+}, verapamil and ryanodine in the isolated rat heart. *J. Mol. Cell. Cardiol.* **25:** 733–740, 1993.

OŠŤÁDALOVÁ I., KOLÁŘ F., OŠŤÁDAL B.: Inotropic effect of low extracellular sodium on perfused perinatal rat heart. *Can. J. Physiol. Pharmacol.* 1995 (in press).

PEXIEDER T., BLANC O., PELOUCH V., OŠŤÁDALOVÁ I., MILEROVÁ M., OŠŤÁDAL B.: Late fetal development of retinoic acid-induced transposition of great arteries: morphology, physiology and biochemistry. In: *Mechanisms of Abnormal Cardiovascular Development.* CLARK E.F., MARKWALD R.R., TAKAO A. (eds), Futura Press, Mount Kisco, N. Y. 1995, pp. 297–307.

Reprint Requests

MUDr I. Ošťádalová, CSc. Institute of Physiology, Academy of Sciences of the Czech Republic, Vídeňská 1083, 142 20 Prague 4, Czech Republic.