Response of Smooth Bronchial Musculature in Bronchoconstrictor Substances in Newborn with Lung Atelectasis at the Respiratory Distress Syndrome (RDS)

Lirim Mustafa1, Pëllumb Islami2, Nora Shabani3, Adelina Jashanica4, Hilmi Islami5

Liri-med, St. Agim Ramadani, SHPK, Prishtina, Kosova
Smartmed, St. Rexhep Krasniqi, EXDC, First Floor, En. 2, Prishtina, Kosova
Laboratory “Biolab”, Ulpiana/D, Prishtina, Kosova
Department of KVPPMS, Hospital st., Prishtina, Kosova
Department of Pharmacology, Faculty of Medicine, University of Prishtina, Clinical Centre, Prishtina, Kosova

Corresponding author: Prof. Hilmi Islami, MD, PhD. E-mail: islamihilmi@hotmail.com

ABSTRACT

Objective: Role of the atelectasis (hypoxia) in the respiratory system of the live and exited newborn (250 up to 3000 g. of body weight), which has died due to different causes was studied in this work. Methods: Response of tracheal rings to dopamine, serotonin and ethanol in the different molar concentrations (dopamine: 0,05 mg/ml, 0,5 mg/ml, 5 mg/ml; serotonin (5-HT): 10^{-4}, 10^{-3}, 10^{-2}, 10^{-1} mol/dm^3; ethanol: 0,2 ml, 0,5 ml, 1,0 ml, 96%) was followed up. Study of the smooth tracheal musculature tone (STM) was elaborated in 16 tracheal preparations taken following the newborn death due to different causes. Results: Based on functional researches of tracheal isolated preparations, it was ascertained as follows: atelectasis (cases born with lung hypoxia) has changed the response of STM to dopamine, serotonin and ethanol in a significant manner (p<0,01) in comparison to cases of controlling group, which has died due to lung inflammatory processes (e.g. pneumonia, bronchopneumonia, cerebral hemorrhage), which have also caused significant response (p<0,05). Conclusion: Results suggest that exited cases from lung atelectasis and cases of controlling group reacts to above mentioned substances by causing significant constrictor action of tracheobronchial system. Key words: Dopamine, serotonin, ethanol, trachea.

1. INTRODUCTION

Sudden infant death syndrome (SIDS) remains one of most often causes of infant death in the period from birth until the end of first year of life. In despite of long term extensive scientific research and submission of many hypotheses, etiology of this syndrome remains unclear, yet (1, 2, 3).

It is assumed that chronic hypoxia, infections (viruses and different bacterial toxins), inflammatory conditions, biochemical disorders and genetic abnormalities are most important causes in the sudden infant death syndrome. (SIDS) (4, 5, 6, 7, 8).

Respiratory infections are another important factor in the etiology of SIDS. According to some data from the medical evidence, infections of the respiratory tract are cause of the SIDS in 33% of cases (9, 10).

Also, at infants following death from sudden death syndrome, a certain number of viruses and bacteria are isolated in some postmortem cultures that were identified by serological reactions or polymerase chain reaction. Results of these researches shows that respiratory syncytial virus, influenza A virus, adenoviruses, rhino viruses, cytomegalovirus and parainfluenza was most often isolated viruses (11, 12, 13, 14).

It is assumed that caliber of airways is under the control of autonomous nervous system, mainly of parasympathetic (cholinergic) nervous system. In despite of many researches, basic mechanism of hyper-reactivity and bronchoconstriction of the respiratory system remains totally unclear. Release of the acetylthiocholine from the parasympathetic nerve fibers activates muscarinic receptors that are present in the airways smooth musculature, submucosal glands and blood vessels of these airways by causing bronchoconstriction, secretion of mucus and vasodilation (15).

Data from different researches “in vitro” presents that smooth musculature of different organs relaxes by two types of nerve fibers of autonomous nervous system: sympathetic or adrenergic nerve fibers and nonadrenergic noncholinergic nerve fibers (16, 17).

In the smooth bronchial and tracheal musculature, epithelium plays also an important role. Removal of epithelium from the bronchial segments or trachea in researches “in vitro” has shown that it is accompanied with an in-
crease in the sensitivity of airways smooth musculature to acetylthiocholine with subsequent bronchoconstriction (18).

All of the above mentioned mechanisms being involved in the process of breathing are assumed to be altered if exposed to the continuous intrauterine and postpartum hypoxia. Different researches has shown that intrauterine hypoxia of the fetus is usually manifested with a high level of immunoglobulin, increase of muscular mass, about 20%, in pulmonary arteries, increase of airways smooth musculature cells and increase of the level of fetal hemoglobin. Increase of immune stimulation in the mucosa of trachea, duodenal mucosa, and palatine tonsils and increase of the level of interferon in the blood circulation appears as other changes. At the fetus and newborn, we need to add the fact that many mechanisms have not achieved the proper scale of their maturity. All these changes have also subsequent modified response of airways smooth musculature with impact to functional performance of the respiratory system, in general (19, 20).

Hence, studying the role of atelectasis (hypoxia) in the respiratory system at live and dead newborns (250 up to 3000 g. of body weight), which have died due to different reasons, was aim of this work. Impact of hypoxia in the respiratory system was followed up through response of tracheal segments in pharmacological substances such are: dopamine, serotonin and ethanol in different molar concentrations.

2. MATERIAL AND METHODS

Research was conducted in cooperation with the Gynecology Obstetrics Clinic, Pathologic Anatomy Institute and Experimental Unit of Medical Faculty in Pristina, with permission of the Ethic Commission by respecting principles of Helsinki Declaration.

Classification of tracheal preparation of newborn babies in different weeks of gestations is made on the basis of histopathological examination of tracheal preparation (in blocks of paraffin). The preparations have been stained with standard: hematomylin-eosin (H & E) methods.

Research has been conducted in 16 experimental studies in vitro in isolated trachea of infants died in different weeks of gestations (weight 250 to 3000 g). Trachea were taken immediately after autopsies. Above the bifurcation of trachea, 6 tracheal rings were taken and placed in Krebs solution DIP (pH=7,4).

During the experiment, the water bath temperature was kept at 37 °C, and solution in bath is aerosolized continually through the bath solution. Rings were prepared and serially connected to each other. The series consisting of 6 rings was placed in bath for isolated organs kept at 37 °C, and solution in bath is aerosolized continually through the bath solution. Rings were prepared and serially connected to each other. The series consisting of 6 rings was placed in bath for isolated organs

3. RESULTS

Results of the research in isolated tracheal preparation in newborn shows that dopamine, serotonin and ethanol are applied in different molar concentrations (dopamine: 0,05 mg/ml, 0,5 mg/ml, 5 mg/ml; serotonin: 10^-1, 10^-2, 10^-3, 10^-4 mol/dm³; ethanol: 0,2 ml, 0,5 ml, 1,0 ml; 96%), which acts in different ways, depending on the applied dose.

Table 1. Serotonin (5-HT) dose response of STM in newborn babies of different age groups with respiratory distress syndrome (RDS). (n= 5; X± SEM).

| Dose (m/dm³) | Control | Atelectasis |
|-------------|---------|-------------|
| 0,05        | 0,5±0,5 | 0,83±1,25   |
| 0,5         | 1,5±0,98| 4,43±1,78   |
| 5,0         | 1,5±2,95|             |

Table 2. Dopamine dose response of STM in newborn babies of different age groups with respiratory distress syndrome (RDS). (n= 5; X± SEM).

| Dose (mg/ml) | Control | Atelectasis |
|--------------|---------|-------------|
| 0,05         | 0,5±0,5 | 0,83±1,25   |
| 0,5          | 1,5±2,88| 4,43±4,47   |
| 1,0          | 1,5±8,68|             |

Table 3. Ethanol dose response of STM in newborn babies of different age groups with respiratory distress syndrome (RDS). (n= 6; X± SEM).

| Dose (ml) | Control | Atelectasis |
|-----------|---------|-------------|
| 0,2       | 0,83±2,35| 1,5±8,68   |
| 0,5       | 1,5±2,88| 4,43±4,47   |
| 1,0       | 1,5±8,68|             |

Results of the research in isolated tracheal preparation, it was ascertained as follows: atelectasis (cases born with lung hypoxia) has changed the response of STM to dopamine, serotonin and ethanol in a significant manner (p<0,01) in comparison to cases of controlling group, which has died due to lung inflammatory processes (e.g. pneumonia, bronchopneumonia, cerebral...
Atelect

Figure 1. Response of STM to 5-HT at newborns with dominant pulmonary atelectatic changes. (X ± SEM).

Figure 2. Response of STM to dopamine at newborns with dominant pulmonary atelectatic changes. (X ± SEM).

Figure 3. Response of STM to ethanol at newborns with dominant pulmonary atelectatic changes. (X ± SEM).

Figure 4. Response of STM to 5-HT, dopamine, and ethanol at newborns with dominant pulmonary atelectatic changes. (X ± SEM).

hemorrhage), which have also caused significant response (p<0.05).

In the Tables 1, 2, 3, 4 and Figures 1, 2, 3, 4 action which have also caused significant response (p<0.05). died due to lung inflammatory processes (e.g. pneumonia, bronchopneumonia, cerebral hemorrhage), which have also caused significant response (p<0.05).

In the Tables 1, 2, 3, 4 and Figures 1, 2, 3, 4 action which have also caused significant response (p<0.05).

4. DISCUSSION

Chronic hypoxia at the fetus and infants, besides organic changes in tissues and different organs, is accompanied also with changes in the level of cell metabolism. These changes in the level of cell metabolism are affected in particular to metabolism of some endogenous lipophilic substances such are: steroids, liposoluble vitamins, prostaglandin, troboxan and some exogenous substances (21, 22).

In children with sudden death syndrome, as a consequence of chronic hypoxia, TNF-[alpha] and other inflammatory cytokines, aradonic acid and polystaurated fatty acids stimulates production of the superoxide from polymorphonuclear leukocytes that affects in damaging of different tissues with different mechanisms, including airways also (23, 24, 25, 26, 27).

In children with sudden death syndrome, as a consequence of chronic hypoxia, TNF-[alpha] and other inflammatory cytokines, aradonic acid and polystaurated fatty acids stimulates production of the superoxide from polymorphonuclear leukocytes that affects in damaging of different tissues with different mechanisms, including airways also (23, 24, 25, 26, 27).

These damages of airways manifest with ultrastructural changes in cells of smooth musculature, tissue matrix and damage of epithelial integrity (28, 29).

Results of the research in isolated segment present that during the stimulation with serotonin, contraction of smooth musculature is significantly more emphasized in the group with atelectasis comparing to the controlling group in all concentrations of serotonin. It is difficult to find any other neurotransmitter that is more widely spread in the organism than serotonin. Author Kinney emphasizes that 5-HT innervate almost “all nervous system” (30).

Due to wide inclusion in the function of vital organs, depletion of serotonin depot in terminal phase prior death of infants is evident. Data from a research in rats shows that average hypoxia has not deranged connection of serotonin to effectors receptors, whilst heavy forms of hypoxia derange the connection of serotonin to effectors receptors including also airways receptors (31).

Therefore, based on the facts of respective authors, it is observed that response of tracheal musculature to serotonin in our research in the group with atelectasis was maintained, whereas in the controlling group is weaker.

During the stimulation of tracheal segments with dopamine in small concentrations, contractile response in the group with atelectasis is lower in comparison to controlling group, without any significant distinction, but contractile response increases significantly along with the increase of the dopamine dose in the group with atelectasis in comparison to controlling group, this distinction is especially emphasized in the concentrations of dopamine 5 mg/ml.

Author Kanairo, with collaborators, presents that dopamine has not changed the tone of smooth musculature in rats (32).

Analyses of gained results during the stimulation of the tracheal segments has showed that ethanol causes constriction of smooth musculature at both groups in concentration of 0.2 ml (96%) with difference in fact that this response is more emphasized in the group with atelectasis comparing to controlling group. Whereas, during the stimulation with ethanol in concentration of 0.5 ml (96%) we have gained constrictor response of smooth tracheal musculature as more emphasized in the group with atel-
Response of Smooth Bronchial Musculature in Bronchoconstrictor Substances in Newborn

Immunol Med Microbiol. 1999; 25: 1-6.
5. Gayer B, Hoyert DL, Martin JA, et al. Annual summary of vital statistics-1998. Pediatrics. 1999; 104: 1229-1246.
6. Gordon AE, Al Madani O, Weir DM, et al. Cortisol levels and control of inflammatory responses to toxic shock syndrome toxin-1 (TSST-1): the prevalence of night-time deaths in sudden infant deaths syndrome (SIDS). FEMS Immunol Med Microbiol. 1999; 25: 199-206.
7. Rambaud C, Guibert M, Briand E, et al. Microbiology in sudden infant death syndrome (SIDS) and other childhood deaths. FEMS Immunol Med Microbiol. 1999; 25: 59-65.
8. Samuels M. Viruses and sudden infant death. Paediatr. Resp Rev. 2003; 4: 178-183.
9. Wener J, Garrow I. Sudden apparently unexplained death in infancy: pathologic findings in infants found dead. Arch Pathol. 1953; 29: 633-675.
10. Hoffman HJ, Damus K, Hillman L, Krongrad E. Risk factors for SIDS: results of the National Institute of Child Health and Human Development SIDS Cooperative Epidemiological Study. Ann N Y Acad Sci. 1988; 533: 13-30.
11. Rambaud C, Guibert M, Briand E, Grangeot-Kerolos, Coulomb L, Herminie A, Dehan M. Microbiology in sudden infant death syndrome (SIDS) and other childhood deaths. FEMS Immunol Med Microbiol. 1999; 25: 59-66.
12. Blackwell CC, Weir DM. The role of infection in sudden infant death syndrome. FEMS Immunol Med Microbiol. 1999; 25: 1-6.
13. Blackwell CC, Mackenzie DA, James VS. Toxigenic bacteria and sudden infant death syndrome (SIDS): nasopharyngeal flora during the first year of life. FEMS Immunol Med Microbiol. 1999; 25: 51-58.
14. Crawley BA, Morris JA, Drucker DB. Endotoxin in blood and tissue in the sudden infant death syndrome. FEMS Immunol Med Microbiol. 1999; 25: 131-135.
15. Cousson FR, Fryer AD. Mucariciacar ylic thiocholine receptors and airway diseases. Pharmacol. Ther. 2003; 98: 59-69.
16. Bumstock G. Purinergic nerves. Pharmacol. Rev. 1972; 24: 509-581.
17. Coburn R, F. and Tomita T. Evidence for nonadrenergic inhibitory nerves in the guinea pig tracheal muscle. Am J Physiol. 1973; 224: 1072-1080.
18. Vanhoutte MP. Epithelial-derived relaxing factor(s) and bronchial reactivity. Journal of Allergy and Clinical Immunology. 1989; 83: 855-861.
19. Prandota J. Possible Pathomechanisms of Sudden Infant Death Syndrome: Key Role of Chronic Hypoxia, Infection/Inflammation States, Cytokine Irregularities, and Metabolic Trauma in Genetically PreDisposed Infants. American Journ of Therapeutics. 2004; 11: 517-546.
20. Jones KL, Krous HF, Nadeau J. Vascular endothelial growth factor in the cerebral spinal fluid of infants who died of sudden infant death syndrome: evidence for antecedent hypoxia. Pediatrics. 2003; 111: 358-363.
21. Vege A, Rognun TO. Inflammatory responses in sudden infant death syndrome: past and present views. FEMS Immunol Med Microbiol. 1999; 25: 67-78.
22. Forsyth KD. Immune and inflammatory responses in sudden infant death syndrome. FEMS Immunol Med Microbiol. 1999; 25: 79-83.
23. Forsyth KD. Weekes SC, Kohli L. Lung immunoglobulins in the sudden infant death syndrome. BMJ. 1989; 298: 26-28.
24. Howat WJ, Moore IE, Judd M. Pulmonary immunopathology of sudden infant death syndrome. Lancet. 1994; 343: 1390-1392.
25. Lorin de la Grandmaison G, Dorandeu A, Carton M et al. Increase of pulmonary density of macrophages in sudden infant death syndrome. Forensic Sci Int. 1999; 104: 179-187.
26. Gleeson M, Clancy RL, Crripps AW. Macousal immune responses in a case of sudden infant death syndrome. Pediatr Res. 1993; 33: 554-556.
27. Bouska I, Klar P, Dvorkov L. Histochemistry and immunohistochemistry of the lung in sudden infant death. Soud Lek. 1997; 42: 48-52.
28. Cullen RA, Cooke AH, Driska PS. The Impact of Mechanical Ventilation on Immature Airway Smooth Muscle: Functional, Structural, Histological, and Molecular Correlates. Biol Neonate. 2006; 90: 17-27.
29. Elliott J, Vullermin P, Carroll N. Increased airway smooth muscle mass in sudden infant death syndrome. Am J Respir Crit Care Med. 1999; 160: 313-316.
30. Kinney HC, Filiano JJ, White WF. Medullary serotoninergic network deficiency in the sudden infant death syndrome: review of a 15-year study of a single database. J Neuropath Exp Neurol. 2001; 60: 228-247.
31. Prioux-Guyonneau M, Mocaa-Cretet E, Redjimi-Hafsi F, Jacob C. Changes in brain 5-hydroxytryptamine metabolism induced by hypobaric hypoxia. Gen Pharmacol. 1982; 13: 251-264.
32. Kanairo M, Shibata O, Saito M. Effects of vasopressors on contractile and phosphodiesterase responses of rat trachea. J Anesth. 2002; 16: 289-293.
33. Trevisani M, Gazzieri D. Benvenuti F. Ethanol Causes Inflammation in the Airways by a Neurogenic and TRPV1-Dependent Mechanism. JPET 309; 2004: 1167-1173.
34. Maier KL, Wippermann U, Leuschel U, Löst M, Pfüugmacher S, Schroder P, Sandermann H J, Takaneda S, Zisenski A, and Heyder J. Enzyme-mediated elastase enzymes in the canine respiratory tract. Inhal Toxicol. 1999; 11: 19-35.

CONFLICT OF INTEREST: NONE DECLARED

REFERENCES

1. Schwartz PJ. The sudden infant death syndrome. In: Scarpelli EM, Cosmi EV, eds. Reviews in perinatal medicine. Vol 4. New York: Raven Press. 1981: 475-524.
2. Schwartz PJ. The quest for the mechanisms of the sudden infant death syndrome: doubts and progress. Circulation. 1987; 76: 677-683.
3. Dewey TR, Ponsoby AL, Blizard L, Newman NM, Cochrane JA. The contribution of changes in the prevalence of prone sleeping position to the decline in sudden infant death syndrome in Tasmania. JAMA. 1995; 273: 783-789.
4. Blackwell CC, Weir DM. The role of infection in sudden infant death syndrome. FEMS Immunol Med Microbiol. 1999; 25: 1-6.

Med Arh. 2014 Feb; 68(1):6-9