The Effect of Salbutamol towards Heart Rate in Neutrophilic and Eosinophilic Asthma Patient

Hanif Purbaya, Moch. Rizki Efendi, Afief Mulyawijaya, and Adika Zhulhi Arjana
Faculty of Medicine, Universitas Islam Indonesia, Yogyakarta, Indonesia
Email: {hanpurbaya, doctorrizki, mulyafief.wijaya}@gmail.com, adika.zhulhi.a@uii.ac.id

***Abstract*—Asthma is categorized into eosinophilic and neutrophilic subtypes based on its blood profile characteristic and each subtypes tend to have different severity. Salbutamol is a first choice drug which used for asthma patients in Indonesia.. Salbutamol leads to a smooth muscle relaxation and bronchodilation. In addition to bronchodilation, salbutamol inhibits the release of bronchoconstricting agents. Salbutamol's administration has tachycardia adverse effect. Since asthma subtypes have different severity, salbutamol's administration might have different result towards each subtypes.This study used retrospective cross-sectional study. We compiled medical records of asthma patient in General Hospital of Kebumen (RSUD Kebumen), Indonesia. Inclusion criteria for the subject is asthma patient in 2016 and exclusion criteria for the study is incomplete medical records data. We successfully obtained 47 medical records to be our subject and were grouped into two groups based on their blood profile characteristic. Ten patients were grouped into eosinophilic asthma and 37 patients were grouped into neutrophilic asthma. We took demographical data from our subjects including age, sex, vital sign, and blood profile. The T-test of age for both asthma groups showed the result of p< 0.05 (0,017) which means there is difference of age on the division of asthma group. Fisher's Exact test of association between gender asthma groups showed the result p = 0.499 which means there is no significant differences of gender on the division of asthma group. Heart rate ratio and asthma group that were tested using independent test T-test showed the result of p> 0.05 (p = 0.278) which means no effect of using salbutamol as asthma therapy to increase the heart rate in patient subject of asthma.There was no association between the use of salbutamol in asthmatic patients with an increase in heart rate for either eosinophilic asthma or neutrophilic asthma.**

***Index Terms*—asthma, salbutamol, tachycardia, eosinophilic, neutrophilic**

I. Introduction

A. Prevalence of Asthma

The word asthma is derived from Greek which means panting and short attacks. Asthma is an airway's abnormal response to various stimuli or allergen which result in the narrowing of the respiratory tracts [1]. Prevalence of asthma in Indonesia had been increased from 4% in 2007 to 4.5% in 2013. The highest prevalence that is 5.7% obtained in the age range 25-34 years [2].

B. Etiology of Asthma

The etiology of asthma is still remain unclear. The most possible cause of asthma is person's high sensitivity to certain substance/situation exposure [1]. Studies nowadays believe that there are a lot of subtypes of asthma. Recently, asthma is classified into allergic and non-allergic asthma. In patients with allergic asthma, there is a tendency of excessive IgE production. Based on its inflammatory process and its blood profile characteristic, asthma is divided into eosinophilic, neutrophilic, and mixed type [3]. The term eosinophilic asthma describes a subtype of asthma that is characterized by elevated levels of eosinophils in bronchial biopsies or sputum whereas neutrophilic asthma is characterized by elevated levels of neutrophil. Although the pathway is different, those two process may become mixed subtype which characterized by elevated of both neutrophil and eosinophil [4].

Eosinophilic asthma occurs through complex immunologic and pro-inflammatory mechanisms, mainly done by T helper 2 (Th2) lymphocytes, which release interleukins such as IL-4, IL-5, and IL-13 as a allergic response towards allergen. In addition, Th2-mediated airway eosinophilia can be also associated with relevant innate immune responses, which depends on intercellular communications involving dendritic cells, bronchial epithelial cells, and innate lymphoid cells [5]. Bronchial eosinophilic infiltration is mostly responsible for mild-to-moderate asthma, more severe disease is generally caused by mixed patterns of inflammation including both eosinophils and neutrophils. Inflammatory cells are detectable in the sputum obtained from patients that experiencing uncontrolled asthmatic symptoms and exacerbations [4].

The late-onset variant of eosinophilic asthma that occurs during adulthood is often non-allergic. Current evidence suggests that a central function in coordinating eosinophilic non-allergic asthma is exerted by type 2 innate lymphoid cells (ILC2s), whose the differentiation process are depend on the expression of the transcription factor RORα . Following stimulation elicited by TSLP, IL-25, and IL-33, ILC2s release Th2-type cytokines, including large quantities of IL-5 and IL-13, but much less IL-4 [6].

Manuscript received July 8, 2018; revised August 27, 2018.

doi: 10.18178/ijpmbs.7.4.88-91

The other category is neutrophilic asthma which is characterized by higher level of neutrophil found in asthma patients. This asthma mainly triggered by Th1 action, especially a specific lineage of CD4+ effector T lymphocytes, expressing IL-17 and thus named Th17 lymphocytes. It appears to play a key role in airway neutrophilia that related to dendritic cells, which direct the differentiation processes leading to polarization towards the various Th subsets [3]. Neutrophilic airway inflammation is often associated with more severe asthma [7].

C. Management of Asthma in Indonesia

Salbutamol is the most common treatment for asthma in Indonesia. It is believed that salbutamol increases cAMP production by activating adenylate cyclase. Increased intracellular cyclic AMP increases the activity of cAMP-dependent protein kinase A and leads to lower intracellular calcium. A lowered intracellular calcium concentration leads to a smooth muscle relaxation and bronchodilation. In addition to bronchodilation, salbutamol inhibits the release of bronchoconstricting agents from mast cells, inhibits microvascular leakage, and enhances mucociliary clearance [8]–[10].

Tachycardia is one of salbutamol's adverse effect. This adverse effect happened because salbutamol acts as β (2)-adrenergic agonist which then increase heart contraction frequency [11]. Different mechanisms have been proposed to explain the increased cardiovascular risk with β –agonists including: (i) pro-arrythmogenic effects from hypokalemia or pro-longed QT interval; (ii) shortened diastole induced by the increase of heart rate; (iii) increased sympathetic outflow (as evaluated by indices of heart rate variability (HRV) or plasma norepinephrine) [12].

There are some differences on both subtypes pathogenesis which may result in different therapy outcome. This information leads us to a question about how beneficial or harmful salbutamol is as a therapeutic agent for asthma patient. The aim of this study is to analyze the differences of heart rate between neutrophilic and eosinophilic asthma patient after salbutamol admission.

II. Materials and Methods

Retrospective cross-sectional study was conducted for this study. We compiled medical records of asthma patient in General Hospital of Kebumen (RSUD Kebumen). Inclusion criteria for subject is asthma patient in 2016 which treated by salbutamol and exclusion criteria for the study is incomplete medical records data.

Subjects then grouped into two groups based on their blood profile characteristic. Ten patients were grouped into eosinophilic asthma and 37 grouped into neutrophilic asthma. We took demographical data from our subjects including age, sex, vital sign, and blood profile. We use IBM SPSS software to analyze statistically. The data then analyzed using independent T-test to see whether there is a difference of heart rate between neutrophilic and eosinophilic group.

Ethical clearance was already approved by Ethical Committee of Faculty of Medicine, Universitas Islam Indonesia and this study was conducted in RSUD Kebumen, Indonesia

III. Results

Our study obtained 47 subjects which consisted of 12 men and 35 women. We grouped them into asthma group consisting of 10 eosinophilic asthma patients and 37 patients with neutrophilic asthma. The youngest subject is 4 years old and the oldest subject is 78 years old. All the subjects we received consumed salbutamol as a therapy for their asthma.

Fisher's Exact test of association between gender asthma groups showed the result $p>0.05$ which means there is no significant difference of gender on the division of asthma group. The T test between age and asthma group showed the result $p< 0.05$ which means there is a significant difference of age on the division of asthma group. Contingency coefficient test between asthma degree and asthma group showed $p > 0.05$ ($p = 0.981$) which means there is no effect between asthma group with asthma degree in this study (Table I.). Independent T test showed the result $p>0.05$ which means there is no significant difference of heart rate between both groups (Fig. 1.).

TABLE I. Baseline Characteristic of Subjects

Category	Eosinophil (n)	Neutrophil (n)	P towards asthma grouping
ale	2	10	0.499 [1]
Female	8	27	
Age	48.3 ±8.99	38.16 ±17.16	0.017 [2]
Mild Asthma	8	30	0.981 [3]
Moderate Asthma	1	4	
Severe Asthma	1	3	

[1]Fisher's Exact test, [2]Independent T-test, and [3]Contingency Coefficient test were used to determine P value

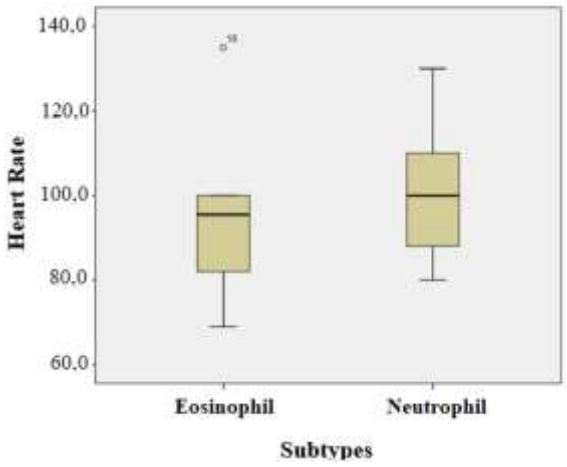

Figure 1. Characteristic of Heart Rate between Eosinophilic and Neutrophilic. P > 0.05 (P=0.278)

IV. Discussion

Salbutamol is used for all form of asthma in Indonesia as first drug choice for relieving asthma symptoms for its bronchodilator effect. Salbutamol; as a selective β_2 agonist receptor; causing relaxation of bronchial smooth muscle, uterus and blood vessels of the skeletal muscle. Salbutamol is classified as a short acting β_2 agonist (SABA) which has been used as asthma therapy for many decades [13]. This mechanism happened through smooth muscle relaxation which creates bronchodilatation. SABAs are recommended to be taken for relief of the symptoms as a inhaled corticosteroids (ICSs) and consumed as regular maintenance treatment [14].

Epidemiological studies linked overuse of SABA therapies at times of asthma exacerbation with increased risk of hospitalisation or mortality [10]. The mechanisms underlying this increased risk have not been clearly determined. Previous study reported a potential cardiac tremor (tachycardia) and hypokalemia adverse effects after administration of salbutamol. This happened because salbutamol act as β_2 agonist which increases the frequency of heart contraction. Increasing of heart rate and the rate of cardiovascular events were occurred significantly in sinus tachycardia and a non-significant trend toward an increase in major cardiovascular events. It is possible β_2 agonist could precipitate arrhythmias, ischemia, and congestive heart failure through the activation of β adrenergic stimulation [14], [15].

Theoritically, salbutamol might increase heart rate or sympathetic activity. A study reported an acute inhalation of 400 µg of salbutamol muscle sympathetic nerve activity (MSNA). The increase in MSNA occured approximately 23% in young healthy participants despite maintained blood pressure. Another effect of acute inhalation of salbutamol in that study is the increase of heart rate. The difference between this study and our study is the subjects were recruited in this study are healthy men and women [12].

Our study found that there was no difference of heart rate in both asthma patient group. Data analysis of heart rate ratio and asthma group using independent test T-test result showed $p > 0.05$ ($p = 0.278$). Similiar result was found in another study. The study reported that there were no statistically significant haemodynamic alterations (heart rate, systolic blood pressure, and diastolic blood pressure) after acute inhalation of 400 µg salbutamol and 12 µg formoterol [16]. This indicates salbutamol may cause slight changes in blood pressure and heart rate but not statistically significant.

Different result may appear when the dose is increased up to 10 times, the heart stimulation effect may be equals to isoproterenol. It is shown that if the dose of the selective β_2 agonist receptor drug is elevated it will result in the loss of selective properties of the drug [17]. Similiar result was found at a case report at University Hospital, Messina, Italy in 2006 found a 3-year-old woman with an increase in pulse rate up to 195 per minute due to the ingested incidence of 24 mg Salbutamol (a dose more than 6 times higher than the maximal one recommended at this age). Sinus tachycardia arises due to the high number of drugs that enter the body [18].

Acknowledgement

The authors would like to thank RSUD Kebumen for providing us a place to make this study and also to Faculty of Medicine Universitas Islam Indonesia for supporting our work.

References

[1] J. L. Dennis, L. Kasper, A. S. Fauci, S. Hauser, D. Longo, and J. L. Jameson, *Harrison's Principles of Internal Medicine 19/E*, New York: McGraw-Hill, 2015, p. 3000.

[2] K Kesehatan, "Riset kesehatan dasar (riskesdas)," *Lap. Nas.*, pp. 1-384, 2013.

[3] A. Ray and J. K. Kolls, "Neutrophilic inflammation in asthma and association with disease severity," *Trends Immunol.*, vol. 38, no. 12, pp. 10-13, 2017.

[4] G. Pelaia, *et al.*, "Cellular mechanisms underlying eosinophilic and neutrophilic airway inflammation in asthma," *Mediators of Inflammation*, vol. 2015, Article ID, 879783, 2015.

[5] D. J. Erle and D. Sheppard, "The cell biology of asthma," *J. Cell Biol.*, vol. 205, no. 5, pp. 621-631, 2014.

[6] S. J. Aujla and J. F. Alcorn, "TH17 cells in asthma and inflammation," *Biochim. Biophys. Acta-Gen. Subj.*, vol. 1810, no. 11, pp. 1066-1079, 2011.

[7] J. Monteseirín, "Neutrophils and asthma," *J. Investig. Allergol. Clin. Immunol.*, vol. 19, no. 5, pp. 340-354, 2009.

[8] L. Brichetto, *et al.*, "Adrenoceptor pathway dysfunction in human isolated bronchi," pp. 133-139, 2003.

[9] L. K. Chong, K. Suvarna, R. Chess-Williams, and P. T. Peachell, "Desensitization of β_2-adrenoceptor-mediated responses by short-acting β_2-adrenoceptor agonists in human lung mast cells," *Br. J. Pharmacol.*, vol. 138, no. 3, pp. 512-520, 2003.

[10] B. Katzung, S. Masters, and A. Trevor, "Farmacologia Básica e Clínica," *Lange*, pp. 790-841, 2012.

[11] J. Collier, R. Dobbs, and I. Williams, "Salbutamol aerosol causes a tachycardia due to the inhaled rather than the swallowed fraction," *Br. J. Clin. Pharmacol.*, vol. 9, no. 3, pp. 273-274, 1980.

[12] H. Edgell, L. E. Moore, C. Chung, B. W. Byers, and M. K. Stickland, "Short-term cardiovascular and autonomic effects of inhaled salbutamol," *Respir. Physiol. Neurobiol.*, vol. 231, pp. 14-20, 2016.

[13] S. Metcalfe, "Asthma medicines (SABAs , LABAs and ICSs) and hospitalisations by age and by ethnicity over time," 2004.

[14] M. R. E. Sebastian L Johnston, "The 2 receptor and airway hyper-responsiveness: Are sensory nerves involved?" *Thorax*, vol. 64, no. 9, pp. 738-739, 2009.

[15] J. Crane, C. Burgess, and R. Beasley, "Cardiovascular and hypokalaemic effects of inhaled salbutamol, fenoterol, and isoprenaline," *Thorax*, vol. 44, no. 2, pp. 136-140, 1989.

[16] G. A. Capuchinho-Júnior, R. M. Dias, and S. R. da Silva de Carvalho, "One hour effects of salbutamol and formoterol on blood pressure, heart rate and oxygen saturation in asthmatics," *Rev. Port. Pneumol.*, vol. 14, pp. 353-361, 2008.

[17] S. Setiawati, Arini., and F. D. Suryatna., *Pengantar Farmakologi dalam Farmakologi dan Terapi*, 5th ed., Jakarta: Departemen Farmakologik dan Terape utik Fakultas Kedokteran, Universitas Indonesia, 2007.

[18] M. P. Calabrò, F. L. De Luca, E. Gitto, and G. Oreto, "Salbutamol-induced narrow QRS tachycardia: What is the mechanism?" *J. Cardiovasc. Electrophysiol.*, vol. 17, no. 7, pp. 792-793, 2006.

Hanif Purbaya was born in Purwokerto on January 17 1996, and is currently studying medicine at Faculty of Medicine Universitas Islam Indonesia, Sleman, Province Daerah Istimewa Yogyakarta, Indonesia.

He is currently a third year medical student of Faculty of Medicine Universitas Islam Indonesia. His current research are "The Immunological Effect of Uric Acid on Coronary Artery Diseas Patient", "The Effect of Soursop Leaves (*Annona muricata)* Extract towards Cyclooxigenase-2 (COX-2) Expression on 7,12-Dimetylbenz(a)anthracene (DMBA) Breast Cancer Induced Rat", and "The Effect of Ethanol Extract of Kumis Kucing Leaves (*Orthosiphon stamineus)* and Starfruit *(Averrhoa carambola)* towards Blood Pressure of Hypertension Induced Rat".

Purbaya has been nominated as finalist of national medical student competition in Medsmotion 2017 and has been awarded as 2nd place in literature review and scientific poster category in the national medical student competition Scripta Research Festival 2018.

Moch Rizki. Efendi was born in Jember in June 13 1997 and is currently studying medicine at Faculty of Medicine Universitas Islam Indonesia, Sleman, Province Daerah Istimewa Yogyakarta, Indonesia.

He now as a third year medical student of Faculty of Medicine Universitas Islam Indonesia, he has a research in histopathology as his final project with title "Effect of Methanol Extract of Mahkota Dewa Fruit *(Phaleria macrocarpa)* in Histopathology Structure of Rat's Hepatocyte". He is also proposing a research to Ministry of Research, Technology, and Higher Education of Republic of Indonesia with title "Effect of JAGAT (Javaneese Language and Culture Training) towards Cultural Competence Awareness of Medical Student in Yogyakarta."

Efendi has been nominated as a finalist at Jember Dentistry Scientific Festival 2017.

Afief. Mulyawijaya was born in Balikpapan on July 8 1996 and is currently studying medicine at Faculty of Medicine Universitas Islam Indonesia, Sleman, Province Daerah Istimewa Yogyakarta, Indonesia.

He now as a first degree, third year medical student of Faculty of Medicine Universitas Islam Indonesia.

He has an ongoing research for his final project with title "Factors that influence the success of empiric antibiotic therapy in patients with severe sepsis and septic shock in the hospitalization ward of the Soedono Hospital in Madiun, Indonesia."

Adika Zhulhi Arjana was born in Kudus on June 17 1991. His educational background is medicine student in Universitas Gadjah Mada, Yogyakarta, Indonesia and it was done from 2009-2013.

He is currently a doctor at RSIY PDHI Hospital and Bhayangkara Hospital (2015 until now) and a lecturer in Faculty of Medicine in Universitas Islam Indonesia. His previous study are "Trend Pro-Inflammatory Leukocyte Activity on Acute Exacerbation of Chronic Obstructive Pulmonary Disease Case", "CKMB and Troponin I Profile of Patients with Angina Pectoris","Eosinophil and Neutrophil on Various Degree of Acute Asthma" etc. He is currently working on several studies including "The Immunological Effect of Uric Acid on Coronary Artery Diseas Patient", "The Effect of Antibiotic towards IL-6 Expression on Infected Surgical Wound", "Activity of CD11b on Asthma Fenotypes", etc.