Relationship Between Prohormone Brain Natriuretic Peptide (NT-proBNP) Level and Severity of Pulmonary Dysfunction in Patients With Chronic Congestive Heart Failure

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Introduction
Heart failure (HF) is a clinical syndrome which occurs due to hereditary or acquired abnormality of structure or function of the heart. The prevalence of HF increases with age and affects 6%-10% of people older than 65 years. Any changes in the structure or function of the LV (left ventricle), would predispose the patient to HF. According to the pathophysiology, patients are mainly divided into two groups; systolic and diastolic heart failure.

In industrial societies, coronary artery disease (CAD) is known as the major cause of HF both in men and women (60%-70% of cases). In 75% of the patients suffering from CAD, hypertension is an added risk for development of HF.

Routine preclinical tests for hospitalized patient with HF include routine laboratory tests, electrocardiography, chest radiography (CXR), two-dimensional Doppler echocardiography and biomarkers. These biomarkers are BNP and its precursor which are released from the dysfunctional heart.

BNP is a peptide hormone that is released from the cardiac ventricles as a result of myocyte stretch. This hormone is an inactive pro-hormones that would be broken into two hormones; Active BNP and inactive NT-proBNP.

The pro-hormone is released due to the hemodynamic stress such as ventricular dilatation, ventricular hypertrophy and increased ventricular wall tension. Systemic effects of BNP include vasodilatation, increased urine output with high sodium level, inhibition of the nervous system and the rennin-angiotensin-aldosterone system.

Prognostic significance of BNP and NT-pro BNP has been widely studied in patients with heart failure, and the levels of pro-hormones are associated with hemodynamic status in patients with HF and are strong predictor of morbidity and mortality.

Restrictive pattern, characterized by decreased vital capacity (VC) and total lung capacity (TLC) and impaired
gas exchange have been recognized in the patients with CHF. On the other hands, small airway obstruction and the airway hyper-responsiveness are reported in patients with CHF. There are several mechanisms such as interstitial edema and airway mucosal vasodilatation, and also vagotonia which result in decreased airway cross-section and airway hyper-responsiveness in CHF. Inhaled glucocorticoids can reduce the airway obstruction, so the inflammatory mediators such as arachidonic acid metabolites, platelet-activating factor, TNF, IL1 and IL6 may play a role in bronchial hyper-responsiveness. Glucocorticoids act in several ways such as inhibition of histamine and IgE dependent LTC4 release and reduction of vascular permeability and mucus secretion. Increased vagal efferent activity resulting from activation of sensory-neural terminals in the lower airways following edema and hyperemia may lead to bronchospasm. The improvement of forced expiratory volume in one second (FEV1), maximal midexpiratory flow (MMEF) and maximum voluntary ventilation (MVV) following the inhalation of ipratropium bromide confirms the involvement of vagal mechanisms in bronchial obstruction in the patients with CHF. Possible involvement of angiotensin converting enzyme inhibitors in bronchial hyper-responsiveness in patients under treatment for CHF has been studied. Since the respiratory dysfunction is definitely observed in patients with heart failure and NT-proBNP level is associated with the severity of cardiac dysfunction, the association between NT-proBNP and lung function is the subject of this study.

The aim of this study is to evaluate the relationship between the NT-proBNP levels and the severity of lung function impairment in the patients with chronic CHF.

Materials and methods
In a cross-sectional analytic study conducted at the Tuberculosis and Lung Disease Research Center at Tabriz University of Medical Sciences. The relationship between the NT-proBNP levels and the severity of lung function impairment studied in patients with CHF. Patients with a diagnosis of chronic systolic HF were enrolled in this study. After a thorough physical examination, CXR and echocardiography were performed. All patients with known lung diseases, respiratory infections and who have a history of smoking were excluded from study. The included patients were referred to the pulmonary function laboratory and the lung function tests such as spirometry, body plethysmography and impulse oscillometry (IOS) were performed. Then two ml of venous blood sample were taken from the patients and the plasma level of NT-pro BNP was measured by electrochemiluminescence.

The studied variables were age, sex, severity of congestive heart failure, EF, plasma levels of NT-pro BNP, FEV1, forced vital capacity (FVC), FEV1/FVC, TLC, residual volume (RV), RV/TLC, intrathoracic gas volume (ITGV), ITGV/TLC, airway resistance at 5 and 20 Hz (Raw at 5 Hz, Raw at 20 Hz) and MMEF rate.

Statistical analysis
Estimated sample size with α=0.05 and power=0.80 and by using power and sample size calculation software version 2.1.3 was 87 patients and we enrolled 95 cases. We used simple random sampling method. Statistical analysis performed by SPSS version 6. For quantitative data analysis, analysis of variance (ANOVA) test and for qualitative data analysis, χ² test were used and then P<0.05 considered significant.

Results
A total of 95 patients; (64 male and 31 female) with CHF were enrolled. The average age of males and females was 62.90 ± 11.54 and 61.61 ± 11.98 years, respectively. The main cause of heart failure was CAD in 69 cases (72.6%), and other causes were hypertension 14 (14.7%) cases, cardiomyopathy 6 (6.3%) cases, valvular diseases 4 (4.2%) cases and myocarditis 2 (2.1%) cases. The average LVEF in males and females was 30.26 ± 9.25 and 29.35 ± 7.22%, respectively. The average NT-proBNP in males and females was 1358.40 ± 2649.03 and 465.06 ± 624.42, respectively (P=0.013). There was an significant inverse linear correlation between NT-proBNP and FEV1 (P<0.001, r = -0.367), FVC (P<0.001, r = -0.444), TLC (P=0.022, r = -0.238), MMEF (P =0.047, r = -0.207) and LVEF (P<0.001, r = -0.461).

On the other hand, there was a significant linear correlation between NT-proBNP and FEV1/FVC (P=0.013, r = 0.257), RV/TLC (P = 0.003, r=0.303) and 5 Hz Raw (r = 0.231, P= 0.024).

There was not any significant linear correlation between NT-proBNP and RV (P= 0.563, r=0.061), ITGV (P =0.235, r = 0.125), ITGV/TLC (P = 0.201, r = 0.135) and Raw 20 Hz (P = 0.988, r=0.002). Relation between NT-proBNP and FVC and RV/TLC are illustrated in Figures 1 and 2.

Discussion
CHF is a common disease that its prevalence is increasing in industrial countries. Pulmonary manifestations of heart failure are very well...
known. In the previous studies, restrictive and obstructive ventilatory impairments and airway hyperactivity have been shown.4-7
In spite of numerous studies, the main mechanism of lung dysfunctions is unknown, but various mechanisms, including; interstitial edema, airways mucosal edema, and vasodilation of bronchiolar vessels have been proposed. These changes lead to a reduction in the cross section of airways and vagotonia.8,9 Moreover, stimulation of sensory-neural endings in lower airways by edema and hyperemia-induced efferent vagal activity may play a role in bronchoconstriction.9,10
Measurement of NT-proBNP is a simple, noninvasive and available tool to put the possibility of heart failure and can assist to diagnose HF from other causes of acute dyspnea in patients presenting to the emergency room.14-23 This marker is a cardiac neurohormone that is released by ventricles in response to overload and increase in volume of ventricles.17
There are some studies performed on the serum level of NT-proBNP in pulmonary diseases. For example, a study was carried out by Maeder et al.24 They found that the levels of NT-proBNP and BNP in patients with pulmonary diseases are significantly related to the levels of VO2 max and FEV1.24 Lee et al.25 measured the level of NT-proBNP in patients with Chronic Obstructive Pulmonary Disease. The NT-proBNP levels were increased and associated with mortality of these patients. Wange et al.26 carried out a study in Detroit (USA) to examine the level of NT-proBNP in critically ill patients. There was a meaningful association between the level of NT-proBNP and respiratory failure among patients.26
In our study, the level of NT-proBNP was measured in patients with heart failure. There was a significant inverse linear relationship between serum levels of NT-proBNP and left ventricular ejection fraction (LVEF) and FEV1, FVC and MMEF. We also found a significant inverse linear relationship between EF and Raw 5 Hz. These findings are consistent with the results of previous research which showed obstructive and restrictive ventilatory impairments in patients with heart failure.4-7 These findings suggest that pulmonary dysfunction is related to the severity of heart failure.
We showed a significant inverse linear relationship between NT-proBNP levels and FVC, FEV1, TLC and MMEF. Also, there was a significant linear relationship between NT-proBNP levels and FEV1/FVC, RV/TLC, and Raw 5 Hz. Maeder et al, reported similar association between the serum NT-proBNP and FEV1.24 There was no significant association was found between NT-proBNP and Raw 20 Hz in our study.
The above results suggest that with an increase in NT-proBNP level, pulmonary volume decreases significantly. Since the level of the aforementioned neurohormone is directly influenced by cardiac output2,3, it can be concluded that with an increase in the severity of hemodynamic disturbance, lung volume decreases as a result of congestion. On the other hand, reduction in MMEF and increase in RV/TLC associated with NT-proBNP level elevation, are in favor of obstructive ventilator impairment in these patients.
The main innovation of this study is direct measurement of airway resistance by IOS which showed that small airway resistance increases with intensification of hemodynamic disturbance reflected by elevated NT-proBNP level. This increase in airway resistance explains the decrease in MMEF and the increase in RV/TLC.

**Conclusion**
The main mechanism of obstructive changes in lung function in CHF has not been clarified, but some mechanisms including; airway mucosal edema, stimulation of nerve endings, vagotonia, or activation of inflammatory processes has been suggested. However, considering the evident relationship between pulmonary dysfunction and hemodynamic changes, it is likely that other mechanisms involved in pulmonary dysfunction may contribute to the development of hyperemia and congestion.

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**Ethical issues**
The research purposes were explained to the patients and informed written consent was obtained. The patients were assured about their personal information secrecy. According to the research design of study, no costs were paid by the patients for performed tests.
Competing interests
Authors declare no conflict of interests in this study.

References
1. Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL, Loscalzo J. Harrison’s Principles of Internal Medicine. 18th edition. New York: McGraw Hill; 2012.
2. Kragelund C, Gronning B, Kober L, Hildebrandt P, Steffensen R. N-Terminal pro-B-type natriuretic peptide and long-term mortality in stable coronary heart disease. N Engl J Med 2005;352:666-675. doi: 10.1056/nejmoa042330
3. Braunwald E. Biomarkers in heart failure. N Engl J Med 2008;358:2148-2159. doi: 10.1056/nejmsra0800239
4. Kadam PP, Pantvaidya SH, Jagtap SR, Raigor KD. Effect of closed mitral valvotomy on spirometric pulmonary function tests in mitral stenosis. J Postgrad Med 1997;43:38-40.
5. Simkova I, Urbanova J. Pulmonary function alterations after correction of mitral stenosis. Bratisl Lek Listy 2001;102(6):276-80.
6. Sasaki F, Ishizaki T, Mifune J, Fujimura M, Nishioka S, Miyabo S. Bronchial hyperresponsiveness in patient with chronic congestive heart failure. Chest 1990; 97:534-538.
7. Pison C, Malo JL, Rouleau JL, Chalauoi J, Ghezzo H, Malo J. Bronchial hyperresponsiveness to inhaled methacholine in subjects with chronic left heart failure at a time of exacerbation and after increasing diuretic therapy. Chest 1989;96:230-235. doi: 10.1378/chest.96.2.230
8. Gülec S, Ertas F, Tutar E, Demirel Y, Karaoğuz R, Omurlu K, et al. Bronchial hyperreactivity in patients with mitral stenosis before and after successful percutaneous mitral balloon valvulotomy. Chest 1999;116:1582-1586. doi: 10.1378/chest.116.6.1582
9. Cieslewicz G, Juszczyk G, Foremny J, Hamelmann E, Religa Z, Zembala M, et al. Inhaled corticosteroid improves bronchial reactivity and decreases symptoms I patients with mitral stenosis. Chest 1998;114:1070-1074. dx.doi.org/10.1378/chest.114.4.1070
10. Nour MM, Mustafa KY, Mousa K. Reversible airway obstruction in rheumatic mitral valve disease. Respiratory 1998;3:25-31.
11. Mueller T, Gegenhuber A, Poelz W, Halmayer M. Diagnostic accuracy of B type natriuretic peptide and amino terminal proBNP in the emergency diagnosis of heart failure. Heart 2005;91:606-12. doi: 10.1136/ hrt.2004.037762
12. Hess OM. Clinical assessment of heart failure. In: Libby P, Bonow R, Zipes D, Mann D, editors. Braunwald’s Heart Disease: A Textbook of Cardiovascular Medicine. 8th ed. Philadelphia: WB Saunders; 2008. p. 569-73.
13. Mueller T, Halmayer M. Natriuretic peptide measurements as part of the diagnostic work-up in pleural effusions: an emerging concept? Eur Respir J 2006;28:7-9. doi: 10.1183/09031936.06.00056306
14. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, et al. Rapid measurement of B type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002;347(3):161-7.
15. Janda S, Swiston J. Diagnostic accuracy of pleural fluid NT-pro-BNP in pleural effusions of cardiac origin: a systematic review and meta-analysis. BMC Pulm Med 2010; 10:58. doi: 10.1186/1471-2466-10-58.
16. Tang WH, Francis GS, Morrow DA, Newby LK, Cannon CP, Jesse RL, et al. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: Clinical Utilization of Cardiac Biomarker Testing in Heart Failure. Clin Biochem 2008;41:210-21. doi: 10.1016/j.clinbiochem.2007.07.002
17. Porcel JM, Chorda JM, Cao G, Esquerda A. Comparing serum and pleural fluid pro-brain natriuretic peptide levels with pleural-to-serum albumin gradient for the identification of cardiac effusions misclassified by light’s criteria. Respiratory 2007;12:654-659. doi: 10.1111/j.1440-1843.2007.01109.x
18. Skouras V, Papankolau I, Papageorgiou E, Kokosi M, Villiotou I. Pleural fluid B-type natriuretic peptide in patients with pleural effusion. Chest 2008;134:550-54.
19. Kolditz M, Halank M, Schiemanck CS, Schmeisser A, Hofken G. High diagnostic accuracy of NT-proBNP for cardiac origin of pleural effusions. Eur Respir J 2006;28:144-150. doi: 10.1183/09031936.06.0013205
20. Tomcsanyi J, Nagy E, Somlói M, Moldvay J, Bezegh A. NT-brain natriuretic peptide levels in pleural fluid distinguish between pleural transudate and exudates. Eur J Heart Fail 2004;6:753-6. doi: 10.1016/j.ejheart.2003.11.017
21. Villar Alvarez F, Médénez Bailón M, de Miguel Díez J. Chronic obstructive pulmonary disease and heart failure. Arch Bronconeumol 2009;45(8):387-93. doi: 10.1016/j.arbres.2008.05.011
22. Gaggin HKI, Januzzi JL Jr. Natriuretic Peptides in Heart Failure and Acute Coronary Syndrome. Clin Lab Med 2014;34(1):43-58. doi: 10.1016/j.cll.2013.11.007
23. von Haehling S, von Bardeleben RS, Kramm T, Thiermann Y, Niethammer M, Doehner W, Anker SD, et al. Inflammation in right ventricular dysfunction due to thromboembolic pulmonary hypertension. Int J Cardiol 2010;144(2):206-11. doi: 10.1016/j.ijcard.2009.04.019
24. Maeder MT, Brutschi MH, Christ A, Reichlin T, Staub D, Noveau M, et al. Natriuretic peptides for the prediction of severely impaired peak VO2 in patients with lung disease. Respir Med 2009;103(9):1337-45. doi: 10.1016/j.rmed.2009.03.015
25. Lee MH, Chang CL, Davies AR, Davis M, Hancox RJ. Cardiac dysfunction and N-terminal pro-B-type natriuretic peptide in exacerbations of chronic obstructive pulmonary disease. Intern Med J 2013;43(5):595-8. doi: 10.1111/imj.12112
26. Jefic D, Lee JW, Jefic D, Savoy-Moore RT, Rosman HS. Utility of B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide in evaluation of respiratory failure in critically ill patients. Chest 2005;128(1):288-95.