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Diagnostic Accuracy of Biomarker N-Terminal Pro-Brain Natriuretic Peptide (NT-proBNP) for Detecting Paroxysmal Atrial Fibrillation (pAF) in Ischemic Stroke

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Abstract

Background and Purpose: 40% of ischemic events remain cryptogenic. pAF is often suspected in these patients. Risk of stroke is similar in pAF and permanent AF. These patients need anticoagulation to cut-down the risk for recurrent stroke by 2/3rd. Thus identification of pAF is highly relevant in patients with stroke and sinus rhythm.

To determine diagnostic accuracy of NT-proBNP for pAF.

Methods: Patients with acute ischemia stroke were included. NT-proBNP were measured within 72 hrs after stroke. Patients free from AF at presentation received 3 days cardiac rhythm monitoring. NT-proBNP levels were compared between patients with AF and sinus-rhythm(SR) at presentation; patients with pAF and no-AF using t-test. Receiver operating curves(ROC) were used to test the ability of NT-proBNP values to identify patients with paroxysmal AF.

Results: 200 patients were included. Among 133 patients with SR at presentation 13 patients had pAF. Mean NT-proBNP values in patients with AF, pAF, no-AF were 2202.3, 1108.3 and 399.84 pg/dl respectively (p value <0.001). ROC curve constructed for stroke of defined etiology had area under curve (AUC) of 0.92. Another curve constructed for patients with pAF had AUC of 0.89. The optimal-cutoff level of NT-proBNP in our study was 334.5 pg/ml with sensitivity 100% and specificity 65.1% for predicting pAF.

Conclusion: In our study 6.5% patients developed pAF during cardiac rhythm monitoring and NT-proBNP had good accuracy in predicting pAF in cryptogenic stroke patients and these patients can be considered for prolonged cardiac rhythm monitoring.

Keywords: Ischemic stroke; Paroxysmal atrial fibrillation; Pro-brain natriuretic peptide

Introduction

Stroke is the third leading cause of death and disability [1]. At least 1 in 6 patients who survive a stroke will suffer another stroke within 5 years [2]. Being etiologically heterogeneous disease, identifying specific cause in every patient is important because prognosis, acute management, and long-term strategies to prevent recurrences vary. Embolic or thrombotic occlusion have been identified as the main cause of ischemic stroke [3]. 40% of ischemic events remain classified as crypto-genic [4]. Cryptogenic stroke is defined by the TOAST classification as cases where the origin is unclear after extensive investigation or where multiple causes are possible and a definitive cause cannot be determined [5]. Atrial fibrillation (AF) is often suspected in cases of cryptogenic stroke, and identification of AF is important because it necessitates a change in therapy from antiplatelet agents to a more effective prophylaxis with oral anticoagulation in almost all patients [6]. AF is usually classified as permanent, persistent, or paroxysmal. Paroxysmal AF (pAF) is reported to have the same risk as persistent or permanent AF to cause ischemic strokes [7]. However, identifying pAF is difficult. Although it is frequently related to structural heart disease, about 45% of patients with pAF have no echocardiographically detectable heart disease [8]. The currently available electrophysiological methods for detecting PAF all have a low sensitivity [9]. Therefore alternative ways to detect pAF in cryptogenic stroke are being evaluated. Recent studies suggest that N-terminal pro-brain natriuretic peptide (NT-proBNP), may be useful to identify cardioembolic stroke

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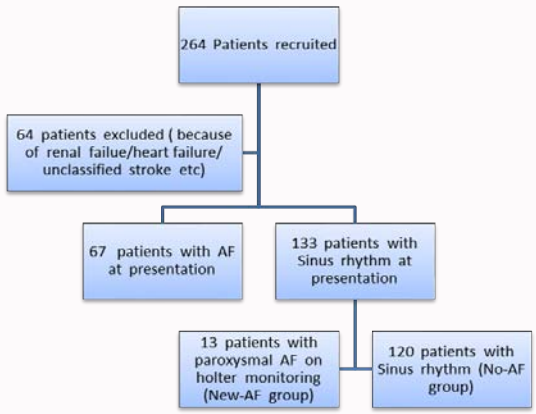

Figure 1: Showing enrollment and classification of patients on the presence of AF.

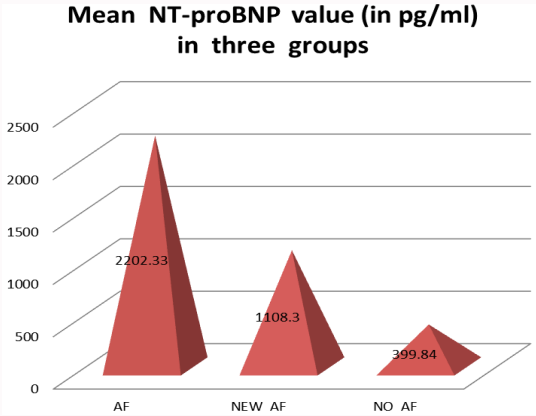

Figure 2: Showing mean NT-proBNP levels in AF, New-AF and No-AF group. The mean NT-proBNP levels in three groups were 2202.33, 1108.3 and 399.84 pg/ml respectively. The difference was statistically significant.

associated with AF [10-12].

Methods

Our study was a prospective study. We studied patients admitted in Neurology ward of our tertiary care institute (sher-i-kashmir institute of medical sciences soura Srinagar Kashmir india) from 1st October 2013 to 31th March 2015. Our institute provides tertiary care services to estimated population of more than 10 million. Our study was approved by the institutional ethical clearance committee.

Inclusion criteria

1. Patients with Ischemic stroke (according to the World Health Organization criteria) [1] or transient ischemic attack (TIA) [13] and

2. Who were admitted to our ward within 72 hrs of stroke onset.

Exclusion criteria

1. Patients with acute renal failure or chronic renal insufficiency.

2. Glomerular filtration rate by the Cockcroft-Gault equation less than 90 ml/min.

3. Acute coronary syndrome.

4. Cardiomyopathies.

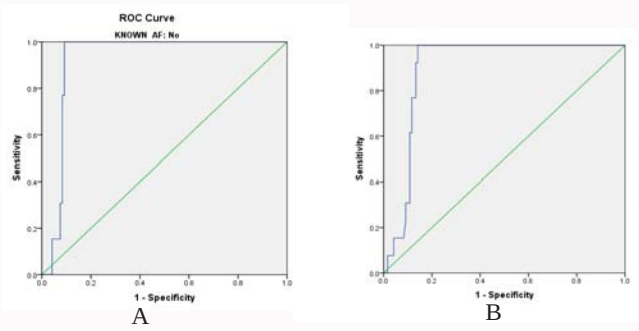

Figure 3: A) Receiver operating characteristics (ROC) curve of NT-Pro BNP for the diagnosis of atrial fibrillation (AF) in patients with known etiology. Area under the curve is 0.92. The cut off value of 334.5 pg/ml had a sensitivity and specificity of 100% and 79.2% respectively. B) ROC of NT-Pro BNP for the diagnosis of paroxysmal atrial fibrillation (AF). Area under the curve is 0.89. The cut off value of 334.5 pg/ml had sensitivity of 100%, specificity of 65.1%, positive predictive value of 63.6% and a negative predictive value of 100%.

5. Mechanical prosthetic heart valve.

6. Heart failure patients.

Information on demography (age, gender), vascular risk factors, previous AF, blood pressure (systolic and diastolic) on admission and National Institutes of Health Stroke Scale (NIHSS) score on admission [14] were collected and functional outcome at hospital discharge using the modified Rankin score (mRS) [15] were noted. Etiological workup included complete blood count, erythrocyte sedimentation rate, hepatic and renal function, glucose and lipid levels and coagulation studies. For NT-proBNP estimation, 3 milliliters of venous blood was collected aseptically in K3 EDTA vacutainer tubes following universal precautions and tubes were rotated gently for proper anticoagulant mixing (within 72 hrs of stroke onset). The tubes were subjected to centrifugation at 2000 rpm for 5 minutes at room temperature and clear plasma was aspirated by disposable pasteur pipettes and stored in polypropylene microfuge tubes at -20°C until assayed. On the day of assay all samples were brought to room temperature. The N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were measured in samples on Elecsys E 411 electro-chemiluminescence analyser (Roches) using commercially available Roche Ecli reagents and calibrators for NT-proBNP. The system was calibrated first for this assay and later samples were tested for NT-proBNP levels. The minimal detectable quantity of NT-proBNP is 3.5 pg/ml.

In all patients, brain computed tomography and/or magnetic resonance imaging, carotid and vertebral doppler and transthoracic echocardiograghic examination (M- mode, two-dimensional, and doppler study) were performed. The following parameters were registered on ECHO: atrial dimensions (atrial dilatation was defined as an end-systolic diameter >40 mm), left atrial spontaneous echo contrast, intra-cardiac thrombus, left ventricular ejection fraction (LVEF), persistence of patent foramen ovale, hypokinetic ventricular wall regions, diastolic dysfunction, and left ventricular hypertrophy. In all patients <55 yrs old contrast agitated saline ECHO (transthoracic/ transes- ophageal) was done to look for a right-left shunt. To detect PAF, at least two ECGs and one 72 hrs Holter monitoring was performed within the first week of the presenting event. AF was defined as a dysrhythmia with at least 30 continuous seconds [8] with no detectable P waves and no other diagnosis. Further the patients were classified according to the presence of AF upon admission into AF (Atrial Fibrillation) and SR (Sinus Rhythm) groups respectively.

Table 1: Showing Age and Gender distribution , mean systolic Blood pressure (SBP), diastolic BP (DBP), National Institutes of Health Stroke Scale (NIHSS) and mRS (modified Rankin scale) among AF and SR groups.

Variables	Atrial Fibrillation (AF)	Sinus Rhythm (SR)	P-Value
No. of Patients	67	133	
Age (years) Mean ± SD	71.15 ± 11.829	62.17 ± 9.445	0.0001*
Female	37 (55.2%)	55 (41.4%)	**0.072**
Male	30 (44.8%)	78 (58.6%)	
SBP(mmHg) Mean ± SD	138.81 ± 13.18	155.58 ± 13.76	<0.001*
DBP(mmHg)	76.78 ± 10.91	80.84 ± 8.48	0.009*
NIHSS at admission	16.96 ± 3.83	7.98 ± 5.37	<0.001*
mRS at discharge	3.24 ± 0.46	1.97 ± 0.94	<0.001*

*Significant at p<0.05. values within parenthesis are percentages.

Table 2: Showing number of patients among sinus rhythm group (SR) who were found to have AF during cardiac rhythm monitoring. 13 patients had documented Paroxysmal AF, their mean age was 73.08 yrs whereas it was 60.99 yrs in patients with sinus rhythm (statistically significant). It also depicts variables like systolic BP, diastolic BP, NIHSS and mRS in the two groups i.e.; pAF and No-AF group.

Variable	Paroxysmal Atrial Fibrillation (AF) (n=13)	Sinus Rhythm (SR) (n=120)	P-Value
AGE (years) Mean ± SD	73.08±3.97	60.99 ± 9.11	<0.001*
FEMALE	5 (38.5%)	50 (41.7%)	0.076
MALE	8 (61.5%)	70 (58.3%)	
SBP (mmHg) Mean ± SD	157.77 ± 14.2	155.34 ± 13.76	0.548
DBP	78.77 ± 9.57	81.07 ± 8.37	0.356
NIHSS at admission	14.38 ± 3.6	7.29 ± 5.08	≤ 0.001*
mRS at discharge	2.77 ± 0.73	1.88 ± 0.93	≤ 0.001*

Furthermore, all patients in the SR group underwent continuous 72 hrs holter monitoring within 7 days of stroke onset to detect AF. If they developed AF during monitoring they were classified into a new-AF group and if not, into a non-AF group. Further if patient had two or more possible causes for stroke they were excluded from the study eg. If patient had AF or detected to have pAF and vascular imaging revealed significant vascular disease in corresponding vessel, they were classified as stroke of undetermined cause and excluded from study.

Statistics analysis

Data was described as mean ± SD and percentage. The categorical variables were compared using Pearsons Chi square test. Quantitative variables were analyzed by using two-sample independent t-test and mann-whitney U-test. The p-value less than 0.05 was considered to be statistically significant. Receiver operating curve (ROC) was used to determine sensitivity, specificity and optimal cut-off value of NT-proBNP for diagnosis of paroxysmal AF (New-AF). The analysis was done using SPSS 20.

Results

In our study we enrolled 264 patients with ischemic stroke and/or TIA who presented within 72 hours of stroke onset. Thirty four (34) patients were excluded because of renal failure (15), acute coronary syndrome (5), heart failure (10), cardiomyopathies (3) and mechanical prosthetic heart valve (1). Thirty patients (30) were excluded because they had more than one possible causes of stroke and were thus classified as strokes of undetermined cause. So we were left with 200 patients. Among 200 patients included, 67 had AF whereas 133 patients were in sinus rhythm (SR) at presentation (Table 1 and Figure 1). All patients in sinus rhythm were monitored for a minimum period of 72 hrs in hospital for paroxysmal AF. Thirteen patients (6.5%) developed pAF after admission during hospitalization in our study (Table 2, Figure1). Mean age of patients with AF at presentation was 71.15 ± 11.83 yrs whereas it was 62.17 ± 9.45 yrs in patients with SR (Table 1). And mean age of patients with pAF was 73.08 ± 3.97 years and in patients with No-AF was 60.99 ± 9.11 years (Table 2). Higher mean age of patients with AF is because of increase in the incidence of AF with age [8]. Among patients with AF at presentation 37 (55.2%) were females and 30 (44.8%) were males (Table 1). Whereas for patients with sinus rhythm at presentation 55 (41.4%) were females and 78 (58.6%) were males (Table 1).

In our study mean systolic blood pressure (SBP) in AF and SR group was 138.81 ± 13.18 mmHg and 155.58 ± 13.76 mmHg at presentation (Table 1). The difference was statistically significant. Mean SBP in patients with pAF and no-AF was 157.77 ± 14.2 mmHg and 155.34 ± 13.76 mmHg respectively (Table 2). Mean diastolic blood pressure (DBP) in AF and SR group was 76.78 ± 10.91 and 80.84 ± 8.48 mmHg and in pAF and no-AF group of 78.77 ± 9.57 and 81.07 ± 8.37 mmHg respectively. The patients with AF tend to have blood pressure on lower side. The mean hemoglobin in AF and SR group was 13.69 ± 1.68 g/dl and 13.30 ± 0.98 g/dl respectively. And mean hemoglobin in pAF and no-AF was 13.15 ± 1.30 and 13.32 ± 0.95 g/dl respectively. The mean creatinine in AF and SR group was 0.88 ± 0.24 mg/dl and 0.91 ± 0.14 mg/dl respectively and 0.92 ± 0.19 and 0.91 ± 0.13 mg/dl in pAF and no-pAF group respectively. In our study mean NIHSS at admission of 16.96 ± 3.84 and 7.98 ± 5.38 in AF and SR group was observed (Table 1). Patients with AF had higher NIHSS in our study as has been reported in other studies. Similarly mRS at discharge in AF and SR group was 3.24 ± 0.46 and 1.97 ± 0.95 respectively. The mean NIHSS score in pAF and no-AF group was 14.38 ± 3.6 and 7.29 ± 5.08 and mRS at discharge of 2.77 ± 0.73 and 1.88 ± 0.93 respectively was reported (Table 2). Patients with AF tend

Table 3: Binary logistic regression analysis models (Multivariate Analysis) for AF after admission. On multivariate analysis using these variables, NT-proBNP levels >334.5 pg/ml was independently associated with new-AF.

Variable	Odds ratio	95% CI	P-value
Age>75yrs	2.111	0.71-8.75	0.135
NIHSS score>6	2.245	0.72-9.74	0.142
NT-proBNP>334.5	7.865	1.65-29.12	0.005*
Atrial dilatation	2.145	0.64-7.65	0.134
Systolic dysfunction	2.234	0.73-8.78	0.148

to have severe stroke with significant disability at discharge.

In our study mean NT-proBNP value in patients with AF (at presentation) and SR (sinus rhythm at presentation) was 2202.33 and 469.09 pg/ml respectively and in patients with pAF (new-AF) and No-AF group was 1108.3 and 399.84 pg/ml respectively (Figure 2). Both differences were statistically significant (P-value of <0.001). We constructed ROC curve for patients with known AF and its AUC (area under curve) was 0.92 (Figure 3A). In our study optimal cutoff value of 334.5 pg/ml had 100% sensitivity with a specificity 79.2%, positive predictive value of 63.6% and a negative predictive value of 100%. We constructed another ROC curve for patients with paroxysmal AF (new-AF) and it had AUC of 0.89 (Figure 3B). The optimal cutoff for our study (334.5 pg/ml) had a sensitivity of 100% and specificity of 65.1%, a positive predictive value of 56.7% and a negative predictive value of 100 % for diagnosis of paroxysmal AF. We also performed multivariate analysis using variables like age >75 years, NIHSS score >6, NT-proBNP levels >334.5 pg/ml , systolic dysfunction and atrial dilatation, only NT-proBNP levels was independently associated with new-AF (Table 3).

Discussion

Atrial fibrillation is an important cause of recurrent ischemic stroke. Often patients with paroxysmal AF are classified as cryptogenic stroke and discharged on antiplatelets. And studies have shown that antiplatelets are not effective for preventing strokes due to AF and these patients need anticoagulation for stroke prevention. Echocardiography and routine electrocardiography easily and routinely misses pAF. Researchers are exhaustively looking for alternative means of diagnosing pAF. In many previous studies, NT-proBNP had good accuracy in predicting ischemic stroke of cardioembolic cause associated with AF. In human BNP is mainly secreted from the heart and mostly from the Ventricle [16]. Pro-BNP is stored in secretory granules in myocytes and it is cleared by a protease into BNP and N-terminal Pro-BNP, the 76 amino-acids. NT-Pro-BNP has a longer half-life than the active form of BNP. Plasma NT-Pro BNP levels are elevated in patients with acute ischemic stroke patients, in particular when accompanied by AF [17-19]. Atrial fibrillation in the absence of left ventricular disease is associated with increased concentrations of BNP [20], and restoration of sinus rhythm can decrease plasma BNP concentrations [21]. From a physiologic stand point, BNP has an important role in heart failure as a counter regulating hormone to angiotensin-II, norepinephrine and endothelin; because it decreases synthesis of some of these neurohormones and acts like a balance vasodilator. It has recently been reported that the peripheral concentration of proBNP, but not pro-ANP, is increased in lone atrial fibrillation [22]. A study by Inoue et al. [23] has in fact suggested mostly atrial BNP secretion in atrial fibrillation. In the atria, the appendages seem to be the logical sources for natriuretic peptide release, as they represent anatomical 'overload sensors'. In one of these studies two cut-off points of 265.5 pg/ml and 912.0 pg/ml, associated with a high negative and high positive predictive value for the diagnosis of AF (97.2% and 90.9%, respectively) were obtained [10].

Conclusion

The most relevant complication of untreated AF is stroke and systemic embolism and it has convincingly been shown that this risk is similar in paroxysmal and sustained (persistent or permanent) AF. Patients with AF and ischemic stroke have an indication for anticoagulation and it cut down the risk for recurrent stroke by nearly 70%. Thus, the identification of an increased risk of paroxysmal AF by a natriuretic peptide is highly attractive and clinically relevant in patients presenting with acute ischemic stroke and sinus rhythm. We have seen in our study that NT-proBNP levels can reliably identify patients at high risk of having paroxysmal AF. These high risk patients can be considered for prolonged cardiac rhythm monitoring. This is a excellent option for identifying patients who will benefit maximum from prolonged cardiac monitoring especially in countries with limited resources.

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References

1. Health Organization. World Health Report 2002. Geneva, Switzerland: world health organization; 2002.
2. Hankey G, Warlow C. Treatment and secondary prevention of stroke: evidence, costs, and effects on individuals and populations. Lancet. 1999;354:1457-63.
3. Brott T, Bogousslavsky J. Treatment of acute ischemic stroke. N Engl J Med. 2000;343:710-22.
4. Kolominsky-Rabas PL, Weber M, Gefeller O, Neundoerfer B, Heuschmann PU. Epidemiology of ischemic stroke subtypes according to TOAST criteria, incidence, recurrence, and long-term survival in ischemic stroke subtypes: a population-based study. Stroke. 2001;32:2735-40.
5. Adams HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke: Definitions for use in a multicenter trial; TOAST, trial of org 10172 in acute stroke treatment. Stroke. 1993;24:35-41.
6. Lin HJ, Wolf PA, Kelly-Hayes M, Beiser AS, Kase CS, Benjamin EJ, et al. Stroke severity in atrial fibrillation: The Framingham study. Stroke. 1996;27:1760-64.
7. Saxonhouse SJ, Curtis AB. Risks and benefits of rate control versus maintenance of Sinus rhythm. Am J Cardiol. 2003;91:27-32.
8. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with AF. Circulation. 2006;114:e257-e354.
9. Thomas G, Lerman BB. Prediction of stroke risk in atrial fibrillation, prevention of stroke in atrial fibrillation, and the impact of long-term monitoring for detecting atrial fibrillation. Curr Atheroscler Rep. 2011;13:290-7.
10. Fonseca AC, Matias JS, Pinho E Melo T, Falcao F, Canhao P, et al. N-terminal probrain natriuretic peptide as a biomarker of cardioembolic stroke. Int J Stroke. 2011;6:398-403.
11. Montaner J, Perea-Gainza M, Delgado P, Ribo M, Chacon P, RoselA, et al. Etiologic diagnosis of ischemic stroke subtypes with plasma biomarkers.

Stroke. 2008;39:2280-7.

12. Okada Y, Shibazaki K, Kimura K, Iguchi Y, Miki T. Brain natriuretic peptide as a predictor of delayed atrial fibrillation after ischemic stroke and transient ischemic attack. Eur J Neurol. 2010;17:326-31.

13. Gross CR, Kase CA, Mohr JP, Cunningham SC, Baker WE. Stroke in south Alabama: Incidence and diagnostic features. A population based study. Stroke. 1984;15:249-55.

14. Lyden P, Brott T, Tilley B, Welch KM, Mascha EJ, Levine S, et al. Improved reliability of the NIH Stroke Scale using video training. NINDS TPA Stroke Study Group. Stroke. 1994;25(11):2220-6.

15. Van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 1988;19:604-7.

16. Mukoyama M, Nakao K, Saito Y, Ogawa Y, Hosoda K, Suga S, et al. Increased human brain natriuretic peptide in congestive heart failure. N Engl J Med. 1990;323:757-8.

17. Mukoyama M, Nakao K, Hosoda K, Suga S, Saito Y, Ogawa Y, et al. Brain natriuretic peptide as a novel cardiac hormone in humans. Evidence for an exquisite dual natriuretic peptide system, atrial natriuretic peptide and brain natriuretic peptide. J Clin Invest. 1991;87:1402-12.

18. Maixent JM, Paganelli F, Scaglione J, Lévy S. Antibodies against myosin in sera of patients with idiopathic paroxysmal atrial fibrillation. J Cardiovasc Electrophysiol. 1998;9(6):612–7.

19. Gaudino M, Andreotti F, Zamparelli R, Di Castelnuovo A, Nasso G, Burzotta F, et al. The −174G/C Interleukin-6 polymorphism influences postoperative Interleukin-6 levels and postoperative atrial fibrillation. Is atrial fibrillation an inflammatory complication? Circulation. 2003;108:II-195-II-199.

20. Knudsen CW, Omland T, Clopton P, Westheim A, Wu AH, Duc P, et al. Impact of atrial fibrillation on the diagnostic performance of B-type natriuretic peptide concentration in dyspneic patients: an analysis from the breathing not properly multinational study. J Am CollCardiol. 2005;46:838-44.

21. Wozakowska-Kapton B. Effect of rhythm restoration on plasma brain natriuretic peptide in patients with atrial fibrillation. Am J Cardiol. 2004;93:1555-8.

22. Ellinor PT, Low AF, Patton KK, Shea MA, Macrae CA. Discordant atrial natriuretic peptide and brain natriuretic peptide levels in lone atrial fibrillation. J Am Coll Cardiol. 2005;45:82-6.

23. Inoue S , Murakami Y, Sano K, Katoh H, Shimada T. Atrium as a source of brain natriuretic polypeptide in patients with atrial fibrillation. J Card Fail. 2000;6:92-6.