N-terminal Pro-Brain Natriuretic Peptide as a Biomarker for a Significant Renal Artery Stenosis in Medically Refractory Hypertensive Patients

Nattawut Wongpraparut MD, FACP, FACC *, Chulaluk Komoltri DrPH **,
Srisakul Chirakarnjanakorn MD*, Rewat Phankingthongkum MD*,
Sarawut Limtangturakulm MD*, Rungtiwa Pongakasira BSc***

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** Division of Cardiology, Department of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand*
*** Clinical Epidimiology Unit, Office of Research and Development, Faculty of Medicine,, Siriraj Hospital, Mahidol University, Bangkok, Thailand*
**** Her Majestry's Cardiac Center, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*

Background: *Although RAS is a relatively uncommon cause of hypertension, it is the most common form of correctable hypertension. There are clinical clues to be gained in identifying the small subset of individuals in whom directed evaluation for RAS may be useful. But its diagnostic accuracy is still poor.*
Objective: *The aim of the present study is to determine the usefulness of N-terminal pro-brain natriuretic peptide (NT-pro BNP) levels in helping improved diagnostic accuracy of a significant renal artery stenosis (RAS) in medically refractory hypertensive patients.*
Material and Method: *The present study included 40 patients with medical refractory hypertension in whom RAS was suspected and who were undergoing magnetic resonance angiogram (MRA) of renal artery and/or renal angiogram. Twenty consecutive patients with a significant RAS by MRA or renal angiogram (RAS group) compared with 20 consecutive patients in whom RAS was suspected but whose MRA/renal angiogram was normal or non-significant (normal group). Baseline clinical characteristics, number of antihypertensive medications before the procedure and NT-pro BNP were obtained from both groups.*
Results: *Age, gender, glomerular filtration rate (GFR) and LV function did not differ significantly between the two groups. NT-pro BNP level was significantly higher in RAS group (1,243 ng/ml, range 156-10,628 ng/ml) compared to normal group (129 ng/ml, range 61-3,457 ng/ml), $p = 0.009$. NT-proBNP level $\geq$ 600 ng/ml has sensitivity and specificity of 80% and 95%, respectively, in diagnosis of significant RAS.*
Conclusion: *In medical refractory hypertensive patients, NT-pro BNP level increased in patients with significant RAS and was an aid in separating a significant RAS from non-significant/normal renal artery.*

Keywords: *Resistant hypertension, Renal artery stenosis, NT-proBNP*

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Renal artery stenosis (RAS) is one of the common causes of secondary hypertension. RAS share the same patho-physiology with other common vascular diseases and its prevalence increases with advance atherosclerosis. The presentation of RAS could range from asymptomatic, resistant hypertension to worsening renal function after receiving ACE-I and/or unexplained flashed pulmonary edema. The patient with clinical presentations of RAS whom revascularization benefits, should be sent for a non-invasive work up to exclude non-significant RAS. According to ACC/AHA guidelines, there are five absolute clinical clues that indicate RAS is highly suspected and that the patient should be sent for further investigation[1].

Correspondence to:
Wongpraparut N, Division of Cardiology, Department of Medicine, Faculty of Medicine, Siriraj Hospital, 2 Prannok Road, Bangkoknoi, Bangkok 10170, Thailand.
Phone: 0-2419-6104, Fax: 0-2412-7412
E-mail: Wongpraparut@yahoo.com

Medical refractory hypertensive patients will benefit from renal revascularization if significant RAS is identified. However, even in the patient who has a high clinical suspicion, diagnostic accuracy is still poor. In the medical refractory hypertensive patients, significant RAS will be found about one of ten patients who were sent for imaging investigation. Natriuretic peptides level elevates in respond to pressure and volume overload. Level of natriuretic peptides elevation correlated well with central aortic pressure in absence of LV dysfunction[2]. Level of natriuretic peptides is also elevated in patients with significant renal artery stenosis and this finding was very helpful in predicting blood pressure reduction after renal artery stent[3]. There is no information with regard to the difference in level of NT-pro BNP in resistant hypertension with and without RAS. The objective of the present study is to compare the value of NT-pro BNP between patients with and without RAS in medical refractory hypertension and to determine the cut off point of NT-proBNP for separating patients with and without significant RAS in medical refractory hypertensive patients.

Material and Method

The authors prospectively enrolled medical refractory hypertensive patients in whom renal artery stenosis (RAS) was suspected and they underwent diagnostic renal angiogram and/or MRA. Patients were included if they met the following criteria: age above 18, resistant hypertension as defined as a blood pressure which could not be reduced below 140/90 mmHg, with three medications (of which one was diuretic) for a period of three months. Patients were excluded if they refused to participate in the clinical trial, if they had congestive heart failure (including history of diastolic heart failure but unexplained flush pulmonary edema whom RAS suspected allowed), if they had LV ejection fraction < 55%, if they had a history of valvular heart disease, if they had pulmonary hypertension, recent acute coronary syndrome or a trial fibrillation and if they had significant impaired renal function when eGFR < 30 mL/min per 1.73 m^2. Baseline clinical characteristics, number of anti-hypertensive medications, LV function and NT-proBNP were obtained at baseline. Twenty consecutive patients with significant RAS who met above inclusion and exclusion criteria's were matched 1:1 with twenty consecutive patients with normal renal artery or non-significant RAS (Fig. 1). Plasma NT-proBNP was determined by using the Roche proBNP electrochemilumiluminescnece immunoassay (ECLIA) on the elecsys 1,010 analyzer (CV 1.6%) by a central lab technician who was blinded to the result of renal angiogram. Quantitative coronary angiogram (QCA) was measured to determine degree of stenosis by renal angiogram. Significant renal artery stenosis has diameter stenosis > 70% stenosis. A skilled

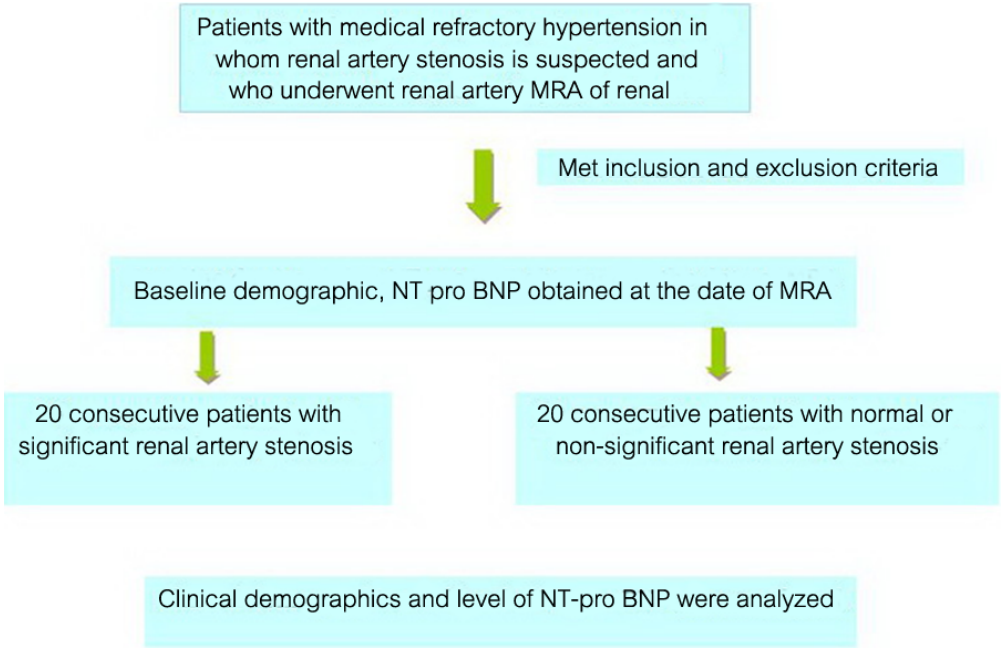

Fig. 1 Study protocol

analyzer blinded to the results of NT-proBNP performed QCA, using validated automated edge detection software (QCA-CMS 7.2 system, CMS-MEDIS). Clinical characteristics such as age, gender, degree and extent of coronary disease, blood pressure and body mass index were recorded. Baseline laboratory such as serum creatinine, eGFR, NT-proBNP and baseline angiographic/MRA characteristics, such as percent of stenosis and quantitative angiographic measurements were compared between the two groups. The institutional review board approved the present study.

Statistical analysis

Comparison of continuous variables between patients with and without RAS was performed using 2-sample t-test or Mann-Whitney U test. Comparison of categorical variables between patients with and without RAS Chi-square test was used. The receiver operating characteristic curve was used to find the optimal cut-off point of NT-proBNP for identifying significant RAS. Multiple logistic regression analysis was performed to determine of the effect of NT-proBNP (> 600 ng/L) on identification of significant RAS (adjusted for body mass index and eGFR). All statistical analysis was performed with the SPSS version 19.0.

Results

Baseline demographic characteristics, including age, sex, history of diabetes, history of hypercholesterolemia and smoking, were not significantly different between the two groups (Table 1). Prior history of unexplained flash pulmonary edema was more frequent in the medical refractory hypertension with significant renal artery stenosis (RAS) group (45% with RAS group versus 15% without RAS group, $p = 0.04$). There was no significant difference in systolic BP, diastolic BP, mean arterial BP, baseline creatinine, glomerular filtration rate (GFR), ejection fraction (EF), LV mass index and number of medications used for blood pressure control (Table 1). Body mass index (BMI) was higher in control group compare to RAS group (28.2 ± 5.1 versus 25.0 ± 3.3 kg/m^2, $p = 0.02$). NT-proBNP was elevated in medical refractory hypertension but the level was significantly higher in patients with significant RAS (median 1,243 versus 129 pg/mL, $p < 0.001$). Fig. 2 shows distribution of NT-proBNP level between medical refractory hypertensive patients with and without significant RAS. The area under receiver operating curve indicating the ability of NT-proBNP in predicting significant RAS in medical refractory hypertensive patients was 0.88 ($p < 0.001$), Fig. 3. The most accurate cutoff of NT-proBNP level for identified patients with significant RAS in medical refractory hypertensive patients was above 600 pg/mL (sensitivity 80%, specificity 95%, area under the curve 0.88), Table 2. After being adjusted for eGFR and body mass index using multiple logistic regression, NT-proBNP > 600 pg/mL is a strong predictor for a significant RAS in medical refractory hypertensive patients (OR 57.05, 95%CI 5.29-614.26, $p < 0.001$).

Table 1. Baseline demographics in medical refractory hypertensive patients with and without significant renal artery stenosis

Parameters	RAS group (n = 20)	Normal group (n = 20)	p-value
Age (yrs in mean ± SD)	64.5 ± 15.6	58.9 ± 16.7	
Diabetes mellitus (%)	40	50	0.75
Hypercholesterolemia (%)	58	75	0.32
Coronary artery disease (%)	50	30	0.33
Smoking (%)	10	32	0.13
Unexplained pulmonary edema (%)	45	15	0.04
Body mass index	25.0 ± 3.3	28.2 ± 5.1	0.02
Systolic BP (mmHg)	170.7 ± 36.7	165.8 ± 12.8	0.51
Diastolic BP (mmHg)	86.9 ± 24.9	89.9 ± 14.1	0.64
Mean arterial BP (mmHg)	128.2 ± 29.2	127.8 ± 9.8	0.95
Creatinine (mg/dL)	1.29 ± 0.3	1.21 ± 0.36	0.43
eGFR (mL/min/1.73 m^2)	54.0 ± 19.4	4.3 ± 18.6	0.09
EF (%)	65.4 ± 6.8	69.7 ± 9.1	0.25
LV mass index (g/m^2)	219 ± 13	260 ± 29	0.17
Number of antihypertensive medications	3.85 + 1.0	3.95 + 0.9	0.75

Table 2. Variable cutoff of NT-Pro BNP in diagnosis of significant renal artery stenosis and its sensitivity, specificity and accuracy

Cutoff point of NT-Pro BNP	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Accuracy (95% confidence interval)
≥ 500	80% (56%-94%)	90% (68%-98.8%)	85% (70%-94%)
≥ 600	80% (56%-94%)	95% (75%-99%)	87.5% (73%-96%)
≥ 700	75% (50%-91%)	95% (75%-99%)	85% (70%-94%)

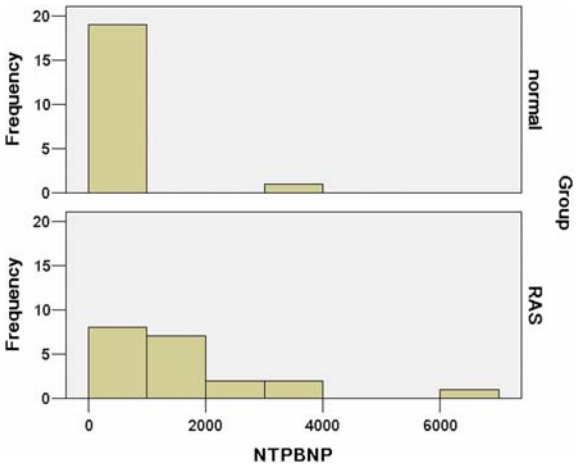

Fig. 2 Distribution of NT-pro BNP level in medical refractory hypertensive patients with and without significant RAS

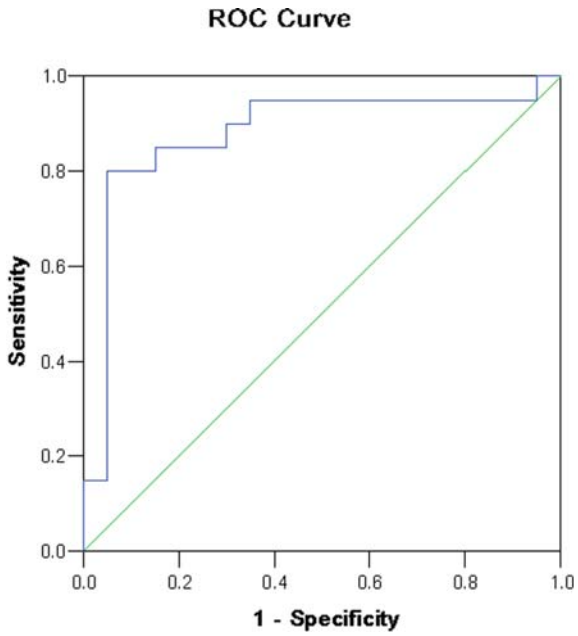

Fig. 3 ROC curve of NT-pro BNP in predicting significant RAS in medical refractory HTN. Area under the curve = 0.88 (95%CI: 0.76 to 1.00)

Discussion

The authors have demonstrated that the level of NT-proBNP is elevated in medical refractory hypertensive patients. The level of NT-proBNP is also helpful in separating medical refractory hypertension secondary to significant RAS from normal/non-significant RAS. The authors find the cut-off of NT-proBNP to be above 600 pg/mL in medial refractory hypertensive patients with EF > 55%, eGFR > 30 mL/min per 1.73 m^2 and no significant history of pulmonary hypertension, valvular heart disease or a trial fibrillation. These parameters have a 87% accuracy in identifying significant RAS as a cause of refractory hypertension. Natriuretric peptides are released from the heart in response to pressure and volume overload. The peptide shows a high degree of a structural homology. It promotes diuresis, natriuresis, arterial vasodilation and antagonizes renin. Stretch cardiac myocyte is the main stimulus of NT-proBNP release[4]. There is evidence that catecholamine, angiotensin II and endothelin may further enhance NP secretion via the paracrine and endocrine mechanism[5]. The level of natriuretric peptide (NP) is markedly elevated in the patients with congestive heart failure (CHF). Natriuretic peptide is also elevated in the setting apart from CHF, such as COPD, pulmonary embolism, atrial fibrillation, hyperthyroid and hypertension, but the level often falls within the grey zone. Bunce et al, found that elevated central aortic pressure is strong predictor for NT-proBNP concentration in diabetic men without clinically apparent LV dysfunction. Natriuretic peptide level correlated with central aortic pressure[2,6,7].

Bilateral renal artery stenosis (RAS) leads to impaired salt and water retention, causing volume expansion, which activated NP release. Unilateral RAS decrease renal perfusion, which activate renin angiotensin system and increase in the level of angiotensin II. The stenotic kidney responds to reduction of perfusion pressure by secreting renin from

juxtaglomerlular cells which lead to an increase in circulating level of angiotensin II[8]. Angiotensin II increases synthesis of BNP[9,10]. Animal study has shown that BNP mRNA upregulated after clipping of the renal artery[5]. Silva et al, measured the BNP in 27 medical refractory hypertensive patients with significant RAS before and after renal stent placement[3]. He found 81% of significant RAS has baseline BNP > 80 pg/mL and elevated BNP was a good predictor for blood pressure response after renal artery stent. In ninety-four percent of patients who have blood pressure improvement at 3.5 months follow-up after renal stent, BNP falls more than 30% within 24 hours after renal stent placement from baseline value. The significant decline of BNP after renal stent placement strongly suggests a cause and effect relationship for significant RAS and BNP elevation. A similar study in 120 unselected hypertensive patients who underwent renal artery stent, showed elevated BNP was a good predictor for BP response after stent[11].

Atrial Natriuretic peptide has been previous used to separate significant RAS from essential hypertension[12,13]. Since ANP has a short half-life, it is not widely used in clinical practice. Our findings of elevated NT-proBNP help in separating significant RAS in medical refractory hypertensive patients and is in line with study of Mussolo et al, which found the usefulness of NT-pro ANP and BNP in this regards[13]. In the present study, NT pro ANP and BNP give a low sensitivity for diagnosis of renovascular hypertension in medical refractory hypertensive patients (NT proANP > 530 pmol/L giving a sensitivity of 67% with a specificity of 86%; BNP > 9.8 pmol/L giving a sensitivity of 58% with a specificity of 90%). However, the present study only excluded known nonvascular nephropathy, diabetic mellitus type 1 and aortic stenosis. Elevated natriuretic peptide is an established marker of congestive heart failure. In a well-selected cohort of patients, of whom those with EF>55% have no significant pulmonary hypertension, or valvular heart disease, no recent ACS and eGFR > 30 mL/min per 1.73 m^2, a cut off of NT-pro BNP > 600 pg/mL report a sensitivity of 80% and specificity of 95%.

NT-pro BNP has inverse correlation with renal function[14]. But it is not practical to find an elderly female with low body weight in whom renal artery stenosis (RAS) is suspected but whose eGFR remains > 60 mL/min per 1.73 m^2. From the Pride study[14], NT-pro BNP was greatly affected when eGFR < 30 mL/min per 1.73 m^2. We used eGFR < 30 mL/min per 1.73 m^2 as our exclusion point since it is more realistic in our patient population.

Diagnostic accuracy of clinical suspicion alone remains poor. In a patient in whom RAS is suspected, but EF > 55%, eGFR > 30 mL/min per 1.73 m^2, and there is no significant history of pulmonary hypertension, valvular heart disease, or atrial fibrillation, we recommend obtaining NT-proBNP as a screening test first. If NT-proBNP is above 600 pg/mL, then imaging for renal artery should be conducted (Fig. 4).

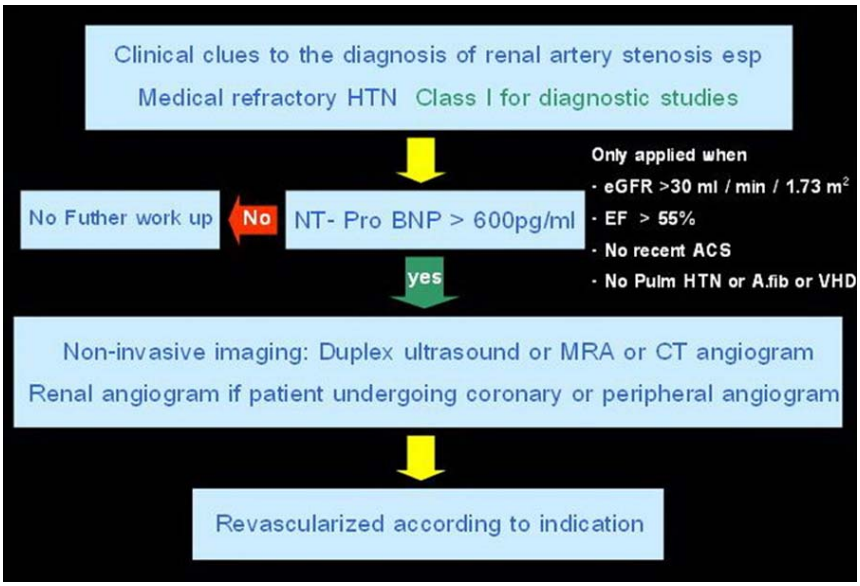

Fig. 4 Suggested algorithm for diagnosis and treatment of RAS

Study limitations

This is a small, non-randomized study. In our country, NT-pro BNP is only commercially available test.

Potential conflicts of interest

None.

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การใช้ค่า N-terminal Pro-Brain Natriuretic Peptide เพื่อช่วยในการวินิจฉัยโรคหลอดเลือดไตตีบในผู้ป่วยที่มีภาวะความดันโลหิตสูงที่ไม่ตอบสนองต่อยา

ณัฐวุฒิ วงษ์ประภารัตน์, จุฬาลักษณ์ โกมนตรี, ศรีสกุล จิรกาญจนากร, เรวัตร พันธุ์กิ่งทองคำ, สราวุธ ลิ้มตั้งตุระกูล, รุ่งทิวา พงษ์อัคคศิรา

ภูมิหลัง: ถึงแม้ว่าภาวะของโรคหลอดเลือดไตตีบ (renal artery stenosis) จะพบไม่ได้บ่อยที่เป็นสาเหตุทำให้เกิดภาวะความดันโลหิตสูง แต่โรคหลอดเลือดแดงของไตตีบก็เป็นสาเหตุหนึ่ง และเมื่อไปดูในกลุ่มผู้ป่วยภาวะความดันโลหิตสูงที่มีสาเหตุมาจากสาเหตุอื่นและสามารถแก้ไขได้ ภาวะหลอดเลือดแดงของไตตีบจะเป็นสาเหตุที่พบได้บ่อยที่สุด โดยปกติในทางคลินิกเราจะวินิจฉัยผู้ป่วยเพื่อส่งตรวจต่อโดยอาศัยประวัติและการตรวจร่างกายที่มีเหตุสนับสนุน แต่อย่างไรก็ดีหากอิงจากประวัติอย่างเดียว ความสามารถในการตรวจก็พบว่ายังค่อนข้างต่ำ

วัตถุประสงค์: การศึกษานี้มีเพื่อศึกษาการนำไปใช้ของ N-terminal proBNP (NT-pro BNP) ในการเพิ่มความสามารถในการตรวจรักษา วินิจฉัยโรคหลอดเลือดไตตีบ (renal artery stenosis) ในผู้ป่วยที่มีภาวะความดันโลหิตสูงที่ไม่ตอบสนองต่อยา

วัสดุและวิธีการ: การศึกษานี้ศึกษาผู้ป่วยทั้งหมด 40 รายที่มีภาวะความดันโลหิตสูงที่ไม่ตอบสนองต่อยา (medical refractory hypertension) มีความสงสัยว่าอาจจะเป็นจากภาวะหลอดเลือดของไตตีบและได้รับการส่งตรวจ magnetic resonance angiogram (MRA) หลอดเลือดแดงของไต 20 คนของผู้ป่วยที่มีภาวะหลอดเลือดของไตตีบเปรียบเทียบกับ 20 คน ของผู้ป่วยที่มีความดันโลหิตสูง แต่ตรวจจาก MRA ไม่พบหลอดเลือดแดงของไตตีบ ได้ทำการศึกษาอาการทางคลินิก จำนวน และปริมาณของยาลดความดัน และเจาะดูค่า NT-pro BNP เพื่อเปรียบเทียบระหว่าง 2 กลุ่ม

ผลการศึกษา: อายุ เพศ การทำงานของค่าไต (GFR) และภาวะการทำงานของหัวใจ (LV dysfunction) เมื่อเปรียบเทียบระหว่าง 2 กลุ่ม ไม่มีความแตกต่างกัน แต่ผลการตรวจค่า NT-pro BNP ในผู้ป่วยที่มีภาวะความดันโลหิตสูงที่ดื้อต่อยาร่วมกับภาวะหลอดเลือดแดงของไตตีบ จะตรวจพบค่า NT-pro BNP ที่ 1,243 นก./มล. Range(156-10,628 นก./มล.) เมื่อเปรียบเทียบกับผู้ป่วยที่มีภาวะความดันโลหิตสูงที่ดื้อต่อยาแต่ไม่มีภาวะหลอดเลือดแดงของไตตีบ ค่า NT-pro BNP เพียง 129 นก./มล range (61-3,457 นก./มล.) ซึ่งมีความแตกต่างกันอย่างมีนัยสำคัญ ($p<0.001$) ค่า NT-pro BNP มากกว่าหรือเท่ากับ 600 นก./มล. มีความไวและความจำเพาะที่ร้อยละ 80 และ 95 ในการวินิจฉัยภาวะหลอดเลือดแดงของไตตีบในผู้ป่วยที่มีความดันโลหิตสูงที่ดื้อต่อยา

สรุป: ในผู้ป่วยที่มีภาวะความดันโลหิตสูงที่ดื้อต่อยาการตรวจค่า NT-pro BNP หากพบในระดับที่สูงมากกว่าหรือเท่ากับ 600 นก./มล. จะช่วยในการวินิจฉัยภาวะหลอดเลือดของไตตีบ และทำให้สามารถแยกภาวะหลอดเลือดแดงของไตตีบเมื่อเปรียบเทียบกับผู้ป่วยที่มีภาวะความดันโลหิตสูงที่ดื้อต่อยาแต่ไม่มีภาวะหลอดเลือดแดงของไตตีบ