Dear Colleagues,

It is our pleasure to provide this EMCREG-International newsletter which discusses NT-proBNP for the evaluation of shortness of breath in the emergency department. The natriuretic peptide is typically produced from the prohormone (pre-proBNP) during stretching of the ventricular myocardium, along with BNP. In the last several years, there have been a number of studies published in the literature regarding NT-proBNP which we believe our clinician readers would enjoy being presented in a summary such as this newsletter.

The incidence of heart failure has been rising over the last decade as more patients survive significant myocardial infarction, as well as other diseases which compromise the heart. All clinicians who care for these patients must be aware of the many diagnostic and therapeutic approaches to these often critically-ill patients. NT-proBNP provides an important diagnostic and prognostic test for these heart failure patients.

Dr. Sean Collins, Assistant Professor of Emergency Medicine at the University of Cincinnati, College of Medicine, is an active clinician and clinical researcher with expertise in the diagnosis and treatment of heart failure. We hope this EMCREG-International newsletter provides clinical information which will help you in the care of your patients with heart failure.

Sincerely,

Andra L. Blomkalns, MD W. Brian Gibler, MD
Director of CME, President,
EMCREG-International

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Use of NT-proBNP in the Emergency Department Evaluation of Shortness of Breath: Implications for Clinical Practice

NEW CONCEPTS AND EMERGING TECHNOLOGIES FOR EMERGENCY PHYSICIANS
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University of Cincinnati College of Medicine, Cincinnati, Ohio

Introduction

The dyspneic emergency department (ED) patient with multiple comorbidities presents a diagnostic challenge. Relying solely on history, physical examination and chest radiography to delineate a cardiac versus non-cardiac etiology of dyspnea is traditionally problematic. Approximately 15-20% of ED patients with dyspnea due to acute decompensated heart failure (ADHF) will be misdiagnosed.

The morbidity associated by withholding proper care for ADHF is well documented. An early, accurate diagnosis is necessary to facilitate proper disposition and care.

It has been known for almost 50 years that the heart is not only a cardiorespiratory organ, but an endocrine organ as well. In 1956, electron microscopy was used to demonstrate granules present in the atria that were absent in the ventricle, eventually shown to contain natriuretic peptides (NP).

Over the last 3 years there have been several reports in the literature suggesting that NP may be useful in the diagnosis of ADHF in the ED.

Natriuretic Peptide Physiology

The major source of NP is the ventricular myocardium, but experimental animal models have found evidence of NP in other extra-cardiac tissues such as the central nervous system, pituitary, lung, thyroid and ovary. The NP are released under conditions of increased myocardial stretching and possess potent vasodilatory and natriuretic properties. This stimulus for release results in secretion of a prohormone (Pre-ProBNP) from the myocyte that is enzymatically cleaved into the biologically active BNP and the biologically inactive N-terminal (NT)-proBNP (Figure 1).

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**Figure 1.** Synthesis and release of B-type natriuretic peptide (BNP). AA = amino acid; RAAS = rennin angiotensin aldosterone system. Reprinted with permission from Wiviot et al. Clin Chim Acta 2004;346:119-128.
NT-proBNP is larger than BNP, has a longer half-life and has improved stability during storage (Table 1). BNP is cleared mainly by NP Receptor-C, with some additional removal by neutral endopeptidase and the kidney. While the exact mechanism of clearance is unclear, there is preliminary data suggesting that renal clearance may have an impact on NT-proBNP levels, making its use in patients with renal disease problematic.

NT-proBNP Assay

The NT-pro BNP assay (Elecsys® proBNP assay, Roche Diagnostics, Indianapolis, Indiana) is a fully automated two-site sandwich immunoassay incorporating polyclonal antibodies against the N-terminal and mid-region of NT-proBNP. It is highly specific for the NT-proBNP peptide, showing less than 0.001% cross-reactivity with BNP. Reported results can range from 5 to 35,000 pg/ml. Sample stability at room temperature is 72 hours, compared to BNP which declines significantly after 4 hours. The coefficient of variation of the NT-proBNP assay is 2.2 to 5.8%, approximately 2-3 times less than that for BNP (POC device). This is not unexpected when comparing a point-of-care device to a device used in the central lab. Considering the analytic and intra-individual variability of the assay, the percentage change in serial NT-proBNP concentrations considered to be statistically significant is 90% (95% bidirectional confidence intervals). This is important to consider when following serial changes in NT-proBNP as a response to therapy.

NT-proBNP Use in Acute Decompensated Heart Failure

Diagnosis

In general, NT-proBNP and BNP correlate quite well in predicting decreased ejection fraction (EF) and symptomatic ADHF (r values ranging from 0.737 to 0.902). There are now multiple platforms for both NT-proBNP and BNP, all with slightly different coefficients of variation and test characteristics. This makes it difficult to make generic comparisons between testing strategies with BNP and NT-proBNP; the type of assay used may make a difference in the endpoint of interest.

NT-proBNP has been evaluated as a predictor of both a decreased EF and symptomatic ADHF. In a pooled analysis of three large epidemiologic studies NT-proBNP had an area under the ROC curve (AUC) of 0.85 for detection of clinical heart failure (75% sensitivity and 79% specificity) and an AUC of 0.69 for detection of LV dysfunction. In a head-to-head comparison with BNP in 205 ED patients with dyspnea, NT-proBNP and BNP (POC assay) had identical AUC (0.89) for prediction of a clinical diagnosis of heart failure. NT-proBNP had moderately high sensitivity (80%), specificity (87%) and accuracy (85%) at its optimum cutpoint (340 pmol/ml = 2,875 pg/ml). BNP had better sensitivity (94%) and worse specificity (70%) at its optimum cutpoint of 208 pg/ml. A comparison of 180 hospitalized patients on a cardiac service revealed similar results. Forty-three patients with symptomatic heart failure and echocardiographic abnormalities were compared with 137 asymptomatic subjects and normal echocardiograms. A cutpoint of 211 pg/ml yielded a sensitivity of 93% and specificity of 82% for NT-proBNP; a BNP (central lab assay) cutpoint of 113 pg/ml had a sensitivity of 81% and specificity of 96%. The AUC of the assays were similar with 0.918 for NT-proBNP and 0.930 for BNP.

### Table 1. Characteristics of BNP and NT-proBNP.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BNP</th>
<th>NT-proBNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>32 AA</td>
<td>76 AA</td>
</tr>
<tr>
<td>Half-life</td>
<td>20 minutes</td>
<td>60-120 minutes</td>
</tr>
<tr>
<td>Stability</td>
<td>Up to 4 hours at room temp</td>
<td>Up to 3 days at room temp</td>
</tr>
<tr>
<td>Clearance</td>
<td>NPR-C, endopeptidase, kidney</td>
<td>Unclear, possibly kidney</td>
</tr>
</tbody>
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The diagnostic accuracy of NT-proBNP was evaluated in 600 dyspneic ED patients in the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) Study. Methodology was very similar to the BNP Multinational Study, patients > 21 years of age with acute dyspnea were eligible for enrollment. Important exclusion criteria included those patients with a serum creatinine > 2.5 mg/dl or ischemic ECG changes. The gold standard for a diagnosis of ADHF was based on a cardiologist’s review of the subject’s medical record, blinded to NT-proBNP levels. The median NT-proBNP level among 209 patients (35%) with ADHF was 4054 pg/ml, compared with 1175 pg/ml in those with a history of heart failure but acute dyspnea due to another cause (35 subjects, 6%), and 114 pg/ml in those without ADHF (355 subjects, 59%) (Figure 2). The optimal cutpoint based on ROC curve (AUC=0.94) analysis was 900 pg/ml (Figure 3). However, age-related increases in NT-proBNP suggested optimal cutpoints to “rule in” ADHF of 450 pg/ml in those less than 50 years of age and 900 pg/ml for those over age 50. The overall optimal cutpoint to “rule out” ADHF was 300 pg/ml. A pooled analysis of three studies of patients with ADHF confirmed the “rule out” cutpoint of 300 pg/ml. However, the optimal strategy to “rule in” ADHF suggested age-related cutpoints of 450 pg/ml, 900 pg/ml, and 1800 pg/ml for the ages < 50 years, 50-75 years, and >75 years respectively (Table 2).
**Prognosis**

Elevated NT-proBNP levels have been shown to predict adverse events in ADHF. A study of 2230 inpatients (161 with ADHF) suggested that above-median NT-proBNP levels taken the morning after admission were predictive of subsequent 1-year mortality. The 50 patients that died over the subsequent year had significantly higher levels of NT-proBNP than the 111 patients that were still alive. In multivariate analysis, ejection fraction added no additional prognostic information to NT-proBNP levels. In another study of 182 hospitalized patients with ADHF, patients with above median NT-proBNP levels measured at hospital discharge were more likely to experience an adverse event in the subsequent 6 months than those with below median levels. O'Brien and colleagues found similar results that indicated pre-discharge NT-proBNP levels were independently predictive of the combined endpoint of death or heart failure hospitalization. A study of admitted patients with ADHF suggested that admission NT-proBNP levels were predictive of future events. Patients with NT-proBNP levels below 1000 pg/ml had a yearly mortality rate of 0.7%; those with levels between 1000 to 4999 pg/ml had a mortality rate of 1.6%; those with levels above 5000 pg/ml had a yearly mortality rate of 28.4%.

**Figure 3.** Receiver operator characteristic analysis of NT-proBNP for the diagnosis of acute congestive heart failure. NT-proBNP was highly sensitive and specific for the diagnosis of acute congestive heart failure with a highly significant area under the curve. A strategy of partitioning patients in categories of <50 and ≥50 years (with cutpoints of 450 and 900 pg/ml respectively) was optimal with areas under the curve of 0.98 and 0.93, respectively (both p values <0.0001). Reprinted with permission from Januzzi et al. Am J Cardiol, 2005; 95:948-54.

**Table 2:** Optimal NT-proBNP cutpoints for ruling in and ruling out acute CHF. NT-proBNP testing was of value to both identify or exclude acute CHF with high accuracy. In the PRIDE Study, the optimal “rule in” strategy using NT-proBNP was an age-stratified approach with two cutpoints, while a single cutpoint of 300 pg/ml was of value for excluding the diagnosis. A pooled analysis suggests a further “rule in” cutpoint of 1800 pg/ml in those patients > 75 years of age. Reprinted with permission from Januzzi et al. Am J Cardiol 2005;95:948-54.
Following Response to Therapy

Because of the impracticality and cost of using right heart catheters in every heart failure patient, physicians are left with following subjective symptom alleviation (dyspnea and fatigue) and often unreliable physical exam findings (S3, jugular venous distension, leg edema) to determine the endpoints of treatment. Changes in NT-proBNP levels with therapy have been investigated as predictors of future adverse events. In a previously mentioned study of inpatients with ADHF, subjects were divided into three groups based on trends in NT-proBNP values during hospitalization. The variation in NT-proBNP levels during hospitalization was the strongest predictor of death or rehospitalization at 6 months. Those patients whose NT-proBNP levels decreased by more than 30% were significantly less likely to have an adverse event (death or rehospitalization) than those whose levels changed by less than 30% (p=0.006), or whose levels increased by more than 30% (p<0.0001) (Figure 4).

A prospective study of 100 NYHA class III-IV ED patients with ADHF found similar NT-proBNP trends with therapy. Patients had NT-proBNP levels measured upon ED presentation, at 24 hours and 7 days after admission to the hospital. Serial NT-proBNP levels correlated with symptom resolution. Those patients with complete symptom resolution (n=30) had mean NT-proBNP levels decrease by 56%, compared to those whose symptoms stabilized to chronic heart failure (n=31, mean NT-proBNP decrease of 37%) and those who had persistent decompensated heart failure (n=13, mean NT-proBNP decrease of 21%). Interestingly, all of the NT-proBNP changes in this study and the previous study are below what is considered statistically significant based on analytic and intra-individual variability with the assay.

Future studies will have to continue to investigate these small, yet apparently clinically important changes in NP and their relationship with adverse events.

NT-proBNP and Acute Coronary Syndromes

NT-proBNP has been investigated as a potential diagnostic and prognostic marker in Acute Coronary Syndromes (ACS). Traditional markers (CK, CK-MB, troponin) for ACS are released when there is irreversible injury to the myocardium. In contrast NT-proBNP is released by intact cells and may be able to detect evidence of ischemia prior to necrosis and cell death (Figure 5).

Coronary angiography has been associated with acute transient elevations in BNP levels. NT-proBNP levels have been shown to be related to the extent of ischemic myocardium on stress thallium and tetrofosmin imaging, as well as the number of diseased vessels at angiography. There are two contributions to the observed elevations of NP during ischemia. The first contribution is likely from transient wall motion abnormalities leading to increased ventricular pressure and stretch, and NP release. The second mechanism is thought to be related to hypoxia. This hypothesis is supported by the aforementioned interventional and imaging studies, as well as an animal model demonstrating hypoxia-induced BNP expression and release without cell death.
Natriuretic peptide levels have been shown to be elevated in those subjects with ACS compared to those without ACS.\textsuperscript{33,34} Unfortunately, the concentrations are in an intermediate range and are similar to levels seen in patients with mild ADHF and pulmonary embolism. As a result, using NP for ACS diagnosis is problematic.

However, the relationship of NT-proBNP with adverse events has been extensively studied, with results suggesting that it is a highly prognostic marker in ACS. An inpatient study of 1756 patients with ACS evaluated the relationship of early NT-proBNP levels (median time from symptom onset was 3 hours) to 30-day mortality. Increasing quartiles of NT-proBNP were associated with increasing risk of death, and was independently associated with death in a logistic regression model. However, systolic blood pressure <100 mm/HG and persistent ST-depression were better predictors of death in those with non ST-segment elevation MI (NSTEMI). In a similar study, NT-proBNP was measured at baseline, 48 and 72 hours in 1791 patients with NSTEMI. Patients were stratified into quartiles based on their baseline NT-proBNP levels. Seven and 30-day event rates were significantly higher in the 3rd and 4th quartile when compared to the first two quartiles. More importantly, in those patients with normal TnT levels, subjects with NT-proBNP levels above 250 ng/L had a significantly increased risk of death or myocardial infarction compared to those with levels below 250 ng/L.\textsuperscript{35}

In order for NP to be universally accepted as a risk marker it must provide information beyond that already available from our current diagnostic strategies. Elevated levels of
troponin I and T now dictate invasive versus conservative management, as well as potential administration of glycoprotein IIb/IIIa inhibitors. While the above studies have suggested that NP may help identify a subset of troponin-negative patients at high-risk, patient benefit from a more aggressive therapeutic strategy has not been shown. TACTICS-TIMI 18 subjects with elevated BNP levels (>80 pg/ml; n=320) were at higher risk of death at seven days and six months. However, invasive versus conservative management made no significant difference in mortality. A study of 2019 NSTEMI patients randomized to an invasive or conservative strategy suggested a trend toward improved outcomes with an invasive strategy in those in the highest tertile of NT-proBNP. The role of NT-proBNP in ACS management will be decided by future studies powered to evaluate outcomes of conservative versus aggressive management of ACS patients dictated by elevated NT-proBNP levels.

**NT-proBNP and Pulmonary Disease**

While the predominant source of NP is the left ventricle, disease processes that cause acute right ventricular strain also produce an elevation in circulating levels of NP. NT-proBNP has been shown to be elevated in patients with acute pulmonary embolism (PE) and primary pulmonary hypertension (PPH). In a study of 50 patients referred for lung transplantation with normal left ventricular function (echocardiography) and coronary arteries (angiography), NT-proBNP levels were elevated over 40-fold in those with PPH compared to those without PPH. NT-proBNP samples from the pulmonary artery were significantly higher than samples from the femoral vein and artery, suggesting a cardiac source of NT-proBNP in these patients.

Two studies each suggested that NT-proBNP levels could be used to risk-stratify patients with acute PE for in-hospital death and adverse events. In a study of 73 patients with acute PE confirmed by spiral CT, high-probability ventilation perfusion scan, or transesophageal echocardiography, NT-proBNP levels less than 500 pg/ml had a sensitivity of 97% for predicting a benign hospital course. In a similar study of 79 patients with acute PE, no patient with normal age and sex specific NT-proBNP levels had an adverse event. While the negative predictive value of a normal NT-proBNP level was 100%, the positive predictive value of an elevated NT-proBNP level was only 36.3%. Unfortunately the majority of the NT-proBNP elevations seen in the cases of sub-massive PE were less than 1000 pg/ml, an area where patients with ADHF and ACS also fall. From the above preliminary studies, it appears that NT-proBNP is best used to predict an uncomplicated hospital course and “rule-out” complications, rather than be used to diagnose PE or predict a complicated course.

**NT-proBNP versus BNP: is one test better than the other for ADHF?**

NT-proBNP and BNP have both been studied extensively in ADHF patients. Head-to-head studies suggest that their accuracy’s are quite similar and both tests may be helpful in the ED patient with undifferentiated dyspnea. There are some differences in the tests that need to be considered when deciding which test is the right one for your institution and cohort of patients (Table 3).

NT-proBNP is a larger protein, leading to a longer half-life and better stability. A longer half-life infers an advantage of accumulating over time, perhaps accounting for its slightly better specificity than BNP, and improved ability to differentiate mild to moderate ADHF from normal subjects. Furthermore, the increased precision of the NT-proBNP assay improves the physician’s ability to measure response to therapy using serial NT-proBNP levels. Conversely, serial measurements following response to therapy can be obtained earlier and more frequently with BNP because of its shorter half-life.

NT-proBNP is the inactive component of proBNP, while BNP is biologically active. Nesiritide is a recombinant form of BNP. Simultaneous measurements of BNP in a patient receiving nesiritide will result in a falsely elevated BNP. Because of negligible cross-reactivity with BNP, the NT-proBNP assay can be used during nesiritide infusion.

Renal disease affects the diagnostic ability of both BNP and NT-proBNP. The optimal BNP cutpoint has been suggested to be increased to 200 pg/ml (from 100 pg/ml) in those with renal disease.
Effect of Renal Function on NT-proBNP levels

Previous research suggests that the kidneys extract BNP and NT-proBNP to a similar extent in both healthy subjects and those with cardiac disease, with renal extraction ratios between 15 and 20%.46-48 Renal clearance (renal extraction × renal blood flow) of both BNP and NT-proBNP may be affected by age-related changes in renal blood flow.43, 45 Given the shorter half-life of BNP compared to NT-proBNP, yet equal renal extraction ratios, it is possible that total body clearance of NT-proBNP is more dependent upon renal clearance than BNP. A comparison of 469 patients with a previous history of MI suggested that both BNP and NT-proBNP levels were affected to a similar degree by renal dysfunction.49 Median BNP and NT-proBNP levels were increased two-fold in patients with impaired (creatinine clearance < 85 ml/min) versus normal renal function. Optimal NT-proBNP cut points were 1360 pg/ml and 500 pg/ml to diagnose ADHF, while BNP had cut points of 300 pg/ml to exclude ADHF and 900 pg/ml to diagnose ADHF.

Use of NT-proBNP in the Emergency Department Evaluation of Shortness of Breath:

Table 3. Test Comparison of NT-proBNP and BNP

<table>
<thead>
<tr>
<th>Property</th>
<th>NT-proBNP</th>
<th>BNP (POC device)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic cutpoints</td>
<td>300 pg/ml to exclude ADHF</td>
<td>100 pg/ml to exclude ADHF</td>
</tr>
<tr>
<td></td>
<td>900 pg/ml to diagnose ADHF</td>
<td>500 pg/ml to diagnose ADHF</td>
</tr>
<tr>
<td>Half-life</td>
<td>60-120 minutes - improved stability; may better differentiate mild ADHF</td>
<td>20 minutes - able to measure</td>
</tr>
<tr>
<td></td>
<td>because of better accumulation over time</td>
<td>response to therapy at more</td>
</tr>
<tr>
<td></td>
<td></td>
<td>frequent intervals</td>
</tr>
<tr>
<td>Use with Nesiritide</td>
<td>Yes</td>
<td>Requires waiting several</td>
</tr>
<tr>
<td></td>
<td></td>
<td>half-lives (2-4 hours) after</td>
</tr>
<tr>
<td></td>
<td></td>
<td>nesiritide discontinued</td>
</tr>
<tr>
<td>Renal insufficiency influences on</td>
<td>Not extensively evaluated- likely to have an influence on diagnostic</td>
<td>Suggested cut point increased</td>
</tr>
<tr>
<td>diagnostic cutpoints</td>
<td>cutpoints</td>
<td>to 200 pg/ml</td>
</tr>
<tr>
<td>Age influences on diagnostic</td>
<td>“Rule out” cutpoint left at 300 pg/ml, “Rule in” cutpoint should be</td>
<td>“Rule out” cutpoint left at 100 pg/ml</td>
</tr>
<tr>
<td>cutpoints</td>
<td>adjusted based on age: 450 pg/ml (&lt;50 years), 900 pg/ml (50-75 years),</td>
<td>to maximize sensitivity, “Rule in”</td>
</tr>
<tr>
<td></td>
<td>1800 pg/ml (&gt;75 years)</td>
<td>cutpoint remains at 500 pg/ml</td>
</tr>
<tr>
<td>Prospectively validated in ED</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>population</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Head-to-head studies suggest that accuracy of BNP and NT-proBNP are quite similar and both tests may be helpful in the ED patient with undifferentiated dyspnea.
Age has an influence on cutoff levels of both NT-proBNP and BNP. The accuracy for BNP improves slightly (78.2 to 79.9) when the cutpoint is increased from 100 pg/ml to 200 pg/ml in those over age 70. However, this is at the expense of a decrease in sensitivity from 93.6% to 84.8%.

The NT-proBNP assay should be adjusted based on age to “rule in” ADHF (450 pg/ml [<50 years of age], 900 pg/ml [50-75 years of age], 1800 pg/ml [>75 years of age]) and one cutpoint to “rule out” (300 pg/ml) ADHF. Practical use of BNP suggests a level of 100 pg/ml to exclude ADHF and a value above 500 pg/ml to diagnose ADHF, creating a similar indeterminate zone (100-500 pg/ml).

The use of a BNP level of 100 pg/ml to exclude ADHF was validated in a large cohort of ED patients with dyspnea. The PRIDE study strongly suggests that NT-proBNP is useful in differentiating cardiac from non-cardiac causes of dyspnea as well. Though age seems to have a slightly bigger influence on diagnostic cutpoints, NT-proBNP was useful as both a “rule in” and “rule out” marker.

Summary

NT-proBNP is released in response to ventricular stretch from a number of underlying disease processes. It has been extensively studied in ADHF and can be used to aid in the diagnosis and risk-stratification of these patients, and is most valuable when the clinician’s pretest probability is intermediate. It is best used to exclude patients with ADHF. When used to diagnose ADHF, age has a significant impact on the diagnostic cutpoint. There is an evolving base of literature that also suggests NP may be useful in risk-stratification of patients with ACS and PE. Whether they will be integrated into the diagnostic workup of this latter group of patients will be determined by future studies that evaluate their use as a guide to therapy.
REFERENCES


CME Post Test

After you have read the monograph, carefully record your answers by circling the appropriate letter for each question.

(Please circle answers below)

1) Is the following statement true or false? NT-proBNP is a larger protein, with greater stability and a longer half-life than BNP.
   a) True
   b) False

2) All of the following characteristics are true about BNP and NT-proBNP except:
   a) They have similar ROC curve test characteristics
   b) They are useful as prognostic markers in ACS and pulmonary embolism
   c) They have been adequately evaluated in patients with renal insufficiency
   d) They are useful as prognostic markers in patients with CHF

Patient age influences the diagnostic cutpoints of NT-proBNP. For the next three questions, match the age group with the “rule-in” diagnostic cutpoint:

3) Age < 50
   a) 1800 pg/ml
   b) 900 pg/ml
   c) 600 pg/ml
   d) 450 pg/ml

4) Age 50-75
   a) 1800 pg/ml
   b) 900 pg/ml
   c) 600 pg/ml
   d) 450 pg/ml

5) Age > 75
   a) 1800 pg/ml
   b) 900 pg/ml
   c) 600 pg/ml
   d) 450 pg/ml

6) NT-proBNP measurements can be made while a patient concurrently receives Nesiritide treatment?
   a) True
   b) False
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