The role of brain natriuretic peptides as a marker for diagnosing cardiac syncope: A narrative review

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ABSTRACT
Cardiac disease is the second common cause of syncope in emergency departments. Patients with cardiac syncope have a higher risk of mortality than those who have a non-cardiac problem. Brain natriuretic peptide (BNP) as a cardiac marker has not thoroughly been evaluated in patients with syncope. This article focuses on the studies that have assessed BNP and NT-pro-BNP in cardiac and non-cardiac syncope patients in emergency departments.

Key words: Brain Natriuretic Peptide, Cardiac, Emergency departments, Syncope

INTRODUCTION
Syncope is defined as a temporary loss of consciousness followed by spontaneous and complete recovery. In general populations, syncope is a common problem with the lifetime prevalence of 42%. It is estimated that 3% of referrals to emergency departments and 2% of inpatient admissions are due to syncope, and 6 out of 1000 people are affected by this problem every year. Kapoor et al. published one of the first prospective syncope studies and showed that the risk of mortality due to syncope in a 12-month follow-up was 14%. Serious underlying conditions such as dysrhythmia, structural heart disease, and significant hemorrhage can be the causes of syncope which ultimately lead to mortality and morbidity. The underlying conditions can be cardiac or vascular. The cardiac conditions are dysrhythmia and myocardial infarction (MI), and the vascular conditions are hemorrhage, aortic dissection, and pulmonary embolism. The serum marker BNP which is increasingly established in emergency departments for the diagnosis of acute heart failure can reflect the presence of structural heart disease. Many studies have stated that cardiac syncope is caused by reduced cardiac output that is associated with impaired hemodynamic in arrhythmia or structural cardiac disorders. Therefore, brain natriuretic peptides are candidates for diagnosis of cardiac syncope. During the last decade, few studies were conducted to assess the role of BNP in isolating cardiac from non-cardiac syncope. This paper aimed to discuss the studies that evaluated the effect of brain natriuretic peptides on diagnosis and prediction of cardiac syncope in emergency departments.

SYNCOPE RISK STRATIFICATION IN EMERGENCY DEPARTMENTS
In risk stratification and diagnosis of syncope, we must consider three major issues addressed by Costantino et al.:

Differentiating patients with syncope from those with loss of consciousness of no syncopeal source
According to the European Society of Cardiology (ESC) guidelines, syncope is defined as a transient loss of consciousness (T-LoC) caused by transient cerebral hypo-perfusion characterized by loss of consciousness followed by spontaneous and complete recovery. Therefore, syncope must be distinguished from T-LoC not induced by cerebral hypoperfusion Table 1.

Distinguishing patients with syncope from those who have fallen
Most of the time, distinguishing syncope from fall in clinical practice is impossible and exhausting. Taking a careful history from a witness plays a crucial role in facilitating the diagnosis during the early evaluation in the ED.

Determining how to manage patients presenting to the ED with near syncope or pre-syncope
Management of the pre-syncope and near syncope patients is largely heterogeneous worldwide at
present\textsuperscript{11,14}. As Costantino \textit{et al.} mentioned, pre-
syncope or near syncope refers to the feeling of im-
pending LoC without losing consciousness. Several
symptoms and physical signs contribute to this feel-
ing, such as weakness, tunnel vision, dizziness, nau-
sea, sweating, and pallor.

Many studies performed in emergency departments
exclude presyncope or near syncope because it is of-
ten assumed that these patients have a good progno-
sis. However, Grossman \textit{et al.} compared the clini-
cal outcomes of the patients with pre-syncope and the
individuals with syncope, and no statistically signif-
ificant difference was found between the two groups.

They concluded that the prognosis of near syncope
was similar to that of syncope.

**SYNCOPE RULES**

In emergency departments, many rules have been es-
tablished to stratify the risk of a single patient pre-
senting with syncope\textsuperscript{14}. Examples of such rules are
the San Francisco Syncope Rule (SFSR), Osservato-
rio Epidemiologico sulla Sincope nel Lazio (OESIL),
Evaluation of Guidelines in Syncope Study (EGSYS),
risk stratification of syncope in the emergency de-
partment (Rose), and Boston Syncope Rules. Among
these rules, only SFRS had external validity in the sys-
tematic review by Saccilotto \textit{et al.}\textsuperscript{15} with the sensitiv-
ity of 87% (95%CI 79–93) and specificity of 52% (95%
CI 43–62). One of these rules that considers the N-
terminal pro-brain natriuretic peptide (NT-proBNP)
and BNP is Rose published in 2010 and derived and
validated in a single ED center in Edinburgh\textsuperscript{16}. The
follow-up time of this tool is 30 days, and it is utilized
in clinical practices for better and more accurate diag-
nosis from BNP marker. The criteria for this diagnosis
are as follows:

- BNP level $ \geq 300 $ pg/mL or bradycardia $ \leq 50 $ in ED
  or pre-hospital
- Rectal examination showing fecal occult Blood (if 
suspicion of gastrointestinal Bleeding)
- Anemia: hemoglobin $ \leq 90 $ g/L
- Chest pain
- ECG showing Q wave (not in the lead III)
- $ O_2 $ Saturation $ \leq 94\% $ on room air

Patients are at high risk if a single variable is present.
The sensitivity and specificity for adverse events in
this rule are 87% and 56%, respectively\textsuperscript{16}. Adverse
events include pacemaker or cardiac defibrillator im-
plant within 1 month from the index syncope, ventric-
ular tachycardia, acute myocardial infarction, cere-
brovascular accidents, life-threatening arrhythmias
(ventricular fibrillation, sustained ventricular tachyc-
ardia [>120 beats/min], ventricular pause $ \geq 3 $ sec-
onds), pulmonary embolism, intracranial or sub-
arachnoid hemorrhage, hemorrhage requiring more
than 2 units of blood transfusion, acute surgical pro-
cedures, or endoscopic intervention. These rules and
biomarkers such as BNP, Troponin, and D-Dimer can
diagnose most of the cardiac syncope patients from
other types of syncope, and this issue is critical to de-
creasing the mortality and morbidity of syncope due
to cardiac causes.

**DIAGNOSTIC VALUE OF BNP IN CHILDREN WITH SYNCOPE**

Syncope is a common problem in children and ado-
lescents. A prevalence rate of 15% has been estimated
for the syncopal episode in children under the age of
18\textsuperscript{21–23}. Syncope in children and adolescents can
be caused by underlying conditions. The most com-
mon type of syncope in children and adolescent is
autonomic-mediated reflex syncope (AMS), resulted
from the syncope caused by cardiac diseases\textsuperscript{17,24,25}. About 1-3% of children's and adolescents’ admission
in ED is associated with syncope (23–24). In our
 electronic search, we identified two studies on BNP
value and syncope in children and adolescents. In
a study by Wójtowicz \textit{et al.}\textsuperscript{26} who evaluated Natri-
uretic peptides in the children and adolescents with
syncope, there was no significant difference in terms
of BNP level between the syncope and control groups
at all. Their study started with 88 and 25 particip-
ants in the syncope and control groups, respec-
tively. The concentration of NT-proBNP in the syn-
cope group was 24.5 pg/mL, and that of NT-proBNP
was 4.8 pg/mL. In the control group, NT-proBNP and
ANP concentrations were 25 pg/mL and 3 pg/mL, re-
spectively, which had no significant difference with
the syncope group. Also, the children who were hospi-
talized due to syncope showed a significant differ-
ence in beats per min and a maximum heart rate dur-
ing the 24-h electrocardiographic Holter monitoring.

In another study, Zhang \textit{et al.}\textsuperscript{28} evaluated “Di-
agnostic value of serum brain natriuretic peptide in
syncope in children and adolescents.” The study con-
cluded that Serum BNP was helpful in differentiating
cardiac syncope from non-cardiac syncope in chil-
dren and adolescents. Sixty-two children and ado-
lescents admitted in ED for syncope were evaluated,
among whom 23 participants had cardiac syncope,
and 39 had non-cardiac syncope. Regarding BNP lev-
els, there was a significant difference between car-
diac syncope ($ 958.78 \pm 2443.41 $ pg/mL) and non-
cardiac syncope ($ 31.05 \pm 22.64 $ pg/mL) groups (P-
value <0.05). Furthermore, a significant difference
Table 1: Life threatening disorders leading to syncope with cardiovascular source

| Arrhythmias                                      | Ventricular tachycardia |
|--------------------------------------------------|-------------------------|
| Pinsent cardiac Mobitz type II or third degree   |                         |
| heart block                                      |                         |
| Significant sinus pause (>3 seconds)             |                         |
| ECG features                                     |                         |
| Long QT syndrome                                |                         |
| Brugada syndrome                                |                         |
| Ischemia                                         |                         |
| Acute coronary syndrome, myocardial              |                         |
| infarction                                       |                         |
| Structural abnormalities                        |                         |
| Valvular heart disease: aortic stenosis/mitral   |                         |
| stenosis                                        |                         |
| Cardiomyopathy (ischemic, dilated, hypertrophic) |                         |
| Atrial myxoma                                    |                         |
| Cardiac tamponade                               |                         |
| Aortic dissection                               |                         |
| Significant hemorrhage                          |                         |
| Trauma with significant blood loss              |                         |
| Gastrointestinal bleeding                       |                         |
| Tissue rupture: aortic aneurysm, spleen/ovarian  |                         |
| cyst, ectopic pregnancy                         |                         |
| Retroperitoneal hemorrhage                      |                         |
| Pulmonary embolism                              |                         |
| Saddle embolus resulting in outflow tract       |                         |
| obstruction or severe hypoxia                   |                         |

was observed in terms of mean age, number of pre-
disposing factors during exercise, number of prodromal
symptoms and number of Standard ECG abnormalities. The Hypertrophic cardiomyopathy and Cardiac arrhythmia had maximum and minimum values of BNP, respectively (2873.88 ± 4378.15 pg/mL and 46.83 ± 25.63 pg/mL). Other aspects of these studies are presented in Table 2.

**DIAGNOSTIC VALUE OF BNP IN ADULTS WITH SYNCOPE**

In the electronic search strategy, six studies were identified in which the inclusion criterion was adult syncope. Summaries of these studies are shown in Table 2. A significant difference was found between the mean ages in cardiac syncope compared to non-cardiac syncope in four studies. In the cardiac syncope groups, age was higher than in the non-cardiac syncope ones, and the cause of this relationship was unclear. The results of these studies showed that measuring the BNP level in EDs was very helpful for diagnosis of the individuals with cardiac syncope, and decreased the chance of mortality due to cardiac syncope by using guidelines or rules. Tanimoto K et al. studied BNP for separating cardiac and non-cardiac syncope, and considered the cut-off value of 40 pg/ml for isolating cardiac and non-cardiac syncope with 82% sensitivity and 92% specificity for identification of cardiac syncope. The authors of this study concluded that a significant relationship was found in terms of BNP level between the cardiac group (118 ± 42 pg/ml) and those in the other three groups (Reflex-mediated, Neurologic, and Unknown). Pfister et al. showed that the assessment of NT-pro-BNP was helpful in differentiating cardiac from non-cardiac syncope. A significant difference was observed in BNP level for cardiac group compared to the non-cardiac one (514 pg/ml vs. 182 pg/ml, P-value <0.05). The authors of this study also concluded that the NT-pro-BNP had a high sensitivity and a high negative predictive value for the cardiac cause in patients with syncope and was a better predictor than clinical and ECG features.

**CONCLUSION**

We concluded that a biochemical marker such as BNP and other forms of this marker was very helpful in separating and diagnosing cardiac syncope patients and predicting their mortality. This marker, as well as other ones, seem to be very helpful in emergency departments. The accuracy and precision of diagnosing and predicting prognosis of cardiac syncope with
Table 2: Characteristics of studies that evaluated BNP level in syncope patients

| Main outcome | Measurement of brain natriuretic peptide concentrations may help confirm cardiac causes of syncope, and merits consideration for incorporation into the algorithm used to Diagnose syncope. | NT-pro-BNP assessment was helpful in differentiating cardiac from non-cardiac syncope. | NT-pro-BNP was a strong and independent diagnostic and prognostic marker and addition to conventional criteria of history and examination improved the discriminatory performance in patients hospitalized for syncope. | BNP may have a role in the risk assessment of syncope patient's in The ED. A BNP cut off of >100 pg/ml has a reasonable sensitivity for serious outcome, while a cut off of >1000 pg/ml has an excellent positive predictive value and specificity. | Demonstrated that BNP levels are dynamic around an episode of syncope, rising from baseline to a peak between 18 h and 1 week after an episode in many patients. Therasons for this are not clear. | Measuring BNP and adding ROSE rule to the standard evaluation of syncope can sufficiently predict short-term serious outcomes for patients presenting to ED with syncope. |
|-------------|---------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|
| specificity | 92% | 93.8% | 51.8% | If BNP>100 pg/ml: 69.8% and if BNP>1000 pg/ml:100% | - | - |
| sensitivity | 82% | 90% | 89.7% | If BNP>100 pg/ml: 66.7% and if BNP>1000 pg/ml:33.3% | - | - |
| Cardiac syncope population | 61 | 20 | 78 | - | 5 | - |
| Cut-off value | 40 pg/ml | 164 pg/ml | 156 pg/ml | >100 pg/ml and >1000 pg/ml | - | 250 pg/ml |
| Patient population | 118 | 61 | 161 | 99 | 31 | 41 |
| Study type | Retrospective | Cross-section | Prospective | prospective | prospective | prospective |
| Author/year | Tanimoto (2002) | Pfister (2004) | Pfister (2012) | Reed (2007) | Reed (2010) | Isbitan (2013) |
Rules were increased. There are few studies on syncope in children, and more studies need to be conducted to clarify the causal relationship.

RECOMMENDATIONS AND FUTURE STUDIES

According to some of the recommendations in previous studies, more research is needed to be conducted to clarify this relationship and the variables that might play the role of confounders in a causal inference. More studies are required on children because there is some controversy in this relationship. And finally, we suggest to study syncope patients with large sample sizes and randomized control trial studies to ensure that this marker is helpful in recognizing and predicting the prognosis of the disease.

ABBREVIATIONS

AMS: autonomic-mediated reflex syncope  
BNP: Brain Natriuretic Peptides  
ECG: electrocardiography  
ED: Emergency Department  
EGSYS: Evaluation of Guidelines in Syncope Study  
ESC: European Society of Cardiology  
MI: myocardial infarction  
NT-proBNP: N-Terminal pro–brain natriuretic peptide  
OESIL: Osservatorio Epidemiologico sulla Sincope nel Lazio  
Rose: risk stratification of syncope in the emergency department  
SFSR: San Francisco Syncope Rule

COMPETING INTERESTS

The authors report no conflicts of interest in this work.

AUTHORS’ CONTRIBUTIONS

Hamideh Feiz Disfani proposed and designed the study, Mostafa Kamani collected the Data and managing manuscripts, Kazem Rahmani contributed in writing and approving the study.

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