



## Summary Review: Elevated BNP levels in ME/CFS associate with cardiac dysfunction

By Charlotte Stephens, 14<sup>th</sup> February 2018.

A recent study from a research group at [Newcastle University](#) has found that patients with ME/CFS have significantly higher levels of a hormone called BNP in their blood and that this also correlated with significantly lower cardiac volumes.

Structural and functional cardiac abnormalities have been reported in ME/CFS before and MRI studies have suggested subclinical cardiomyopathy in some.

Finding a cause for the cardiac abnormalities and raised BNP levels seen in patients could help in the discovery of the physiological mechanisms behind the disease and could also help to direct treatment routes.

### Overview of the study

The study aimed to look at BNP levels and how these associate with the cardiac abnormalities recently identified in ME/CFS.

Cardiac magnetic resonance (MR) examinations and BNP measurements were performed on 42 patients with ME/CFS (meeting the Fukuda criteria) and 10 sedentary controls, all with an average age of 46.

BNP levels were found to be significantly *higher* in the ME/CFS cohort compared with controls. The authors also found that those with higher BNP levels had significantly *lower cardiac volumes*.

There were no relationships between fatigue severity, length of disease and BNP levels, suggesting that the findings are unlikely to be related to deconditioning.

‘This study confirms an association between reduced cardiac volumes and BNP in CFS. Lack of relationship between length of disease suggests that findings are not secondary to deconditioning. Further studies are needed to explore the utility of BNP to act as a stratification paradigm in CFS that directs targeted treatments.’

### What is BNP (Brain Natriuretic Peptide)?

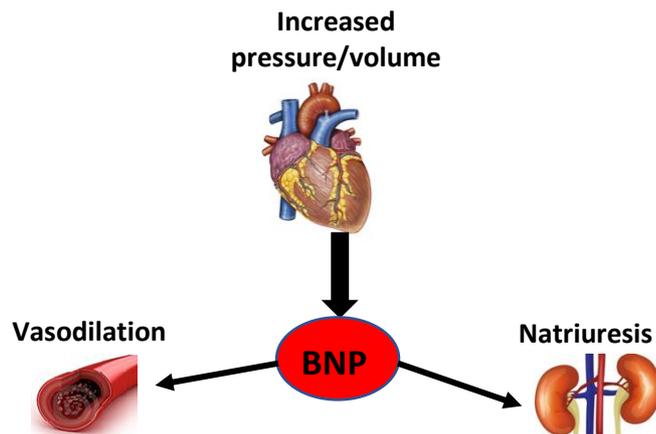
Despite its name, Brain Natriuretic Peptide (BNP) is a hormone secreted by the heart in response to stretching caused by increased ventricular blood volume.

When BNP is released, its actions include:

- decreasing systemic vascular resistance (making the veins throughout the body dilate/become wider),
- decreasing central venous pressure (the amount of blood returning to the heart), and,
- increasing natriuresis (excretion of sodium in the urine).

The overall effects of BNP are lowered blood pressure and decreased cardiac output (volume of blood the heart is pumping out).

It can also cause a reduction in renal sodium reabsorption (Kidneys taking up salt), resulting in decreased blood volume (Felker *et al.*, 2006).



BNP is measured by a routine blood test, often used to diagnose and monitor heart failure. The test is quite sensitive – able to spot heart failure more than 80% of the time. BNP levels tend to increase as heart failure gets worse, however, levels also increase with age (Felker *et al.*, 2006).

High levels of BNP are also seen in other conditions (see table below), such as kidney disease (Austin *et al.*, 2006). Perhaps counterintuitively, lower levels of BNP are often seen in obese patients (Wang *et al.*, 2004).

Causes of elevated BNP levels	
Cardiac	Non-Cardiac
Heart Failure	Acute/chronic Pulmonary embolism
Diastolic Dysfunction	Pulmonary hypertension
Acute Coronary Syndrome	Sepsis
Hypertension with left ventricular hypertrophy	Hyperthyroidism
Atrial Fibrillation	Acute/Chronic Kidney Disease
Valvular heart disease	Age>70
Tachycardia	Diabetes

The normal reference range for BNP levels for 46-year olds (the mean age of the participants in this study) is 10-140pg/ml. Levels above 400pg/ml are consistent with congestive heart failure in under 50-year olds (Mangla, 2014).

BNP levels alone cannot be used for a definitive diagnosis of heart failure, there must also be other investigations (such as ECGs, echocardiogram, renal function and electrolyte tests, lipid profiles), along with a careful review of the patient's history and symptom profile (NHS).

**The study:**

Elevated brain natriuretic peptide levels in chronic fatigue syndrome associate with cardiac dysfunction: [a case control study](#)

*Authors*

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*Recruitment*

Participants were only included if they had no comorbidity, normal renal blood tests (kidney function) and a normal BMI. They were excluded if they had a history of a major depressive episode.

The two groups consisted of 42 ME/CFS patients and 10 sedentary controls. A sample size of 10 for the controls is very small, it would have been better to match this to the number of participants in the main group as the control results may not give an accurate picture of the average levels of BNP in that cohort.

On the positive side, the use of sedentary controls was good as it helps to rule out 'deconditioning' as an explanation. However, this control group were not recruited by fatigue severity or the presence or absence of other symptoms; meaning they could have had other underlying conditions which may have influenced the results.

The average length of diagnosis for the ME/CFS patients was 13.8 years, which is quite long. It would be interesting to see if patients who had been ill for less would produce different results. This also prompts the question; are high BNP levels a cause or *consequence* of ME/CFS?

Fatigue impact in the ME/CFS group was assessed using the Fatigue Impact Scale. The FIS measures the impact of fatigue on cognitive, physical and psychosocial function. It is considered a widely used, robust and validated tool for patients with a wide range of chronic illnesses, including ME/CFS (D'Souza, 2016).

*Methods*

Plasma (from the blood) BNP levels were taken and cardiac imaging was carried out in the 42 ME/CFS patients and 10 controls.

The measurement of BNP levels was carried out by a researcher who was blinded, meaning they didn't know which group each sample belonged to, eliminating the possibility of biased results.

A BNP level threshold was established before the study began, which is good because that means that they didn't reduce or increase this to make their results more significant.

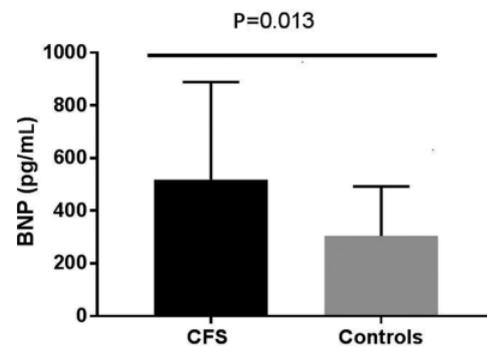
A BNP value above 400pg/ml was considered consistent with moderate to severe cardiac disease and this range matches up with suggested reference ranges in the literature.

### Results

Overall, BNP levels were significantly *higher* in the ME/CFS cohort compared with matched controls (figure 1).

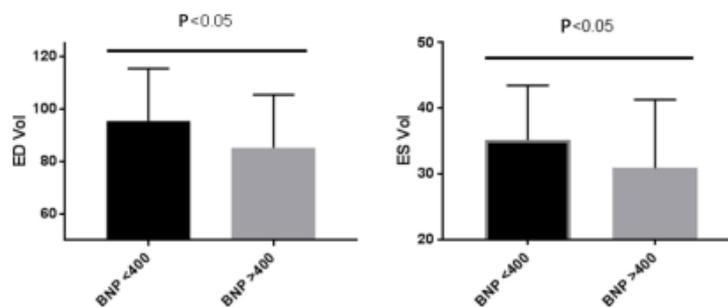
The ME/CFS group was split exactly in half; 21 participants had BNP levels over 400 pg/ml and 21 participants had BNP levels under 400 pg/ml.

Therefore, this test could represent a possible method for identifying and grouping different ME/CFS phenotypes; it could show the proportion of people with ME/CFS that have a degree of cardiac impairment.



**Figure 1** BNP levels were significantly higher in the CFS cohort compared with the matched controls. BNP, brain natriuretic peptide; CFS, chronic fatigue syndrome.

The researchers then compared cardiac volumes between those with high BNP levels and those with low BNP levels. There were significantly *lower cardiac volumes* in those with the higher BNP levels (figure 2).



**Figure 2** When we compared cardiac volumes (ED and ES) between those with high BNP levels (BNP > 400 pg/mL) and low BNP (< 400 pg/mL), there were significantly lower cardiac volumes in those with the higher BNP levels in both ES and ED volumes. BNP, brain natriuretic peptide; CFS, chronic fatigue syndrome; ED, end diastolic; ES, end systolic.

There were no differences in age, fatigue severity or length of history between the two groups (table 1).

There were no relationships between fatigue severity, length of disease and BNP levels. This lack of relationship suggests that the findings are unlikely to be secondary to deconditioning.

In general, the cardiac MR measurements were lower in the CFS group compared with the controls.

Special populations				
Table 1 Cardiac magnetic resonance parameters in CFS compared with matched control values expressed as mean (SD) unless stated				
	Controls	CFS		
		Total	BNP >400	BNP <400
N	10	42	21	21
Age (years)	46 (13)	46 (12)	46 (11)	48 (12)
Females (%)	8 (80%)	32 (76%)	15 (71%)	17 (81%)
Fatigue Impact Scale	N/A	92 (34)	89 (32)	95 (36)
Ejection fraction (%)	62 (5.4)	63 (5.1)	64 (6)	63 (4)
Stroke volume (mL)	60 (10)	57 (13)	54 (12)	60 (13)
ED volume (mL)	96 (14.4)	91 (21.4)	85 (20)	95 (20)
ES phase (ms)	327 (47)	320 (48)	308 (33)	336 (58)
ES volume (mL)	37 (8)	34 (10)	31 (10)	35 (8)
ED wall mass (g)	72 (13)	70 (19)	72 (18)	68 (20)
ED wall+Pap mass (g)	80 (13)	77 (21)	80 (20)	75 (22)

BNP, brain natriuretic peptide; CFS, chronic fatigue syndrome; ED, end diastolic; ES, end systolic.

### Explanations

It is possible that the smaller cardiac volumes seen in those with CFS are causing the elevated BNP levels. However, this is counterintuitive, as BNP is usually a sign of cardiac ventricular wall strain/stretch due to volume overload.

Another explanation is that the higher BNP levels are causing natriuresis (loss of sodium in the urine) and that this is depleting the plasma/blood volumes and leading to the smaller cardiac volumes. Previous studies from the Newcastle university research group and others have shown smaller plasma volumes in ME/CFS, supporting this theory (Newton *et al.*, 2016).

### Conclusion

This study confirms an association between reduced cardiac volumes and BNP levels in ME/CFS. Measurement of BNP could represent a method of identifying the 1/3 of patients with ME/CFS who were found in previous studies to have impaired cardiac function.

This could potentially help in subtyping ME/CFS patients, enabling more targeted treatment. Furthermore, this could facilitate research to identify the characteristics of a cardiac phenotype within the ME/CFS cohort.

The authors comment, “We believe that this kind of stratified approach to identifying specific phenotypes and facilitating targeted interventions is an important step in our understanding of the heterogeneous nature of those with CFS.”

Larger studies are needed to investigate the viability of BNP as a potential phenotype marker and to discover why we are seeing raised BNP and reduced cardiac output in ME/CFS.

However, this is another great piece of research from Prof. Newton’s team at Newcastle University and it will be interesting to see what they will produce next.

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