

THE AFIB REPORT

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The Role of BNP in Atrial Fibrillation

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Brain natriuretic peptide (BNP), a cousin of atrial natriuretic peptide (ANP), is a hormone released from the walls of the ventricles when stretched such as during unusually strenuous activity. It is stored as a prohormone within secretory granules in the ventricles and is secreted as an N-terminal fragment, N-terminal pro-brain natriuretic peptide (nt-pro-BNP), and the smaller active hormone BNP. BNP has effects similar to those of ANP, that is, it decreases sodium reabsorption rate, renin release, and aldosterone release; it also increases vagal (parasympathetic) tone and decreases adrenergic (sympathetic) tone. Because nt-pro-BNP is easier to measure than BNP it is often used as a marker for BNP.

It is well established that BNP and nt-pro-BNP levels are elevated in heart failure and that the degree of elevation is directly proportional to the seriousness of the failure. However, researchers at the Massachusetts General Hospital have reported that lone afibbers also have elevated nt-pro-BNP values even when in sinus rhythm. Their study involved 150 participants with lone atrial fibrillation (LAF) and 75 afib-free controls matched according to age, gender, race, and ethnicity. The majority of participants (81%) were men, the average age at enrolment was 54 years, and the average age at first diagnosis was 45 years. The demographics of the study group thus closely mirrors that of the much larger groups involved in our own LAF surveys and, once again, puts "paid" to the still widely held notion that afib is solely a disease of old age, which it clearly is not. At the time of enrolment 130 afibbers had the paroxysmal variety, while 20 were in permanent AF.

Blood samples were obtained from all participants at enrolment. The researchers found that the median level of nt-pro-BNP was significantly higher among lone afibbers (even when in sinus rhythm) than among controls (166 versus 133 fmol/mL or 48 pg/mL versus 39 pg/mL); they also observed that nt-pro-BNP levels were higher in afibbers with permanent LAF than in those with paroxysmal LAF (55 pg/mL versus 45 pg/mL), and that afibbers with high nt-pro-BNP levels at study entry were more likely to progress to the permanent version than were those with lower levels (57 pg/mL versus 47 pg/mL). There were no significant differences in ANP levels between afibbers and healthy controls, but ANP levels in afibbers who later developed hypertension were significantly higher than in those who did not (1090 versus 470 pg/mL). The researchers speculate that BNP may be involved in sustaining fibrillatory rotors through its potentiating effect on vagal nerve impulses transmitted from the brain.[1]

BNP and Cardioversion

Polish researchers investigated a group of afibbers with hypertension or coronary heart disease and found that BNP levels rise during an afib episode and tend to return to normal following a successful cardioversion. The decline in BNP level was quite significant with a drop from 95 to 28 pg/mL in paroxysmal afibbers and a drop from 75 to 41 pg/mL in persistent afibbers.[2]

In January 2010 Dr. Qi-xian Zeng and colleagues at the Shandong Communication Hospital in Jinan, China confirmed that patients with atrial fibrillation have elevated levels of both BNP and ANP when compared to healthy controls and that these levels decrease significantly after a successful cardioversion. The study included 100 consecutive patients with paroxysmal or persistent AF and 20 healthy controls. About half the patients had coronary heart disease or hypertension, but none had heart failure. Prior to their scheduled cardioversion (chemical using amiodarone or propranolol) all patients had their blood levels of BNP and ANP measured. The cardioversion was initially successful in 60 patients, but 18 experienced recurrence within 24 hours and were, together with the 40 patients not successfully cardioverted, classified as permanent afibbers.

Thus, 24 hours following the cardioversion 42 patients (42%) were in normal sinus rhythm (NSR), while 58 were still in afib. Both BNP and ANP levels decreased significantly immediately following the cardioversion with BNP levels dropping from an average of 162 pg/mL to 124 pg/mL and ANP levels declining from 200 pg/mL to 164 pg/mL. Both BNP and ANP levels were significantly higher in the 16 patients who relapsed into AF within 24 hours of being cardioverted than among those who remained in NSR (BNP of 180 versus 132 pg/mL and ANP of 188 versus 138 pg/mL).

The 42 patients still in NSR after 24 hours were followed for an additional 500 days. At the end of this period, 26 were still in NSR corresponding to an overall 500-day success rate of 26% for the 100 patients originally undergoing cardioversion. The average baseline BNP value for those who remained in NSR for 500 days was 122 pg/mL as compared to 147 pg/mL for the patients who relapsed during the 500 days. Corresponding numbers for ANP were 129 and 153 pg/mL. In comparison, BNP and ANP values for healthy controls were 81 and 100 pg/mL respectively.

The Chinese researchers conclude that baseline BNP and ANP levels can be used to predict the likely outcome of cardioversion and that afibbers with a BNP level of less than 138 pg/mL have a good chance of being successfully converted.[3]

In contrast to the findings of the Chinese researchers, Polish researchers recently reported that, while baseline ANP levels are substantially higher among persistent afibbers than among healthy controls, there was no correlation between the maintenance of sinus rhythm during 30 days after electrical cardioversion and baseline ANP level. They did confirm that ANP levels decreased significantly after a successful cardioversion.[4]

Thus, it would appear that, while a low baseline BNP is likely associated with better cardioversion outcome, a similar correlation with ANP is in doubt.

BNP and Catheter Ablation

Japanese researchers conducted a study involving 66 (54 men) paroxysmal afibbers with no underlying heart disease (lone afibbers). The average age of the study participants was 61 years (range of 51-71 years); they had suffered from afib for 1-7 years, had failed 2-4 class I or class II antiarrhythmic drugs, and experienced episodes that self-converted in less than 24 hours. Their average left atrial diameter was 35 mm (range of 25-45 mm).

The participants all underwent a segmental, ostial PVI targeting all 4 pulmonary veins and were followed up for 3 months after their last ablation. The follow-up included monthly 24-hour Holter recordings and ANP and BNP determination at baseline and 3 months. Three months after the initial PVI, only 53% of the study participants were still in normal sinus rhythm without the use of antiarrhythmic drugs. Nine (14%) of the unsuccessfully ablated patients underwent second and third procedures. Five became afib-free after the second procedure, and two achieved continuous normal sinus rhythm (NSR) after the third procedure.

The Japanese researchers made the following observations:

- At baseline, both ANP and BNP levels were elevated in 14 patients (21%) and in the remaining 52 patients (79%) only BNP level was elevated.
- There were no significant correlations between episode frequency and duration and ANP/BNP levels or left ventricular (LV) ejection fraction.
- There was a significant, but weak correlation between ANP and BNP levels and afib burden (episode frequency x duration) prior to the PVI.
- BNP level was positively correlated with left atrial dimension.
- Patients with elevated ANP levels tended to experience more episodes and a higher afib burden than those with normal levels.
- Both ANP and BNP levels decreased significantly after the first PVI whether ultimately successful or not (ANP from an average of 69 to 25 pg/mL and BNP from 58 to 23 pg/mL).
- In patients with elevated ANP only (at baseline) the ANP concentration returned to normal after the initial PVI.
- Average BNP levels decreased from 55.7 to 12.3 pg/mL in the 35 patients whose first PVI was successful.
- An enlarged left atrium at baseline was associated with a greater chance of the PVI being unsuccessful.
- No association was observed between ANP/BNP level at baseline and the outcome of the PVI.
- The decrease in afib burden post-PVI was proportional to the decrease in BNP, which eventually returned to normal level after a successful PVI.

The researchers conclude that ANP/BNP levels are elevated in paroxysmal afibbers even if they don't have structural heart disease. Both ANP and BNP levels decrease significantly after a PVI and a return to normal of BNP post-ablation is a good indication that the PVI was successful.[5]

The finding that a return to normal of BNP post-ablation is a good indication of the short-term success of a PVI was recently confirmed by a group of German researchers. Their study involved 68 patients (78% men) with symptomatic lone AF – 48 with paroxysmal AF and 20 with persistent AF. BNP values were measured one day before a scheduled PVI procedure (anatomical [CARTO] protocol) and again 3 months following the ablation. At the 3-month follow-up 7-day Holter monitor recordings were also obtained.

Baseline BNP values were significantly higher in patients with persistent AF than in those with paroxysmal (146 pg/mL versus 84 pg/mL). Three months after the PVI 79% of paroxysmal afibbers and 55% of persistent afibbers were still in NSR. Patients whose PVI had been successful had a significantly lower BNP at baseline than did those with a high BNP. For paroxysmal afibbers baseline BNP values associated with successful and unsuccessful PVIs were 69 pg/mL and 144 pg/mL respectively. Corresponding numbers for persistent afibbers were 106 pg/mL and 193 pg/mL. The German researchers conclude that a BNP measurement may be helpful in selecting patients most likely to benefit from a PVI procedure.[6]

BNP and Risk of AF

In November 2009 researchers at the University of Washington reported that BNP is the strongest known predictor of the risk of developing atrial fibrillation. Their study included 5445 participants in the Cardiovascular Health Study who were enrolled between 1990 and 1993 and, at that time, underwent a thorough clinical evaluation. The baseline examination included a standardized questionnaire assessing a variety of risk factors, including smoking, alcohol intake, history of diabetes mellitus, stroke, coronary heart disease, heart failure, self-reported health status, medication use, and history of prior cardiovascular disease.

The physical examination included measurements of height, weight, and blood pressure as well as a resting ECG and echocardiogram. Numerous blood tests were also performed including determination of C-reactive protein, cholesterol, fasting glucose and BNP. Participants were contacted every 6 months for follow-up over the next 10 years.

At baseline, 148 participants were found to have AF and another 1126 developed AF over the next 10 years giving a total prevalence of AF of 25% at the 10-year mark. The following variables, as expected, were predictive of future AF development:

Advanced age	History of heart failure
Male gender	Hypertension
Black race	Elevated total cholesterol
Elevated body mass index	Elevated C-reactive protein
Tallness	Elevated creatinine
Diabetes mellitus	Elevated glucose
History of coronary heart disease	Enlarged left atrium

In addition, baseline nt-pro-BNP was strongly correlated with both prevalence of AF at baseline and the development of AF during follow-up. Study participants whose baseline BNP level was greater than 290 pg/mL (5th quintile) had an AF prevalence of 11.75% at baseline as compared to those with a baseline BNP of less than 50 pg/mL (1st quintile) among whom the prevalence was only 0.1%, or a 128:1 prevalence ratio. After adjusting for possible confounding variables, the prevalence ratio rose to 147:1. The strong correlation between BNP and AF was also noted for participants who developed afib during the 10-year follow-up. Here the AF incidence associated with the lowest quintile of baseline BNP was 1.2% as compared to 5.1% in the 5th quintile. After adjusting for possible confounders, the researchers conclude that high BNP levels are associated with a 4-fold increase in the risk of developing AF during the 10-year following initial determination of BNP.[7]

As part of Boston University's Framingham Study, Emelia Benjamin and colleagues just recently confirmed that BNP level predicts the development of AF. Their study included 3120 afib-free participants (average age of 58 years, 54% women) who had an extensive clinical evaluation in 1995-1998 and were followed for an average (median) of 10 years. Blood samples were taken at baseline to measure the level of 10 biomarkers that might be important in predicting the later development of AF. The 10 biomarkers were:

C-reactive protein	Aldosterone
Fibrinogen	Homocysteine
BNP	D-dimer
N-ANP	Plasminogen activator inhibitor type 1
Renin	Urinary albumin-to-creatinine ratio

At the end of the 10-year follow-up, 209 study participants (6.7%) had been diagnosed with AF. In addition to confirming the conventional risk factors for AF (advanced age, male sex, hypertension, elevated body mass index, and cardiovascular disease) the Framingham group also noted that

participants who developed AF had significantly higher baseline blood levels of C-reactive protein, BNP and ANP. There was also a trend for low renin levels to be associated with an increased risk of AF ($p=0.08$). Upon adjusting for possible confounding variables the researchers concluded that an elevated BNP level is a powerful predictor of future AF and significantly improves risk prediction beyond a risk score based on hitherto known clinical risk factors.[8]

Conclusion

Brain natriuretic peptide (BNP) is an important hormone released from the walls of the ventricles and, to some extent, the atria when stretched. It is well established that a high BNP level is associated with heart failure, but it is now also clear that elevated BNP levels are closely associated with atrial fibrillation including lone AF. BNP levels are higher in afibbers than in non-afibbers and those in permanent afibbers are higher than those in paroxysmal afibbers. A high BNP level is associated with a lower probability that cardioversion will be successful and also predicts a poor outcome of catheter ablation. There is also evidence that an elevated BNP level in paroxysmal afibbers is associated with a quicker progression to the permanent state. Finally, some very recent research provides convincing evidence that an elevated BNP level is strongly associated with the risk of developing AF over a 10-year period following the baseline BNP determination. It is to be hoped that electrophysiologists will soon include a measurement of BNP or nt-pro-BNP in their initial evaluation of all afibbers and their relatives.

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