Original Research Article

Are Brain Natriuretic Peptide Levels Related to Flow through Autologous Aterio-Venous Fistulae for Chronic Haemodialysis?

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Abstract

Formation of arterio-venous-fistulae (AVF) may exacerbate cardiac failure in the ever increasing, elderly population on haemodialysis. Brain Natriuretic Peptide (BNP) may prove a useful marker of cardiac failure in this population. We aimed to determine effect of creation of an AVF and flow in AVF on BNP levels. Ten patients undergoing primary formation of an upper limb autologous AVF (pre-dialysis), were recruited. Serum BNP (pg/ml) and flow in AVF (cm^3/s) were documented pre-operatively, and then 2, 6 and 12 weeks post-operatively. The relationship between flow and BNP levels was assessed. Ten patients (6 male), mean age of 66yrs were recruited. Five patients had a radio-cephalic and 5 had a brachio-cephalic AVF formed. There was no correlation between BNP levels and flow within the AVF (r=0.34, *p*=0.28) at any time point. There was a general trend towards increased flow in the AVF over time, with only the change between flow at 2-weeks and 3-months postoperatively reaching significance, *p*=0.043. There was a general trend for BNP to fall over time in the postoperative period, with no significant change between the postoperative sampling time points. BNP levels do not correlate with flow across an AVF.

Keywords: Arterio-venous fistula; brain natriuretic peptide; haemodialysis

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Introduction

Creation of an arteriovenous fistula (AVF) for chronic haemodialysis therapy provides convenient access to the circulation in patients with end-stage renal disease (1). High output cardiac failure is a recognized complication of AVF (2-4). The reported incidence of this complication has been low, with less than 1% of patients requiring ligation of an AV fistula for this. However, the population of patients undergoing renal replacement therapy has changed dramatically in recent years, and more than half of all patients starting haemodialysis are greater than 60 years of age (5). Consequently, a significant larger proportion of patients present with cardiac dysfunction at the time of requiring dialysis. Furthermore, in this population of patients, symptoms of cardiac failure could be pre-existing and may be in part similar to the symptoms of renal failure. Therefore, insidious onset of these symptoms may not raise the same degree of alarm in clinicians.

B-type natriuretic peptide (BNP) is one of four cardiac natriuretic peptides. It is synthesized as pre-proBNP

mainly in the ventricular endocardium in response to ventricular stretch and pressure overload. The levels of BNP strongly correlate with left ventricular (LV) chamber size and LV end diastolic pressures (6). Pre-proBNP is enzymatically cleaved to form proBNP and is subsequently released in the form of hormonally active BNP and inactive N-terminal pro-BNP (NT-proBNP).

The major role of natriuretic peptides is to induce natriuresis through their action on renal haemodynamics and tubular function. Other functions of natriuretic peptides include vasodilation, decrease in sympathetic outflow as well as inhibition of vasopressin and aldosterone release (7-9). The net result of natriuretic peptide release is reduction in cardiac preload. BNP is a very powerful tool in the diagnosis of heart failure (10-12).

Serum BNP is known to be elevated in patients with renal failure by several orders of magnitude [(7)], this has been considered to limit its value as a diagnostic tool in the management of such patients if cardiac failure is suspected. In addition to this, renal dialysis has a significant impact on the serum BNP levels with a significant reduction in levels following haemodialysis. However, there is accumulating evidence to suggest that serum BNP levels have a prognostic value in patients with end stage renal failure (11, 13-16). Chronic volume overload in end stage renal disease predisposes patients to left ventricular hypertrophy which may be exacerbated by formation of an AV fistula.

We aimed to assess serum BNP levels pre and post formation of an AVF in order to determine the feasibility of utilizing serum BNP for predicting cardiac outcome following AV fistula formation. Furthermore, we aimed to determine the blood flow across the newly formed fistula to see if this impacts on BNP levels. If a change in serum BNP is detected following the formation of an AV fistula we aim to follow up with a study to assess the role of BNP as a predictor of medium term survival in patients following the formation of AV fistula and investigate serial changes in cardiac performance before and after the formation of AV fistula.

Materials and Methods

Ethical approval was granted from Tayside Research Ethics Committee. Ten patients were prospectively recruited prior to the formation of their AV fistula, following informed consent. All ten patients were referred to a vascular surgeon with a specialist interest in renal access, for pre-emptive primary formation of an autologous AVF (i.e. none of the patients were on dialysis prior to the formation of the AV) for chronic haemodialysis as advised in recent guidelines (17, 18). All patients underwent duplex imaging of the upper limb veins and arteries. The unit's preference was to form distal AVF prior to central AVF, non dominant over dominant limb, depending on time requirement for commencement of dialysis or presence of central venous dialysis line, preferably using vein >3mm and artery greater > 2mm with biphasic flow. The veins were assessed for central stenosis/occlusion, with venography performed in situations of doubt. AVF formation was performed under either local anaesthesia or regional block with or without sedation. The anastomosis was fashioned in an end to side fashion using either 6/0 or 7/0 prolene depending on calibre of vessels.

Information collected included: age; sex; operation; American Society of Anesthesiologists score (ASA); pre-operative ischemic heart disease (as defined by Lee *et al* (19); congestive heart failure (as defined by Swedberg *et al* (20)); New York Heart Association score (NYHA); diabetes mellitus; cerebro-vascular disease; Chronic Obstructive Pulmonary Disease (COPD; operative duration; pre-operative serum creatine (µmol/l); pre-operative estimated glomerular filtration rate (eGFR). All patients were followed up for a minimum of one year or until death.

Patient inclusion criteria include: Age > 18 years; Age < 85 years.

Patient exclusion criteria include: Pre-existing AV fistula; Already established on dialysis; Diagnosis of severe cardiac failure; Life expectancy < 12 months; Unable to perform 6-minute walking performance test due to physical disability

BNP Analysis

Venous blood was sampled for BNP on the same day, but prior to surgery and then at regular intervals in the post-operative period (2 weeks, 6 weeks, 3 months and 6 months post-operative). The sample was collected in spray coated, K_2-EDTA tubes (Becton Dickinson, BD Vacutainer®, Oxford, United Kingdom) and immediately centrifuged and stored at -70°C until analysis as a batch at the end of patient recruitment. BNP levels were measured by a standard commercially available radioimmunoassay kit (Peninsula Laboratories, Merseyside, UK), by an experienced biochemist blinded to patient outcome.

Fistula Assessment

Duplex surveillance of the AVF was performed at regular intervals in the peri-operative period (2 weeks, 6 weeks, 3 months and 6 months post-operative), after 20 minutes rest to exclude exertional effects, documenting time averaged velocity and diameter in the venous limb of the AVF and AVF patency. Flow (cm^3/s) within the AVF was calculated using the following formula: time averaged velocity in venous limb x (venous diameter/2)^2 X π at same site. The average of three separate recording was taken. Clinical evaluation was assessed in terms of 6-minute walking test, according to the guidelines of the American Thoracic Society (21) and NYHA status at the same pre and post-operative follow up appointments as BNP sampling.

Statistics

Test of association used the ANOVA and Chi-squared statistic. Spearman rank correlation was performed to assess relationship between flow in AVF and serum BNP, with paired sample T test performed to compare data before and after AVF formation. Analysis was performed on the Statistical Package for Social Sciences (Statistical Package for the Social Sciences V17.1, Chicago, USA). A p-value of less than 0.05 denotes significance.

Results

Ten patients (6 male) undergoing primary formation of AVF for chronic haemodialysis were recruited following informed consent, with a mean age of 66 years (range 48-82), with patient characteristics displayed in Table 1. Five of the AVF were autologous radio-cephalic fistulae, the remaining five were autologous brachio-cephalic fistulae. Median operative time for RC AVF was 90 minutes (range 35 -120), and for BC AVF 60 minutes (range 45 -75), p=0.14. One patient died five days post formation of her AVF of a myocardial infarction, having the second highest pre-operative BNP (393 pg/ml). One fistula occluded during the follow up period on day 63 post formation (brachio-cephalic fistula). All other fistulae matured successfully. Irrespective of timing of BNP sampling and assessment of AVF flow, there was no correlation between BNP levels and flow within the AVF (r=0.34, p=0.28), figure 1. On comparing change in mean flow over time (Figure 2), there was a general trend towards increased flow in the AVF over time, with only change between flow at 2 weeks and 3 months postoperative reaching significance, p=0.043. On comparing change in mean serum BNP over time (Figure 3), there was a general trend for serum BNP to fall over time in the postoperative period, with no significant change between the postoperative sampling time points. Pre-operative median distance walked during the 6 minute walking test was 180m. Following AVF formation, performance on this test deteriorated gradually over a 3 month period with median difference in distance walked reduced by 5m, 10m and 24m at 2, 6 and 12 weeks respectively, although this did not reach

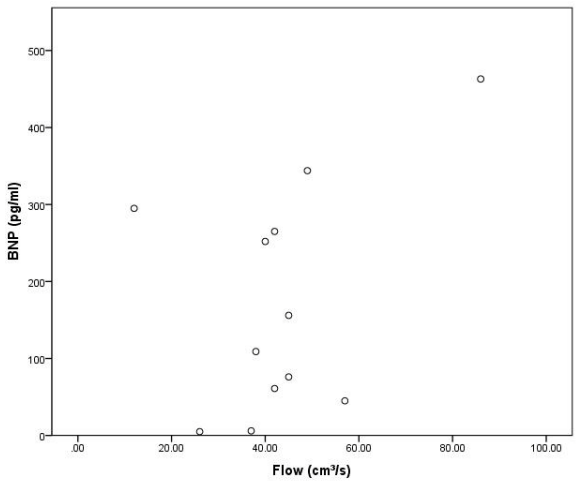

Figure 1: Correlation between serum BNP and flow

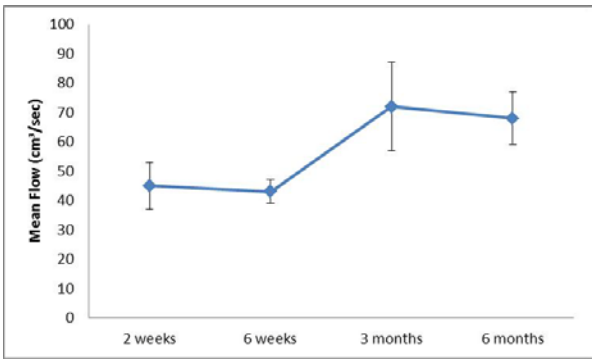

Figure 2: Mean change in flow (cm^3/sec) over time (+/- S.E.M.)

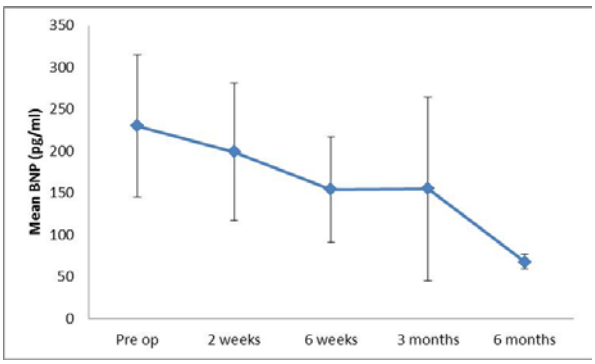

Figure 3: Mean change in serum BNP (pg/ml) over time (+/- S.E.M.)

significance. Pre-operatively patients fell equally into Class 1 and 2 of NYHA Classification (50:50). There was no noticeable change in NYHA class during the follow up period despite there being a downward trend in the 6 min walk test.

Discussion

BNP has been shown to be a marker of left ventricular dysfunction in patients established on long term dialysis therapy (22, 23), and an effective marker of left ventricular dysfunction and predictive of congestive cardiac failure in patients with known chronic renal impairment not yet established on dialysis (1). BNP levels do not undergo marked fluctuation in patients on established dialysis compared with other natriuretic peptides, and best correlated with left ventricular function rather than volume status (24). In a study on 164 patients on established haemodialysis, Naganuma et al determined that BNP levels taken post haemodialysis were associated with volume overload, even more so in those patients with cardiovascular disease (14). With regards to the two main forms of BNP, the hormonally active BNP and the inactive NT-proBNP, despite BNP and NT-proBNP levels being inversely proportional to GFR, BNP may be a better marker of cardiac function in those with renal impairment compared to NT-proBNP, as NT-proBNP clearance is reduced in correlation with decreased eGFR (25). In contrast to this, Anwaruddin and colleagues (26) in an analysis of nearly 600 patients in the PRIDE study, found that although NT-proBNP was inversely related to eGFR, this relationship was not purely due to reduced clearance but more likely reflecting underlying cardiac disease and increased plasma volume. In a small study of patients with chronic kidney disease stage 5 on stable chronic haemodialysis, David and co-workers showed that NT-proBNP levels sampled post dialysis, were predictive of volume overload, even in those patients with normal cardiac function (based on echocardiography and indices of hydration status), and as such was a marker of left ventricular dysfunction in patients on stable haemodialysis (27).

Few studies have looked at the effect of AVF formation on serum BNP levels, let alone correlated these levels with flow through the AVF. Ori et al, investigating a group of 10 patients pre and two weeks post formation of AVF, discovered that in the short term the formation of an AVF leads to fluid overload which is off set by reduced peripheral vascular resistance (28). Jin et al reported on a case of recurrent high output cardiac failure with preserved cardiac ejection fraction in a patient with an aneurysmal AVF and markedly raised BNP (29). In this case, flow through the AVF was calculated at over 25% of the cardiac output (29). In our **study**, we noted the formation of an AVF resulted in a non-significant decrease in BNP over the post-operative period, whilst flow rates in the AVF increased over time, with no significant correlation between flow in the AVF and serum BNP levels. In contrast, two small studies assessing the effect of AVF formation on cardiac function (5, 30), showed an increase in BNP in the post-operative period. Malik et al, studying the effects of AVF creation (6 weeks and 6 months post AVF formation) in 35 patients already established on dialysis via a central venous catheter, found the creation of an AVF with ‘normal’ flow (<1500ml/min, >300ml/min) lead to a significant increase in BNP, which was related to flow across the AVF only at the 6 week time point. Similar flow rates were found between this study and ours. They concluded that the increase of BNP probably mirrors worsening of clinically silent heart failure. Iwashima and colleagues studied the effects of AVF formation on ANP, BNP and cardiac function (as determined by echocardiography) in the first two weeks post AVF formation in 16 patients not established on dialysis (5). They found that the formation of an AVF for chronic haemodialysis had significant effects on both cardiac systolic and diastolic function. Serum BNP levels increased in the post-operative period, related to left ventricular dysfunction (5).

A limitation of our study, as well as others, is the small number of patients included and the subsequent death of one patient and occlusion of another AVF may have had an adverse impact. Another possible factor that may bear influence on BNP levels, are prescribed cardiac medications used in the treatment of cardiac failure. Irrespective of this, we would expect that in those patients with documented cardiac failure requiring medications, the formation of an AVF would have an adverse effect on the cardiac function and subsequently lead to an increased BNP level. We plan to undertake further evaluation of the patients in our study once they have been established and are stable on long term haemodialysis, to assess the impact of commencement of haemodialysis on flow and BNP levels.

The creation of autologous arterio-venous fistulae in patients not established on haemodialysis, did not lead to increased serum BNP levels. Furthermore flow across the arterio-venous fistula did not correlate with serum BNP levels.

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Conflict of Interest

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