

B-TYPE NATRIURETIC PEPTIDE IN LYMPHEDEMA

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ABSTRACT

Lymphedema often responds to compression therapy which can also cause undesirable cardiac overload if heart failure coexists. We hypothesized that the biomarker B-type natriuretic peptide (BNP) can be used to screen lymphedema patients for undetected cardiac dysfunction. We studied unselected consecutive patients with lymphedema to determine their BNP status and compared these data with those obtained from healthy subjects without known cardiovascular diseases. Out of a total of 305 subjects with lymphedema screened, 102 (33%) consented to take part in this study. The majority (87%) were female with a mean age of 60.5 ± 13.2 (SD) years, and 47% had just lower limb swelling. The groups were equally divided between cancer and non-cancer related causes. There were 45 females and 4 males under 60 years old, and 44 female and 9 male patients over 60 years old. Median (IQR) BNP (ng/L) were as follows: <60 years females = 17.9 (15.2) (median [RR: 3 - 64] and males = 12.4 (14.7) [RR: 0.2 - 44], >60 years females = 35.8 (57.9) [RR: 2 -247]) and males = 47.2 (44.1) [RR: 2 - 238]. For this population, the BNP concentration 100 ng/L was adopted as the value to exclude heart failure. Using this definition, 7 lymphedema subjects had BNP concentrations of 120 (19.8) ng/L, and all were found to have cardiac abnormalities on echocardiography. This study demonstrated that 93% of unselected subjects with

lymphedema had BNP concentrations that exclude a diagnosis of heart failure. Those subjects with elevated BNP were found on subsequent echocardiography to have cardiac abnormalities. The use of a BNP assay is of potential value in screening patients who are more likely to have cardiac failure. Indicative factors include bilateral leg swelling, over the age of 50 years, breathlessness, where there is no known cause for the swelling. A BNP assay using a BNP concentration threshold of 100 ng/L (29 pmol/L) will identify those patients who require more detailed investigations.

Keywords: Lymphedema, B-type natriuretic peptide (BNP), cardiac edema

Lymphedema is a form of chronic edema that is the result of lymphatic dysfunction. It is a chronic and progressive condition that is usually treated using non-invasive physical therapies, and long-term improvement can be achieved using a combination of physical therapies which are undertaken on a daily basis as part of a self-treatment program with compression therapy in the form of bandages or garments enhancing the pumping force of skeletal muscle and preventing re-accumulation of lymph. In cases of chronic heart failure, compression may have a detrimental effect by forcing extravascular fluid into the intravascular compartments and increasing the risks of raised cardiac preload and afterload. Therefore, preliminary screening is recommended to exclude a

diagnosis of chronic heart failure prior to the commencement of treatment. However, conventional cardiological investigations such as echocardiography would be too costly to use as a general screening tool.

There is a growing body of evidence to support the utilization of the biomarker, B-type Natriuretic Peptides (BNP), both as a prognostic and diagnostic indicator of chronic heart failure (1). This biomarker has been incorporated in a recent British national guidance, which recommends the use of BNP to aid the diagnosis of heart failure (2). Elevated concentrations of BNP (and NT-proBNP) have also been shown to be proportional to the extent of cardiac dysfunction (3,4).

To date, there is no literature on the effect of chronic lymphedema on the circulating concentrations of BNP. Moreover, lower limb swelling may make a clinical diagnosis of congestive heart failure more difficult. One set of guidelines on lymphedema has recommended the use of BNP in breathless subjects (5). A systematic review of heart failure management has exposed weaknesses of utilizing clinical features to diagnose heart failure and shown the benefit of BNP over other diagnostic investigations such as electrocardiography and chest radiography (6).

We studied a group of unselected subjects with lymphedema to determine their BNP status. The objective was to provide evidence to clarify the potential diagnostic value of BNP in individuals with lymphedema. We tested the hypothesis that BNP is useful to screen lymphedema patients for undetected cardiac dysfunction.

METHODS

Consecutive patients with lymphedema were recruited from a Hospital Trust based specialist lymphedema clinic. Inclusion criteria included age between 18 and 90 years with visible limb swelling, and established lymphedema defined by one or more of the

following criteria: unilateral limb swelling, >10% excess volume, digit swelling, positive Stemmers sign, shape distortion as measured by a distal proximal ratio >1.0, or enhanced skin folds. Exclusion criteria were chronic respiratory disease, liver cirrhosis with ascites, acute infection and/or cellulitis or suspected advanced cancer.

Control data were obtained by collecting redundant blood samples [EDTA samples; n=300 (males 150, females 150)] in a routine laboratory from subjects with no apparent suggestion of cardiovascular disease. Details of age, gender, clinical details and location were used to ensure a comparable group from which to establish a reference range. Plasma samples were anonymized after collection of demographics (age & gender) prior to analysis (7).

Protocol for Lymphedema Patients

All eligible patients received information and an invitation to participate with their first appointment letter. Recruitment occurred between February 16, 2006, and November 10, 2007. All who consented underwent a BNP assay and agreed to subsequent echocardiography in the case of an elevated BNP, and blood samples were obtained. Ethical approval was obtained from the Leeds West Research Ethics Committee, and signed consent was obtained from all lymphedema participants.

Laboratory Analysis

Blood samples were collected in EDTA containing tubes. Plasma was separated and stored at -20°C prior to analysis in a single batch. BNP was measured with an immunometric assay on Advia Centaur using Centaur reagents according to the manufacturer's protocols (Siemens Healthcare Diagnostics, Strawberry Hill, Newbury, UK). The within batch coefficient of variation was <2.4% at 44, 459, and 1652 ng/L.

TABLE 1
BNP Test Results in Lymphedema Patients Compared with Control Subjects

	BNP median (ng/L)	Range (ng/L)	95% reference intervals (ng/L)
Females <60 (n=45)	17.9	2.6 - 120	7.7 - 157
Females >60 (n=44)	35.8	4.5 - 204	5.5 - 605
Males <60 (n=4)	12.4	6.9 - 32	0.4 - 107
Males >60 (n=9)	47.2	10.8 - 133	5 - 583

Number of subjects with lymphedema is in parentheses. Each of the 4 control groups consisted of 75 subjects.

Statistics

Descriptive statistics were used to analyse the range of values within and between both groups using the Analyse-it add-in package (version 2.10) for Microsoft Excel (Analyse-it, Leeds, UK. www.analyse-it.com).

RESULTS

A total of 305 subjects with lymphedema were approached, and 102 (33%) agreed and gave informed consent to participate. There were 89 (87.25%) females and 13 (12.75%) males. The mean age was 60.5 ± 13.2 (SD) years with a range of 29 to 89 years.

Of the 102 subjects, 83 (81%) had a secondary lymphedema. 48 had lower limb edema which in 23 patients was a bilateral swelling. 54 had upper limb lymphedema and none had combined upper and lower limb lymphedema. The numbers with a cancer and non-cancer related swelling were relatively equal. The mean duration of swelling prior to referral to the service was 7 years (median duration 19 years, range 3 months to 39 years).

The control data have been divided into four groups by gender and age using a cut-off at 60 years. There were 75 subjects in each of the four groups. Data on BNP measurement in lymphedema subjects and controls are shown in *Table 1*.

Seven lymphedema subjects had elevated BNP concentrations (>100 ng/L, median 120

(19.8) ng/L (see *Table 2*). Of this number, two had breast cancer related lymphedema, three had unilateral leg swelling, and two had bilateral leg swelling. In both the leg swelling categories, one of the participants developed swelling following cancer treatment, and the other was a non-cancer referral. A third participant with unilateral leg swelling had primary lymphedema.

Echocardiography was performed on these subjects, and all of them showed cardiac abnormalities as summarized in *Table 2*.

DISCUSSION

We have shown that 93% patients with uncomplicated chronic lymphedema have normal and low BNP concentrations that exclude heart failure (7). A subgroup of subjects (7%) had marginally elevated concentrations and were referred for echocardiography to clarify cardiac status and diagnose heart failure. These patients did not have heart failure, but were all noted to have cardiac abnormalities. The presence of these cardiac abnormalities was sufficient to account for the elevated BNP concentrations. It is uncertain how these relate to the BNP status as we did not perform echocardiography on the subjects with normal BNP. Since the biomarker is not an indicator specifically for heart failure, raised BNP concentrations are not necessarily indicative of heart failure per se although

TABLE 2
Echocardiographic Findings in Lymphedema Subjects with Elevated BNP

Age (yrs)	Type of swelling	Gender	BNP (ng/L)	Cardiac abnormality
67	Unilateral leg primary lymphedema	F	102	Moderate left ventricular (LV) systolic impairment: mild global hypokinesis which is more marked apically, inferiorly and septally. LV Ejection fraction estimated at ~45%.
72	Unilateral arm cancer-related secondary lymphedema	F	111	Mild mitral regurgitation into a borderline dilated left atrium.
71	Unilateral arm cancer-related secondary lymphedema	F	112	Mild LV hypertrophy. E-A reversal seen in transmitral flow waveform (E/A ratio 0.8) suggestive of diastolic impairment.
49	Unilateral leg cancer-related secondary lymphedema	F	120	Small rim of anterior pericardial effusion (~6mm).
74	Bilateral leg Cancer-related secondary lymphedema	F	125	Mildly impaired LV systolic function. Right heart chambers are dilated. Poor RV free wall contraction. Elevated pulmonary artery pressure (estimated PAP=62mmHg).
81	Bilateral leg non cancer-related secondary lymphedema	M	133	Dilated left atrium. Moderate concentric LV hypertrophy.
84	Unilateral leg non cancer-related secondary lymphedema	F	204	Concentric LV hypertrophy. Dilated left atrium.

the risk of heart failure does increase with increasing BNP concentrations (3,4,8). Further studies might be performed to investigate the relationship between total body water and BNP in these patients to determine the intravascular volume. Our data would confirm that BNP can be used as an initial assessment of individuals with lymphedema to screen for concomitant cardiac abnormalities. Patients with bilateral leg swelling are the group that are more usually associated with an increased

likelihood of heart failure; however, only two with elevated BNP concentrations had lymphedema in both lower limbs. It was not possible to predict which group of patients would be more likely to have elevated BNP based on the nature and site of swelling in our study. The numbers of participants involved in this study may be too small to demonstrate any tendencies among the patient groups, and a larger sample size would help to identify these relationships.

Diagnostic tests are used to predict whether a subject has a disorder. Their accuracy will depend on the incidence of false-positive and false-negative results and the prevalence of the disease in the group examined (9). In the case of BNP, a clinical decision threshold is used to stratify patients into groups who would benefit from echocardiography. Reference intervals are not used in view of the poor specificity of this approach as is illustrated by our evaluation of reference intervals. We have therefore used accepted cut-off values (10) which can be used to exclude heart failure. These data suggest that lymphedema treatment including compression therapy can be introduced in those patients with specificity of >95% using BNP concentration threshold of 100 ng/L (29 pmol/L) using the Centaur BNP assay (9). It should be noted that other analytical methods would use different values; for example, a recent primary care study proposed a value of 40 ng/L (11.6 pmol/L) using the Biosite Triage assay (11).

The differential diagnosis of leg edema is based on its duration, painfulness, medication and presence of systemic disease, known malignancy, or sleep apnea. It is likely that venous insufficiency will be present in some adults over 50 years with leg swelling. However, if the underlying cause is unclear in this age group after physical examination, it may be of use to rule out systemic disease with laboratory and/or radiological investigations. Over recent years, BNP has been widely recognized as a valuable tool to exclude heart failure and is recommended in breathless patients suspected of having heart failure (12).

Compression therapies in the form of garments or bandages are regularly used in the treatment of lymphedema to enhance the effect of skeletal muscle activity and control capillary filtration. The use of a multi-layered bandaging system (known as multi-layer lymphedema bandaging) is a key component of intensive therapy programs and can result in large edema volume reductions (13). On

completion of intensive treatment, bandages are replaced with compression hose which are applied as part of a maintenance or self-management program (14). The type and level of compression is determined by a number of factors including the severity of the lymphedema, medical history and dexterity of the patient. Compression levels range from 14 mm to >49mmHg (5). The effect is to reduce local fluid volume and redistributing blood towards central parts of the body (15). These potential fluid shifts can lead to an increase in the preload of the heart and affect cardiac output by up to 5% (16). In addition, the compressive forces also affect the systemic arterial system, and these can also unduly raise the cardiac afterload (17) which can be detrimental in heart failure as well (2). Before instituting compressive therapy, for lymphedema, it is considered good clinical practice to first exclude the presence of undetected heart failure or occult cardiac dysfunction. The deployment of a BNP measurement is recommended as a screening method in the following cases:

- in patients over 50 years who are breathless
- in bilateral leg swelling where the cause of the chronic edema is unclear
- if heart failure is suspected

The BNP screening method will identify those patients who require more detailed cardiac investigations such as echocardiography. BNP concentrations in excess of 100 ng/L (29 pmol/L) should be referred for further detailed investigation. Such an approach would allow a rational and efficient utilization of cardiac investigations.

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