Biomarkers, 2010; 15(6): 533–537

informa
healthcare

ORIGINAL ARTICLE

Elevation of B-type natriuretic peptide is a sensitive marker of left ventricular diastolic dysfunction in patients with maintenance haemodialysis

Hong Liu, Ying-Zi Zhang, Min Gao, and Bi-Cheng Liu

Institute of Nephrology, Zhong Da Hospital, Southeast University, Nanjing, Jiangsu Province, China

Abstract

Objective: To determine the clinical value of B-type natriuretic peptide (BNP) in diagnosing left ventricular diastolic dysfunction (LVDD) associated with maintenance haemodialysis (MHD) population.

Methods: Plasma BNP was determined in 59 MHD patients with normal ejection fraction. The ratio of early to late annular velocity (E′/A′) was determined by tissue Doppler imaging as a parameter of diastolic function. *Results*: LVDD occurred in 66% of the patients. Receiver-operating characteristic curve analyses identified a cut-off of 353.6 pg ml^{-1} as the one with the highest sensitivity and specificity for detecting LVDD.

Conclusions: Plasma BNP may serve as a potential biomarker in diagnosing LVDD in MHD patients with normal systolic function.

Keywords: *B-type natriuretic peptide; haemodialysis; left ventricular diastolic dysfunction*

Introduction

The number of patients requiring maintenance haemodialysis (MHD) is steadily increasing worldwide (Meguid & Bello 2005). Despite technical and pharmacological improvements achieved over the past years, long-term prognosis of patients undergoing chronic haemodialysis is still quite poor (Pozzoni et al. 2004). Cardiovascular disease is the leading cause of mortality and morbidity in this population, leading to 50% of the deaths (Collins 2003). It is well recognized that patients with end-stage renal disease (ESRD) showed a very high prevalence of left ventricular (LV) hypertrophy (Bossola et al. 2008). Both LV hypertrophy and systolic dysfunction make major contributions to the cardiovascular death (Foley et al. 2000). Recent studies have demonstrated that LV diastolic dysfunction (LVDD) is common in ESRD patients, and ESRD-associated mortality was even higher in those with diastolic rather than systolic dysfunction (Ahmed et al. 2007). However, the clinical diagnosis of diastolic dysfunction with a normal ejection fraction (EF) remains challenging to physicians (Thomas et al. 2002).

B-natriuretic peptide (BNP) is a cardiac neurohormone secreted from the ventricles in response to ventricular volume expansion and pressure overload (Potter et al. 2009). Studies in the general population demonstrated superiority of BNP as a hormonal marker of LV hypertrophy and systolic dysfunction over other natriuretic peptides (de Sa & Chen 2008, Troughton & Richards 2009). Zeng et al. (2006) also showed that BNP had a high sensitivity in diagnosing LV hypertrophy and systolic dysfunction in dialysis patients. BNP levels may also reflect diastolic dysfunction in patients with normal systolic function (Lubien et al. 2002). However, the clinical value of BNP in diagnosing diastolic dysfunction in MHD patients has not been studied previously.

The current study was to investigate the changes of serum BNP level in MHD patients. Specifically, we explored whether the increasing of BNP level could

Address for Correspondence: Bi-Cheng Liu, Institute of Nephrology, Zhong Da Hospital, Southeast University School of Medicine, 87 Dingjiaqiao Road, Nanjing 210009, Jiangsu Province, China. Tel: 0086 25 83285132. Fax: 0086 25 83285132. E-mail: liubc64@yahoo.com.cn

(Received 15 March 2010; revised 11 May 2010; accepted 13 May 2010)

ISSN 1354-750X print/ISSN 1366-5804 online © 2010 Informa UK, Ltd.
DOI: 10.3109/1354750X.2010.493973

serve as a reliable biomarker to detect the LVDD in MHD patients with normal EF.

Materials and methods

Patients

In this cross-sectional study, 59 patients with ESRD undergoing HD were recruited from a single Chinese haemodialysis centre from January 2009 to April 2009. All patients were dialysed using standard dialysis technique with Fresenius machines, polysulfone dialyser membranes and standard bicarbonate-based dialysate.

The inclusion criteria were patients aged over 18 years who were on regular haemodialysis for at least 6 months prior to the study, and with three standard haemodialysis sessions per week. The exclusion criteria were patients with decreased EF (<50%), valvular heart disease (moderate to severe aortic stenosis or mitral stenosis), acute coronary syndrome or history of acute myocardial infarction within 6 months, chronic atrial fibrillation, primary cardiomyopathy and recent (<2 weeks) change for antihypertensive drugs.

The clinical characteristics of the study population are shown in Table 1. The causes of ESRD were chronic glomerulonephritis (78.0%), diabetic nephropathy (8.5%), hypertensive nephrosclerosis (6.8%), polycystic kidney disease (3.4%), obstructive nephropathy (1.7%) and lupus nephritis (1.7%).

The whole protocol was approved by the local medical ethnic committee. Written agreements were acquired from every participant.

Laboratory methods

Blood samples were obtained from the arterial site of the arteriovenous fistula at the start of the dialysis session 2 days after the previous haemodialysis. Within a 15-min period, plasma BNP was measured using the Triage™ B-Type Natriuretic Peptide test (Biosite Inc., San Diego, CA, USA).

Table 1. Demographic and clinical characteristics of the study population.

Age (years)	48.1 ± 11.9
Sex (male), *n* (%)	31 (52.5)
Duration of HD (months)	48.2 ± 27.6
Dry weight (kg)	60.5 ± 9.7
BMI	22.2 ± 3.1
Systolic BP (mmHg)	144.5 ± 17.3
Diastolic BP (mmHg)	86.9 ± 11.4
EF (%)	67 ± 6
LV diastolic diameter (mm)	50.9 ± 5.4
LV mass index (g m^{-2})	165.1 ± 60.1
Hb (g l^{-1})	95.6 ± 15.9
BNP (pg ml^{-1})	186.0 (18.5–2266.0)

Data are expressed as mean ± SD or median (range) unless otherwise indicated. HD, haemodialysis; BMI, body mass index; EF, ejection fraction; Hb, haemoglobin; BNP, B-type natriuretic peptide.

Echocardiographic examination and tissue Doppler measurements

The left ventricular function was assessed by 2-dimensional and Doppler echocardiography (iE33 cardiovascular ultrasound system; Philips, Bothell, WA, USA) by the same experienced cardiologist who was blind to the study groups of all patients. Echocardiography was performed on the same day as blood sampling for biomarkers before the HD session. All echocardiographic data were recorded according to the guidelines of the American Society of Echocardiography (Schiller et al. 1989). LVEF was obtained using a modified biplane Simpson's method from apical two- and four-chamber views (Otterstad et al. 1997). LV mass was calculated with the method of Devereux and Reicheck (1977) and indexed by body surface area. The mitral annulus movement was recorded using a tissue Doppler technique as previously described (Kasner et al. 2007). Analysis was performed for the early (E') and late (A') diastolic peak velocities. Systolic dysfunction was defined by an EF <50%. Diastolic dysfunction was considered if E'/A' <1 (Kasner et al. 2007).

Statistical analyses

All data were expressed as mean ± SD or median (range) depending on the distribution. Comparisons of continuous variables for two groups were performed by means of the Student's *t*-test or the Mann–Whitney *U* test, as appropriate. The χ^2 test was used for comparison of categorical variables. Correlations of the different biomarkers were evaluated using Spearman's rank correlation analysis. The diagnostic utility of BNP alone was compared with the echocardiographic probability of LVDD through the use of receiver-operating characteristic (ROC) curves. Results are expressed in terms of the area under the curve (AUC) and 95% confidence interval (CI) for this area. All analyses were carried out using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA). The *p*-values reported are two-sided and significant at <0.05.

Results

BNP and clinical parameters

Serum BNP ranged from 18.5 to 2266.0 pg ml^{-1}, with a median of 186.0 pg ml^{-1}. BNP levels correlated with systolic blood pressure (BP) ($r = 0.285$, $p = 0.029$), diastolic

BP ($r=0.259$, $p=0.048$), LV diastolic diameter ($r=0.316$, $p=0.015$), LV mass index ($r=0.390$, $p=0.002$) and Hb ($r=-0.338$, $p=0.009$). No significant correlation was found between BNP and the other clinical parameters, including age, duration of HD and body mass index (BMI) ($p>0.05$).

BNP in patients with or without LVDD

Thirty-nine of the 59 patients (66%) had LVDD. Plasma BNP levels were significantly higher in patients with LVDD (LVDD(+)) than without LVDD (LVDD(-)) ($p=0.01$; Figure 1). Systolic BP, LV diastolic diameter and LV mass index were also higher in patients with LVDD than without LVDD ($p=0.012$, $p=0.007$, $p=0.002$, respectively). There were no differences in gender, age, duration of HD or BMI levels between patients with and without LVDD ($p>0.05$; Table 2).

Values of plasma BNP in diagnosing LVDD

By creating ROC curves we identified a cut-off value for BNP that discriminates between patients with LVDD and those without LVDD (Figure 2). The AUC was 0.86 ± 0.05 (95% CI 0.76–0.96; $p<0.001$). A cut-off point of 156.4 pg ml^{-1} of BNP offers the best sensitivity, whereas 742.0 pg ml^{-1} gives rise to the highest specificity for the diagnosis of LVDD. When the plasma BNP level is at the level of 353.6 pg ml^{-1}, it is associated with 80% diagnostic sensitivity and 84% specificity. A BNP value of 353.6 pg ml^{-1} resulted in 84.6% specificity and an acceptable sensitivity of 80%

Table 2. Comparison between patients with and without left ventricular diastolic dysfunction (LVDD).

	LVDD (-) ($n=20$)	LVDD (+) ($n=39$)	p-Value
Sex (male), n (%)	21 (53.8)	10 (50.0)	NS
Age (years)	46 ± 11.6	52.2 ± 11.6	NS
History			
Diabetes, n (%)	2 (5.1)	3 (15.0)	NS
Hypertension, n (%)	35 (89.7)	19 (95.0)	NS
Coronary artery disease, n (%)	6 (15.4)	7 (35.0)	NS
Duration of HD (months)	48.3 ± 24.7	48.1 ± 33.3	NS
BMI	21.8 ± 2.8	23.1 ± 3.5	NS
UF (ml)	2204 ± 719	2403 ± 766	NS
Systolic BP (mmHg)	140 ± 15	153 ± 18	0.012
Diastolic BP (mmHg)	86 ± 9	89 ± 15	NS
EF (%)	67 ± 6	65 ± 4	NS
LV diastolic diameter (mm)	49.6 ± 5.4	53.5 ± 4.5	0.007
LV mass index (g m^{-2})	146.1 ± 48.3	201.2 ± 64.6	0.002
Hb (g dl^{-1})	9.9 ± 1.5	8.9 ± 1.6	0.014
BNP (pg ml^{-1})	132.6 (18.5–842)	966.5 (85.5–2266)	0.001

Data are expressed as mean ± SD or median (range) unless otherwise indicated. HD, haemodialysis; BMI, body mass index; UF, ultrafiltration volume; BP, blood pressure; EF, ejection fraction; LV, left ventricular; Hb, haemoglobin; BNP, B-type natriuretic peptide; NS, not significant.

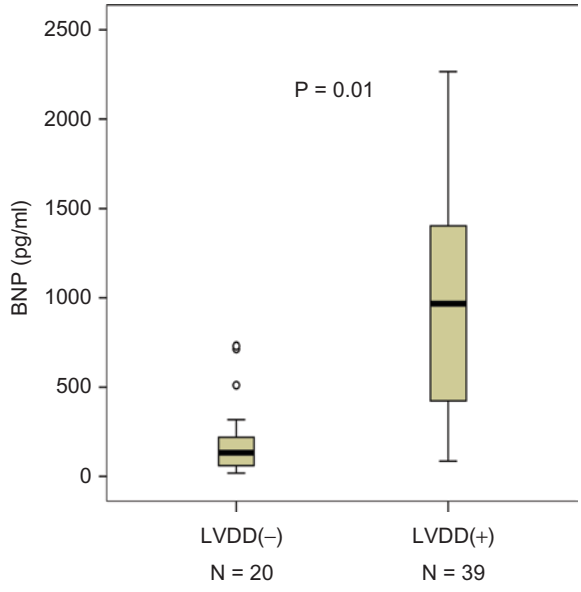

Figure 1. Box plots demonstrating increased levels of plasma B-type natriuretic peptides (BNP) in patients with left ventricular diastolic dysfunction (LVDD) compared with those without. Open circles indicate mild outlier patients.

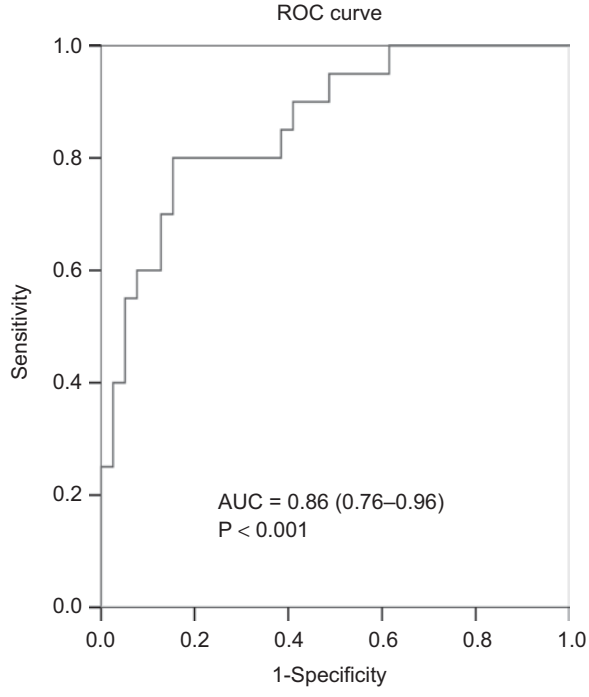

Figure 2. Receiver-operating characteristic (ROC) curves for B-type natriuretic peptides (BNP) in predicting left ventricular diastolic dysfunction (LVDD). The area under the ROC for BNP to detect LVDD was 0.86 (95% confidence interval 0.76–0.96; $p<0.001$). BNP at 353.6 pg ml^{-1} showed a sensitivity of 80.0% and a specificity of 84.6% for detecting LVDD.

in diagnosing LVDD. Table 3 presents four calculated BNP values with different sensitivities and specificities.

Discussion

Cardiovascular disease is a major cause of death in patients on MHD, which accounts for more than 50% of the deaths (Collins 2003). In these patients, congestive heart failure (CHF) is one of the main causes of mortality. It is well known that CHF is a complex syndrome in which both systolic and diastolic functional abnormalities can be identified. As many as 40–50% of patients with a diagnosis of heart failure have normal systolic function, which implicates diastolic dysfunction as the most likely abnormality causing this disorder (Kindermann et al. 2008). Ahmed et al. (2007) found that chronic kidney disease-associated mortality was more than 1.7-fold in patients with diastolic dysfunction compared with patients with systolic dysfunction. Therefore, it is of great importance to identify diastolic dysfunction for patients with MHD to facilitate early therapeutic interventions and improve the prognosis.

The diagnosis of diastolic dysfunction has been challenging mainly due to lack of consensus on specific criteria and absence of a 'single' non-invasive test (Thomas et al. 2002). The current gold standard for evaluation of LV diastolic function remains direct measurement of LV pressures via a catheter. However, it was restrained for the routinely clinical application due to its invasiveness and complexity of the procedures. Doppler echocardiography has also been assumed to play a key role in the non-invasive assessment of cardiac diastolic function, but its main parameters such as the peak early (E) and peak late (A) flow velocities are affected by blood volume and mitral valve anatomy and function. Furthermore, these wave velocities are less useful in the situation of atrial fibrillation (Khouri et al. 2004). In these cases, tissue Doppler imaging (TDI) is useful for measuring mitral annular motion (a measure of transmitral flow that is independent of the aforementioned factors). TDI has been proved to be more accurate than conventional Doppler for detection of impaired diastolic function in patients with normal EF (Nagueh et al. 1997, Kasner et al. 2007). In contrast to E/A, E'/A' showed better linear correlation with diastolic parameters measured by conductance catheter analysis and provided a simple means of diagnosing diastolic dysfunction (Kasner et al. 2007). But because the TDI is time-consuming and costly, it is quite difficult to use as a regular practice in clinic. It is therefore imperative to find more reliable, cost-effective markers for diagnosing diastolic dysfunction.

Table 3. Diagnostic sensitivity and specificity for left ventricular diastolic dysfunction using different B-type natriuretic peptide (BNP) values.

BNP (pg ml^{-1})	Sensitivity	Specificity
156.4	0.900	0.590
353.6	0.800	0.846
536.9	0.700	0.872
742.0	0.600	0.923

BNP is a cardiac neurohormone secreted from the ventricles in response to excessive cardiac ventricular wall distension, various pathological states (for instance, myocardial ischemia or cardiomyopathies) and increased release of catecholamines, renin, angiotensin II and endothelin (Racek et al. 2006, Haapio & Ronco 2008). In the general population, BNP levels are known to be elevated in patients with LV hypertrophy and systolic dysfunction (de Sa & Chen 2008, Troughton & Richards 2009). In HD patients, Mallamaci et al. (2001) also found that BNP could be useful for the identification of dialysis patients with LV hypertrophy with a sensitivity of 88%. Nitta et al. (1998) found a positive correlation between BNP levels and LV mass index ($r = 0.57$, $p < 0.05$), whereas BNP levels were significantly increased in patients with a low LVEF (<60%). However, the clinical value of plasma BNP in identifying LVDD has not yet been fully established. In the present study, we first demonstrated that MHD patients with LVDD had a significant elevation of BNP levels compared with those with normal ventricular function. The area under the ROC curve was used to assess the specificity and sensitivity of BNP in diagnosing LVDD. Given that the sensitivity in diagnosing LVDD was only 80%, it is not high enough to rule-out LVDD in a patient with a BNP of less than the cut-off value.

The underlying pathophysiology for elevated BNP levels in diastolic heart failure is not fully understood. In MHD patients, the plasma BNP level may be affected by many factors such as impaired glomerular filtration, hypertension, diabetes mellitus, ischemia, inflammation and secondary hyperparathyroidism (Bertinchant 2004, Komaba et al. 2007, Matayoshi et al. 2008). In this study, we found that plasma BNP levels correlated well with systolic BP, diastolic BP and Hb ($p < 0.05$, respectively), but in considering the r^2 less than 0.25, a larger sample size is obviously needed for future studies.

Several limitations should be considered in interpreting our results. First, the study was based on a relatively small number of patients with end-stage renal failure. Further studies with large numbers of HD patients would allow us to understand the clinical value of BNP more clearly. Second, we excluded patients with abnormal systolic function for the simplicity of this preliminary study, thus the generalization of our finding is limited to stable HD patients without LVSD.

In summary, based on the results of our study, plasma BNP values are closely related to the diastolic functional status measured by TDI in stable MHD patients. It could be considered as a low-cost, widely available tool for the

first-step screening of MHD patients, particularly in the presence of normal or mildly abnormal functional status. Further studies are warranted to confirm our observation in larger cohorts and to validate further the cut-off values.

Declaration of interest

The project was supported by grants from the provincial key projects of the Natural Science Foundation of Jiangsu Province (no. 2007709), Jiangsu Provincial Key Medical Talent (no. RC 2007072) and the Health Bureau of Jiangsu Province (no. H200936). The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

Ahmed A, Rich MW, Sanders PW, Perry GJ, Bakris GL, Zile MR, Love TE, Aban IB, Shlipak MG. (2007). Chronic kidney disease associated mortality in diastolic versus systolic heart failure: a propensity matched study. *Am J Cardiol* 99:393–8.

Bertinchant JP. (2004). Brain natriuretic peptide (BNP) and N-terminal-pro BNP in chronic haemodialysed renal failure. *Arch Mal Coeur Vaiss* 97:881–8.

Bossola M, Tazza L, Vulpio C, Luciani G. (2008). Is regression of left ventricular hypertrophy in maintenance hemodialysis patients possible. *Semin Dial* 21:422–30.

Collins AJ. (2003). Cardiovascular mortality in end-stage renal disease. *Am J Med Sci* 325:163–7.

de Sa DD, Chen HH. (2008). The role of natriuretic peptides in heart failure. *Curr Cardiol Rep* 10:182–9.

Devereux RB, Reichek N. (1977). Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. *Circulation* 55:613–18.

Foley RN, Parfrey PS, Kent GM, Harnett JD, Murray DC, Barre PE. (2000). Serial change in echocardiographic parameters and cardiac failure in end-stage renal disease. *J Am Soc Nephrol* 11:912–16.

Haapio M, Ronco C. (2008). BNP and a renal patient: emphasis on the unique characteristics of B-type natriuretic peptide in end-stage kidney disease. *Contrib Nephrol* 161:68-75.

Kasner M, Westermann D, Steendijk P, Gaub R, Wilkenshoff U, Weitmann K, Hoffmann W, Poller W, Schultheiss HP, Pauschinger M, Tschöpe C. (2007). Utility of Doppler echocardiography and tissue Doppler imaging in the estimation of diastolic function in heart failure with normal ejection fraction: a comparative Doppler-conductance catheterization study. *Circulation* 116:637–47.

Khouri SJ, Maly GT, Suh DD, Walsh TE. (2004). A practical approach to the echocardiographic evaluation of diastolic function. *J Am Soc Echocardiogr* 17:290–7.

Kindermann M, Reil JC, Pieske B, van VDJ, Böhm M. (2008). Heart failure with normal left ventricular ejection fraction: what is the evidence? *Trends Cardiovasc Med* 18:280–92.

Komaba H, Igaki N, Goto S, Yokota K, Takemoto T, Hirosue Y, Goto T. (2007). Adiponectin is associated with brain natriuretic peptide and left ventricular hypertrophy in hemodialysis patients with type 2 diabetes mellitus. *Nephron Clin Pract* 107:c103–8.

Lubien E, DeMaria A KP, Clopton P, Koon J, Kazanegra R, Gardetto N, Wanner E, Maisel AS. (2002). Utility of B-natriuretic peptide in detecting diastolic dysfunction: comparison with Doppler velocity recordings. *Circulation* 105:595–601.

Mallamaci F, Zoccali C, Tripepi G, Benedetto FA, Parlongo S, Cataliotti A, Cutrupi S, Giacone G, Bellanuova I, Stancanelli B, Malatino LS. (2001). Diagnostic potential of cardiac natriuretic peptides in dialysis patients. *Kidney Int* 59:1559–66.

Matayoshi T, Kato T, Nakahama H, Nakata H, Yoshihara F, Kamide K, Horio T, Nakamura S, Kawano Y. (2008). Brain natriuretic peptide in hemodialysis patients: predictive value for hemodynamic change during hemodialysis and cardiac function. *Am J Nephrol* 28:122–7.

Meguid ENA, Bello AK. (2005). Chronic kidney disease: the global challenge. *Lancet* 365:331–40.

Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quiñones MA. (1997). Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. *J Am Coll Cardiol* 30:1527–33.

Nitta K, Kawashima A, Yumura W, Naruse M, Oba T, Kabaya T, Nihei H. (1998). Plasma concentration of brain natriuretic peptide as an indicator of cardiac ventricular function in patients on hemodialysis. *Am J Nephrol* 18:411–15.

Otterstad JE, Froeland G, St JSM, Holme I. (1997). Accuracy and reproducibility of biplane two-dimensional echocardiographic measurements of left ventricular dimensions and function. *Eur Heart J* 18:507–13.

Potter LR, Yoder AR, Flora DR, Antos LK, Dickey DM. (2009). Natriuretic peptides: their structures, receptors, physiologic functions and therapeutic applications. *Handb Exp Pharmacol* 191:341–66.

Pozzoni P, Del VL, Pontoriero G, Di FS, Locatelli F. (2004). Long-term outcome in hemodialysis: morbidity and mortality. *J Nephrol* 17:s87–s95

Racek J, Kralova H, Trefil L, Rajdl D, Eiselt J. (2006). Brain natriuretic peptide and N-terminal proBNP in chronic haemodialysis patients. *Nephron Clin Pract* 103:c162–72.

Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Gutgesell H, Reichek N, Sahn D, Schnittger I. (1989). Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 2:358–67.

Thomas JT, Kelly RF, Thomas SJ, Stamos TD, Albasha K, Parrillo JE, Calvin JE. (2002). Utility of history, physical examination, electrocardiogram, and chest radiograph for differentiating normal from decreased systolic function in patients with heart failure. *Am J Med* 112:437–45.

Troughton RW, Richards AM. (2009). B-type natriuretic peptides and echocardiographic measures of cardiac structure and function. *JACC Cardiovasc Imaging* 2:216–25.

Zeng C, Wei T, Jin L, Wang L. (2006). Value of B-type natriuretic peptide in diagnosing left ventricular dysfunction in dialysis-dependent patients. *Intern Med J* 36:552–7.