The First Affiliated Hospital of Harbin Medical University[1]; The Third Affiliated Hospital of Harbin Medical University[2], Harbin, P.R. China

The effect of B-type brain natriuretic peptide on patients with acute decompensated heart failure coexisting with lung cancer: a randomized controlled clinical trial

Shaojun Wang[1], Xiufen Qu[1], Yuanyuan Qu[2], Yanwei Yu[1], Wei Feng[1]

Received June 13, 2013, accepted September 20, 2013

Xiufen Qu, Division of Cardiology,The First Affiliated Hospital of Harbin Medical University, Heilongjiang Province, 150001, China
qxiufen@yahoo.com

Pharmazie 69: 212–216 (2014) *doi: 10.1691/ph.2014.3738*

Congestive heart failure (CHF) as a common comorbidity in patients with lung cancer, especially those of old age. The tumor combined with heart failure makes the reasons of dyspnea more complicated and effective drugs to improve symptoms are urgently needed. Recombinant human B-type natriuretic peptide (rhBNP) is a member of the natriuretic peptide family that exerts cardiovascular effects. The major goal of this study was to study the effect of rhBNP on patients with decompensated heart failure coexisted with lung cancer. Emergency decompensated HF patients with lung cancer admitted for dyspnea were randomly assigned to openlabel therapy with standard treatment (control group) or standard treatment + rhBNP(rhBNP group) for up to 7 days. Then we recorded the changes of symptoms, examined and followed up every 3 months to evaluate the effect of rhBNP on decompensated heart failure patients with lung cancer. We found that dyspnea, fatigue and edema of lower extremity were significantly improved in the rhBNP group compared to the control group after 7 days of treatment. Survival rate was not significantly different in the mean 18.4 ± 8.6 months of follow-up. Results from our study suggested that rhBNP significantly improved symptoms in emergency decompensated HF patients with lung cancer admitted for dyspnea in the short term, but did not improve survival rate in the long term.

1. Introduction

Congestive heart failure (CHF) as a common comorbidity in patients with lung cancer, especially those of old age. The tumor combined with heart failure makes the treatment as well as the patients' conditions more complicated. Because of this severe heart disease, a certain percentage of patients are unable to undergo surgery, and even in those who are going to receive chemotherapy and/or radiotherapy, it is an important risk factor of treatment related morbidity. There are two situations of CHF in patients with lung cancer: 1) it has existed upon the diagnosis of lung cancer (a comorbid illness); 2) onset occurred during the anti-cancer treatment (a secondary disease). The latter could be induced by chemotherapeutic drugs or by overwhelming intravenous infusion. No matter which the situation is, it compromises anti-cancer therapy and is associated with short-term mortality. To improve the symptoms and prolong the survival of patients with lung cancer, it is imperative to treat CHF beforehand or simultaneously.

Aside from traditional medication for CHF such as diuretics, vasodilators, and inotropic agents, recombinant human B-type natriuretic peptide (rhBNP) is clinically used (Colucci et al. 2000; O'Connor et al. 2011; Scroggins et al. 2005). RhBNP has shown multiple functions in vasodilation, diuresis, natriuresis, and suppression of the renin-angiotensin-aldosterone and sympathetic nervous systems (Reichert and Ignaszewski 2008). It has been reported that the infusion of nesiritide, an rhBNP resulted in improvement in dyspnea and pulmonary capillary wedge pressure (PCWP) (Young et al. 2002).

For patients with lung cancer comorbid with CHF, the most common reason being hospitalized to the cardiovascular department is the acute onset of dyspnea. RhBNP is likely to rapidly alleviate dyspnea (Ezekowitz et al. 2012; Young et al. 2002). With the control of dyspnea, a portion of patients could resume the anti-cancer treatment. To evaluate the therapeutic role of rhBNP in treating patients with lung cancer combined with CHF, and to investigate the survival and prognosis of this specified population, we studied 443 patients with lung cancer hospitalized into our institution to treat CHF with NYHA class III∼IV, 48.5% (215 patients) of which received rhBNP infusion.

2. Investigations and results

2.1. Patient baseline characteristics

The control group had a mean (± SD) age of 64.6(± 12.0) years (median 67.5; range 28–87), 84(36.8%) were female and the rhBNP group had a mean (± SD) age of 66.1 (± 12.3) years (median 69.0; range 27–89), 91(42.3%) were female. All baseline characteristics are displayed in Table 1, including medication intake, symptoms and signs of heart failure, NYHA functional class, heart rate, respiratory frequency, blood pressure, chest radiograph findings, laboratory tests and ultra-

Table 1: Baseline characteristics of acute HF patients with lung cancer treated by standard therapy (control group) and treated by standard therapy + rhBNP(rhBNP group)

	control group (N = 228)	rhBNP group (N = 215)	p-value
Age (y)	64.6 ± 12.0	66.1 ± 12.3	0.43
Gender			0.14
Female, N (%)	84(36.8)	91(42.3)	
Male, N(%)	144(63.2)	124(57.7)	
History			
Heart failure duration (months)	32.1 ± 30.1	33.2 ± 20.7	0.65
Hypertension, N (%)	104(45.6)	94(43.7)	0.76
Diabetes mellitus, N (%)	26(11.4)	33(15.3)	0.28
Chronic kidney disease, N (%)	12(5.3)	14(6.5)	0.72
Medications			
Digoxin, N (%)	120(52.6)	112(52.1)	0.99
ACE inhibitors, N (%)	210(92.1)	197(91.6)	0.99
Diuretics, N (%)	219 (96.1)	201 (93.5)	0.32
Aldosterone-inhibitors, N (%)	97(42.5)	84(39.1)	0.52
Beta-blockers, N (%)	76(33.3)	68(31.6)	0.78
Symptoms and signs of heart failure			
Dyspnea at rest, N (%)	127(55.7)	112(52.1)	0.51
Dyspnea on exertion, N (%)	228(100)	215(100)	1.00
Jugular venous distension, N (%)	188(82.5)	164(76.3)	0.14
Lower extremity edema, N (%)	176(77.2)	170(79.1)	0.72
NYHA functional class			0.18
III	98(43.0)	78(36.3)	
IV	130(57.0)	137(63.7)	
Heart rate (beats/min)	109 ± 36	114 ± 28	0.10
Respirations (numbers/min)	21 ± 6	22 ± 8	0.16
Blood pressure (mmHg)			
Systolic	130 ± 44	136 ± 38	0.12
Diastolic	86 ± 39	90 ± 47	0.33
Chest radiograph findings			
Pulmonary congestion, N (%)	198(86.8)	185(86.0)	0.92
Cardiothoracic ratio > 0.5, N (%)	210(92.1)	202(94.0)	0.57
Laboratory			
Creatinine (mg/dL)	1.38 ± 0.41	1.41 ± 0.35	0.41
NT-proBNP (ng/L)	3946 ± 2897	4397 ± 3345	0.13
High sensitivity-CRP (mg/L)	98 ± 180	120 ± 110	0.12
CK-MB (U/L)	15.7 ± 9.4	16.7 ± 5.9	0.18
Troponin I (ng/ml)	0.16 ± 0.07	0.15 ± 0.09	0.19
Oxygen saturation (arterial) (%)	90.1 ± 11.7	89.2 ± 5.6	0.37
Ultrasonic cardiogram (UCG)			
LVEDD (mm)	67.7 ± 15.2	70 ± 17.2	0.14
LAD (mm)	48 ± 9.8	50 ± 17	0.13
LVPW (mm)	11.5 ± 2.5	11.0 ± 2.8	0.43
Left ventricular ejection fraction (%)	25 ± 9	26 ± 8	0.22

Values expressed as N (%) or mean ± SD. No statistically significant differences were found between the control group characteristics and rhBNP group characteristics at baseline. NYHA = The New York Heart Association,LVEDD = left ventricular end-diastolic dimension,LAD = left atrial dimension,LVPW = left ventricular posterior wall.

sonic cardiogram (UCG). All baseline covariates were balanced between the two groups and all absolute standardized differences were below 11% and most were below 5%, suggesting acceptable covariate balance and bias reduction.

Lung cancer baseline data for survival duration, histological classification, international union against cancer (UICC) lung cancer stage and methods of treatment (radiotherapy, chemotherapy and /or surgery) are displayed in Table 2.

2.2. Assessment of symptoms

In the trial, clinical status and symptoms of congestive heart failure (dyspnea, fatigue, dizziness and edema of lower extremity) were assessed at base line and at seven days after the treatment. General clinical status and symptoms were also evaluated after 24 h and at the end of therapy (lasting up to 7 days). General clinical status was rated independently by both the patient and the investigator on a three-category scale (improved, no change, or worse) that has been used previously in trials of long-term therapy for congestive heart failure.

2.3. Hemodynamic, laboratory and arterial oxygen saturation assessment

At base line, repeated measurements of the pulmonary-capillary wedge pressure and of the cardiac index were required before administration of the study-drug. Systolic and diastolic blood pressure, respiratory frequency and heart rate were recorded every six hours in the first seven days of the trial. Plasma levels of creatinine, NT-proBNP, high sensitivity-CRP, troponin I and CK-MB were assessed at base line and 7 days after the start of the study-drug infusion. Arterial oxygen saturation was assessed at

Table 2: Lung cancer baseline data of acute HF patients with lung cancer

Lung cancer data	control group (N = 228)	rhBNP group (N = 215)	p-value
Lung cancer duration (months)	22.4 ± 18.5	24.4 ± 22.7	0.31
Histological classification			
Adenocarcinoma, N (%)	92 (40.4)	88(40.9)	0.90
Squamous cell cancer, N (%)	98(43.0)	95(44.2)	0.80
Large cell lung cancer, N (%)	6 (2.6)	5 (2.3)	0.84
Small cell lung cancer, N (%)	32(14.0)	27(12.6)	0.65
UICC* lung cancer stage			
Small cell lung cancer	32(14.0)	27(12.6)	0.65
Limited stage, N (%)	8 (3.5)	6(2.8)	0.67
Extensive stage, N (%)	20(8.8)	18 (8.4)	0.88
Recurrent stage, N (%)	4(1.7)	3(1.4)	0.76
Non-small cell lung cancer	196(86.0)	188(87.4)	0.65
I, N (%)	21(9.2)	17(7.9)	0.62
II, N (%)	71(31.1)	64(29.8)	0.75
III, N (%)	91(39.9)	86(40.0)	0.99
IV, N (%)	13(5.7)	21(9.8)	0.11
Radiotherapy, N (%)	211(92.5)	198(92.1)	0.86
Chemotherapy, N (%)	199 (87.3)	187(87.0)	0.92
Surgery, N (%)	114(50.0)	109(50.7)	0.88

*UICC = International Union Against Cancer(Union Internationale Contre le Cancer)

base line and every 3 months to reach study end points described in the experimental section.

2.4. Changes of patients at 7 days

2.4.1. Improvement and worsening of the symptoms

Dyspnea, fatigue, dizziness, edema of lower extremity of the patients are were displayed in Table 3 excluding patients without symptom change after 7 days of treatment. Dyspnea, fatigue and edema of lower extremity were improved significantly in the rhBNP group than the control group. Respiratory frequency, systolic blood pressure, pulmonary capillary wedge pressure and troponin I of rhBNP group were decreased significantly and cardiac index, urine volume per 24 h and Creatinine were increased significantly compared to the control group.

2.4.2. Ultrasonic cardiogram changes

Figure 1 illustrates ultrasonic cardiogram changes—left ventricular end-diastolic dimension (LVEDD), left ventricular end-diastolic dimension (LAD), and left ventricular posterior wall (LVPW) were not significantly different between control group and rhBNP group, not only at the beginning of treatment but also 7 days later. But LVEF (left ventricular ejection fraction) of rhBNP group was significantly improved than control group 7 days later (p value < 0.01).

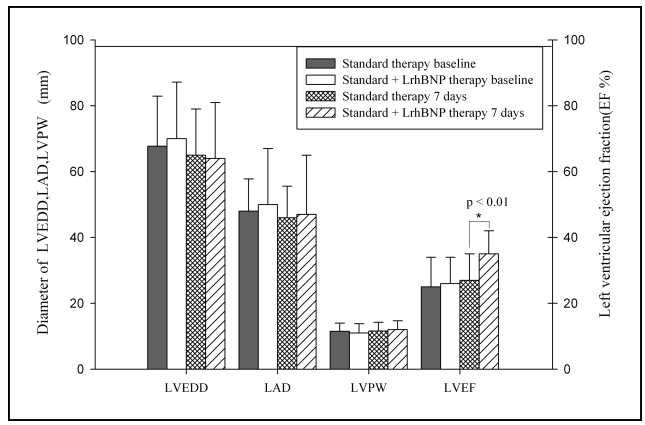

Fig. 1: LVEDD, LAD and LVPW were not significantly different between standard therapy group (control group) and standard + LrhBNP group (rhBNP group) both at the beginning of treatment and at 7 days. LVEF and standard + LrhBNP group (rhBNP group) at 7 days significantly improved than standard therapy group (control group) at 7 days. $p < 0.01$. LVEDD, left ventricular end-diastolic dimension; LAD, left atrial dimension; LVPW, left ventricular posterior wall; LVEF, left ventricular ejection fraction.

2.5. Changes of patients' long-time follow-up

2.5.1. Arterial oxygen saturation(%)

Mean and standard deviation of arterial oxygen saturation (%) were exhibited in the follow-up linear chart (Fig. 2). At 6, 9, 12, 27 months, arterial oxygen saturation(%) of the rhBNP group was higher than that of the control group.

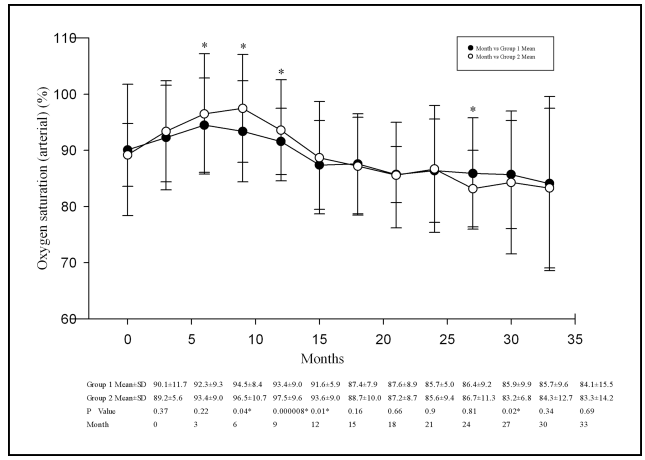

Fig. 2: Mean and standard deviation linear chart of arterial oxygen saturation (%) of followed up survival patients at admission time and 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33 months. P value also be calculated and presented at every matched time point.p value < 0.05 was marked by "*". Group 1: control group; Group 2: rhBNP group.

2.5.2. Survival curves

The trends of survival rates were exhibited (Fig. 3). The mean living time of rhBNP group was longer than that of control

Table 3: Changes in baseline values of patients treated and not treated by rhBNP at 7 days

Variable	control group (N = 228)	rhBNP group (N = 215)	p-value
Dyspnea			
Improvement, N (%)	157	180	< 0.01
Worsening, N (%)	26	9	0.005
Fatigue			
Improvement, N (%)	137	178	< 0.01
Worsening, N (%)	21	7	0.01
Dizziness			
Improvement, N (%)	197	190	0.53
Worsening, N (%)	16	5	0.02
Edema of lower extremity			
Improvement, N (%)	183	200	< 0.01
Worsening, N (%)	3	2	0.7
Respiratory frequency (numbers/min)	-2.1 ± 5.2	-3.8 ± 4.2	0.0002
Hemodynamic variables			
Heart rate (beats/min)	-16.1 ± 26.1	-20.3 ± 28.7	0.11
Blood pressure (mmHg)			
Systolic	$+10.2 \pm 16.5$	-1.1 ± 20.4	< 0.01
Diastolic	$+3.2 \pm 16.9$	-2.2 ± 12.3	0.48
Pulmonary capillary wedge pressure (mmHg)	-4.8 ± 6.9	-7.2 ± 8.1	0.0009
Cardiac index (liters/min/m^2)	$+0.2 \pm 0.61$	$+0.5 \pm 0.74$	< 0.01
Urine volume (ml/24h)	$+445 \pm 632$	$+800 \pm 915$	< 0.01
Creatinine (mg/dL)	$+0.02 \pm 0.03$	$+0.03 \pm 0.04$	0.003
NT-proBNP (ng/L)	-1160 ± 1291	-1398 ± 1697	0.099
High sensitivity-CRP (mg/L)	-16 ± 34	-19 ± 44	0.42
Troponin I (ng/mL)	-0.12 ± 0.09	-0.23 ± 0.11	< 0.01
CK-MB (u/L)	0 ± 7.2	0 ± 9.4	1

*Improvement- worsening values are number(%) of the group.Improvement denote an improvement of symptom than the beginning,and worsening denote a worsening of symptom than the beginning. **Plus-minus values are means ± SD. Plus signs denote an increase, and minus signs a decrease. ***P values are for the comparison between the two groups and were calculated with the omnibus F test.

group in the mean 18.4 ± 8.6 months of follow-up, although the statistics analysis result was not significant (p value= 0.07).

2.6. Adverse cardiovascular events in rhBNP group and control group

Adverse cardiovascular events are displayed in Table 4. Symptomatic and asymptomatic hypotension onset rates in the rhBNP group were higher than those in the control group. The significance (p value) was 0.024 and 0.004 for Fisher's exact test.

3. Discussion

Dyspnea is difficult to be alleviated in heart failure patients with lung cancer for which is caused by complicated etiological factors including pneumonedema, bronchiospasm, tracheal occlusion, etc (Attar et al. 2000; Burjonroppa et al. 2007; Dudgeon and Lertzman 1998). The whole disease procedure is accompanied by the activation of the renin–angiotensin–aldosterone system (RAAS) and the increasing of pulmonary capillary wedge pressure (PCWP) (Bründler et al. 1985; Braunwald and Bristow 2000; Solin et al. 1999). RAAS aggravates heart function and makes pulmonary vascular contract, then exacerbates dyspnea. In recent trials nesiritide has been shown to reduce the activation of RAAS (Liu et al. 2012). Pharmacological doses of rhBNP have also been shown to have an acute pulmonary vasodilator effect in unresponsive pulmonary hypertension (Bhat and Costea 2003). Intravenous infusion of human BNP (0.01 ug/kg/min) blunts the acute pulmonary vasoconstrictor response to hypoxia and reduces pulmonary artery pressure (PAP) in patients with severe pul-

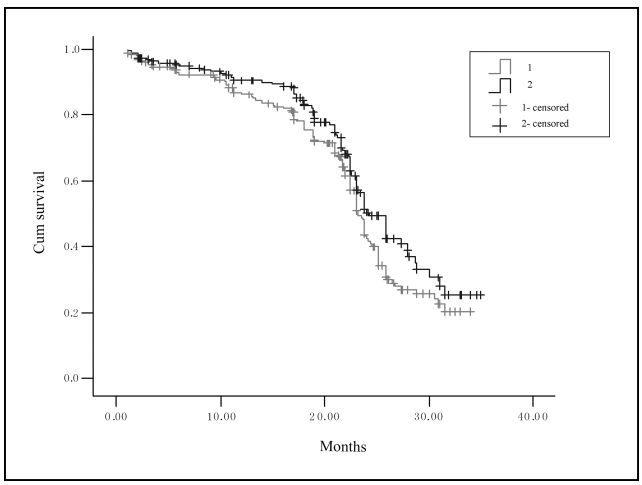

Fig. 3: Survival curves of two groups: 1. control group; 2. rhBNP group. Comparison between control group and rhBNP group curves, p = 0.07.

Table 4: Adverse cardiovascular events after 7 days treatment

Event	control group (N = 228)	rhBNP group (N = 215)	p-value*
Hypotension			
Symptomatic	4	13	0.024
Asymptomatic	5	18	0.004
Atrial fibrillation	6	5	1.0
Atrial tachycardia	7	6	1.0
Ventricular extrasystole	6	5	1.0
Ventricular tachycardia			
Nonsustained	3	5	0.49
Sustained	4	7	0.37
Cardiac arrest	1	1	1.0
Bradycardia	4	6	0.53

*P values are for the comparisons between the two groups and were calculated with Fisher's exact test.

monary hypertension (Michaels et al. 2005; Zakir et al. 2005). These preliminary studies demonstrate that rhBNP is capable of reducing elevated PAP in some forms of heart and pulmonary disease. Meanwhile rhBNP exerts antifibrotic as well as antihypertrophic effects on the heart and plays an important role in mitigating maladaptive cardiac hypertrophic responses (Burger and Burger 2005). So we conclude that the anti-RAAS effect of rhBNP and its vasorelaxant properties make the combination—rhBNP + traditional heart failure therapeutic drugs (rhBNP) more effective than traditional therapeutic drugs alone (Wilop et al. 2009). It has been further supported by our result that the patients' arterial oxygen saturations (%) of rhBNP group were higher than those of control group at 6, 9 and 12 months. But during a longer follow-up period of more than one year, there were no significant differences between the rhBNP group and the control group except at 27 months. Possible explanation may be statistical bias because of too small sample surviving at 27 months.

Hypotension was the main adverse cardiovascular event of rhBNP due to diuresis and vasodilatation which both can decrease blood pressure.

Although the rhBNP group showed a trend of improving survival compared with the control group, there was no statistically significant difference of survival rate between the two groups.

In conclusion, acute decompensated heart failure patients with lung cancer benefit from rhBNP application with an improvement in patient symptoms, an increase in LVEF, and an improvement in arterial oxygen saturations (%) in one year.

4. Experimental

4.1. Patient selection, randomization and study-drug administration

Patients with acute decompensated CHF and lung cancer were recruited from 7 August 2008 to 7 May 2011. We randomly assigned 443 consecutive lung cancer patients with CHF to receive therapy. All participants received standard therapies, including morphine, diuretics, and other vasoactive medications, as determined by the investigator with the 2008 ESC Guidelines (Dickstein et al. 2008). In the control group, participants received standard therapies. In the rhBNP group, rhBNP was administered as an intravenous bolus of 2 μg/kg followed by a continuous infusion at a rate of 0.01 ug/kg/min for up to 7 days besides standard therapies. The changes of symptoms and examinations were recorded and followed up every 3 months to evaluate the effect of rhBNP according to symptoms, hemodynamic measures and survival rate.

4.2. Study end points and study limitations

In the mean 18.4 ± 8.6 months of the comparative trial, primary end points were the changes of dyspnea, fatigue, dizziness and edema of lower extremity. The secondary end points were all-cause death, arterial oxygen saturation assessment and complications. The shortest follow-up time was 1.05 months, and the longest follow-up time was 35 months. During the median follow-up of 21.0 months (25/75th percentiles: 12.0/24.0 months), the clinical symptoms, and hemodynamic measurements were recorded and analyzed.

We acknowledge that the main limitation of this study is that the findings are subject to confounding variables including different reasons of dyspnea, baseline coexisting conditions that we cannot control. Additionally, the study is limited by its relatively small sample size, and relatively short follow-up period possibly affected the validity of the results.

4.3. Statistical analysis

Data are presented as means ± SD. In the trial, the effect of the treatment assignment on hemodynamic variables was analyzed by one-way analysis of variance. In the trial, overall comparisons between rhBNP group and control group were performed with the omnibus F test. Repeated measurements were made on the same participants (at baseline and after treatment) in rhBNP group and control group. Outcomes with respect to general clinical status, symptoms of congestive heart failure, and levels of creatinine, NT-proBNP, high sensitivity-CRP, troponin I and creatine kinase-MB(CK-MB) were analyzed by nonparametric methods. All reported P values are two-sided, and P values of less than 0.05 were considered to indicate statistical significance, and P-values < 0.001 were considered statistically very significant.

This work was supported by the 2011 research funding of the First Affiliated Hospital of Harbin Medical University.

References

Attar EC, Ervin T, Janicek M, Deykin A, Godleski J (2000) Side effects of chemotherapy. J Clin Oncol 18: 697–697.

Bhat G, Costea A (2003) Reversibility of medically unresponsive pulmonary hypertension with nesiritide in a cardiac transplant recipient. ASAIO J 49: 608–610.

Bründler H, Chen S, Perruchoud A (1985) Right heart catheterization in the pre-operative evaluation of patients with lung cancer. Respiration 48: 261–268.

Braunwald E, Bristow MR (2000) Congestive heart failure: fifty years of progress. Circulation 102: Iv-14-Iv-23.

Burger AJ, Burger MR (2005) Nesiritide: past, present, and future. Minerva Cardioangiol 53: 509–522.

Burjonroppa SC, Tong AT, Xiao L-C, Johnson MM, Yusuf SW, Lenihan DJ (2007) Cancer patients with markedly elevated B-type natriuretic peptide may not have volume overload. Am J Clin Oncol 30: 287–293.

Colucci WS, Elkayam U, Horton DP, Abraham WT, Bourge RC, Johnson AD, Wagoner LE, Givertz MM, Liang C-s, Neibaur M (2000) Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure. New Engl J Med 343: 246–253.

Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Strömberg A, van Veldhuisen DJ, Atar D, Hoes AW (2008) ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. Eur Heart J 29: 2388–2442.

Dudgeon DJ, Lertzman M (1998) Dyspnea in the advanced cancer patient. J Pain Symptom Manage 16: 212–219.

Ezekowitz JA, Hernandez AF, O'Connor CM, Starling RC, Proulx G, Weiss MH, Bakal JA, Califf RM, McMurray JJ, Armstrong PW (2012) Assessment of dyspnea in acute decompensated heart failure: insights from ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) on the contributions of peak expiratory flow. J Am Coll Cardiol 59: 1441–1448.

Liu SQ, Xie HW, Yan HY, Lu YQ, Wang LX (2012) Recombinant B-type natriuretic peptide nesiritide attenuates vascular remodelling by reducing plasma aldosterone in rabbits. Heart Lung Circ 21: 551–555.

Michaels AD, Chatterjee K, De Marco T (2005) Effects of intravenous nesiritide on pulmonary vascular hemodynamics in pulmonary hypertension. J Card Fail 11: 425–431.

O'Connor CM, Starling RC, Hernandez AF, Armstrong PW, Dickstein K, Hasselblad V, Heizer GM, Komajda M, Massie BM, McMurray JJV, Nieminen MS, Reist CJ, Rouleau JL, Swedberg K, Adams KF, Anker SD, Atar D, Battler A, Botero R, Bohidar NR, Butler J, Clausell N, Corbalán R, Costanzo MR, Dahlstrom U, Deckelbaum LI, Diaz R, Dunlap ME, Ezekowitz JA, Feldman D, Felker GM, Fonarow GC, Gennevois D, Gottlieb SS, Hill JA, Hollander JE, Howlett JG, Hudson MP, Kociol RD, Krum H, Laucevicius A, Levy WC, Méndez GF, Metra M, Mittal S, Oh B-H, Pereira NL, Ponikowski P, Tang WHW, Tanomsup S, Teerlink JR, Triposkiadis F, Troughton RW, Voors AA, Whellan DJ, Zannad F, Califf RM (2011) Effect of nesiritide in patients with acute decompensated heart failure. New Engl J Med 365: 32–43.

Reichert S, Ignaszewski A (2008) Molecular and physiological effects of nesiritide. Can J Cardiol 24 Suppl B: 15B-18B.

Scroggins N, Edwards M, Delgado R, 3rd (2005) Increased cost effectiveness with nesiritide vs. milrinone or dobutamine in the treatment of acute decompensated heart failure. Congest Heart Fail 11: 311–314.

Solin P, Bergin P, Richardson M, Kaye DM, Walters EH, Naughton MT (1999) Influence of pulmonary capillary wedge pressure on central apnea in heart failure. Circulation 99: 1574–1579.

Wilop S, von Hobe S, Crysandt M, Esser A, Osieka R, Jost E (2009) Impact of angiotensin I converting enzyme inhibitors and angiotensin II type 1 receptor blockers on survival in patients with advanced non-small-cell lung cancer undergoing first-line platinum-based chemotherapy. J Cancer Res Clin Oncol 135:1429–1435.

Young JB, Abraham W, Stevenson L, Horton D, Elkayam U, Bourge R (2002) Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure-A randomized controlled trial. JAMA 287:1531–1540.

Zakir RM, Berkowitz RL, Saric M, Ashtyani H (2005) A comparison of nesiritide vs. epoprostenol in a patient with precapillary pulmonary hypertension due to scleroderma complicated by postcapillary pulmonary hypertension. Congest Heart Fail 11:331–334.