B-type natriuretic peptides and thyroid disease

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ABSTRACT

Natriuretic peptide hormones, a family of vasoactive peptides with many favorable physiological properties, have emerged as useful markers in cardiovascular disease. In particular, B-type natriuretic peptide (BNP) is a cardiac neurohormone secreted by the left cardiac ventricle as a response to ventricular volume expansion, pressure overload and resultant increased wall tension, directly correlated with both left ventricular filling and pulmonary wedge pressure. It is nowadays considered an important diagnostic tool, adding information to clinical judgment in the evaluation of patients with acute dyspnea and a potential guide to the treatment of chronic heart failure. Moreover, the prognostic value of BNP has been established in several studies, both in post-myocardial infarction patients with asymptomatic left ventricular dysfunction and in patients with overt heart failure. A wide spectrum of cardiac changes is observed in thyroid dysfunctions. In this paper we review the relationship between natriuretic peptide concentrations and different thyroid states.

INTRODUCTION

B-type natriuretic peptide (BNP) is produced in ventricular cardiomyocytes and secreted in response to volume expansion or pressure overload. BNP (32 amino acids), which is the C-terminal part of the proBNP molecule, is secreted together with an N-terminal fragment (76 amino acids) [N-terminal pro-B-type natriuretic peptide (NT-proBNP)] and both peptides are present in human plasma. NT-proBNP seems to have a longer plasma half-life than BNP and it might therefore be more stable in plasma (1).

BNP and NT-proBNP have proven to be a useful tool for diagnosing and monitoring congestive heart failure (2-4). Both peptides are mostly elevated in patients with heart failure: their elevations correlate to the degree of cardiac insufficiency, giving the same information when diagnosing left ventricular dysfunction (5-7).

BNP (or NT-proBNP) concentrations seem to be the most powerful measure in identifying congestive heart failure as the cause of dyspnea, when measured at admission to hospital (8). Thus, BNP or NT-proBNP measurements are expected to provide considerable information in the clinical situation with dyspnea of unknown origin (6, 8, 9), and the peptides have a strong prognostic value in predicting death or future cardiac events (10).

The neurohormonal responses to heart failure is strongly related to vasopressor systems, including the sympathetic, renin–angiotensin– aldosterone, endothelin and vasopressin systems (which tend to have antinatriuretic, antidiuretic, vasopressor and hypertrophic effects), counterbalanced by vasodilator systems, including dopamine, some prostaglandins, adrenomedullin and cardiac natriuretic peptides (with natriuretic, diuretic, vasodilating and anti-proliferative effects). The increase in synthesis and release of the natriuretic peptides in heart failure represents a true beneficial compensatory response. Secretion of cardiac peptides is modulated by circulating and tissutal angiotensin II and endothelin I (11, 12). Additional modulating influences upon plasma concentrations of natriuretic peptides include age, sex, renal function, thyroid and glucocorticoid status, obesity and cardioactive drugs.

The relationship between cardiac dysfunction and plasma concentrations of cardiac natriuretic peptides gives strength to their diagnostic and prognostic applications and their potential utility in adjusting anti-heart failure therapy (13).

Serum natriuretic peptide concentrations may be altered in different thyroid states (14). Wei et al. (15) reported a significant elevation in plasma BNP concentrations in patients with hyperthyroidism and this increase was largely due to hyperthyroidism-induced left ventricular dysfunction. An experimental study demonstrated that thyroid hormones directly increased myocardial gene expression of natriuretic peptides (16). This seems to reflect distinct atrial and ventricular cardiac dysfunction in thyroid hormone excess or, alternatively, mirrors a direct effect of thyroid hormones on gene expression of natriuretic peptides (16, 17).

Only a limited number of reports in the medical literature investigate the relationship between thyroid hormones and serum NT-proBNP concentrations. Schultz et al. (18) demonstrated that serum concentrations of NT-proBNP were strongly influenced by thyroid function: the higher the thyroid function, the

higher the NT-proBNP concentrations. Furthermore, treatment of thyroid disfunction resulted in a significant increase in NT-proBNP in hypothyroid patients and a decrease in hyperthyroid patients.

STUDIES ON CORRELATION BETWEEN NATRIURETIC PEPTIDES AND THYROID DISEASE

In the study of Arikan et al. (19) 36 patients with hyperthyroidism, 25 patients with hypothyroidism and 34 age-matched euthyroid control subjects were included. They evaluated serum NT-proBNP concentrations in both hyperthyroid and hypothyroid patients to determine the relationship between NT-proBNP and echocardiographic parameters in hyperthyroid or hypothyroid conditions. Serum NT-proBNP concentrations in hyperthyroid patients were higher than those of both control subjects and hypothyroid patients. However, mean serum NT-proBNP concentrations in the hypothyroid group were not significantly different from those in control subjects. There was a significant positive correlation between serum NT-proBNP concentrations and thyroid hormones. However, they could not determine any correlation between serum NT-proBNP and thyroid stimulating hormone (TSH) concentrations. Serum NT-proBNP concentrations were positively correlated with left ventricle end-diastolic diameters (LVDd), interventricular septum thickness (IVS) and negatively correlated with left ventricular ejection fraction (LVEF). Mean heart rate in the hyperthyroid group was significantly higher than in the control group; however, there was no significant difference between control subjects and the hypothyroid group. There was a positive correlation between serum NT-proBNP concentrations and heart rate.

These findings demonstrated that serum NT-proBNP concentrations may be more affected by high thyroid hormone concentrations. In hyperthyroidism, cardiac output increases as a result of increased stroke volume and rapid heart rate, and congestive heart failure is a frequent complication in patients with thyrotoxicosis (20, 21). However, serum NT-proBNP concentrations correlated positively with LVDd and IVS in all subjects (control, hyperthyroid, hypothyroid). These cardiac changes themselves may lead to secretion of NT-proBNP. Hyperthyroidism may lead to cardiac structural changes in ventricular myocytes that are undetermined by conventional echocardiography and these changes in cardiac functions may be responsible for elevation of NT-proBNP concentrations.

Less is known about correlation between NT-proBNP and hypothyroidism. Manuchehri et al. (22) reported that NT-proBNP concentrations decreased in hypothyroidism. On the other hand, Christ-Crain et al. (14) suggested that atrial natriuretic peptide and NT-proBNP concentrations were altered, with a more pronounced effect in hyperthyroidism than in hypothyroidism.

EFFECT OF THYROID DISEASE TREATMENT ON NATRIURETIC PEPTIDE CONCENTRATIONS

Schultz et al. (18) studied clinical and subclinical thyroid diseases to evaluate the influence of thyroid disease treatment on NT-pro-BNP. Hypothyroid patients as well as subclinical hypothyroid subjects were treated with L-thyroxine (L-T4), aiming at normalization of free T4, free T3 and TSH concentrations; hyperthyroid patients were treated with mercaptoimidazole and/or radio-iodine, aiming at normalization of free T4 and free T3; finally, subclinical hyperthyroid subjects were treated with radio-iodine, aiming at normalization of serum TSH.

These Authors found that serum concentrations of NT-pro-BNP were highly affected by thyroid function. Over the broad range of thyroid function from hypothyroidism to hyperthyroidism, both serum free T4 and free T3 and TSH concentrations correlated significantly with NT-proBNP. Treatment of dysthyroid states resulted in significant reductions in NT-proBNP concentrations in hyperthyroidism and increased concentrations in hypothyroidism.

Even treatment of subclinical disease resulted in a change in NT-pro-BNP concentrations: increasing when subclinical hypothyroid subjects were given L-T4 and reducing when subclinical hyperthyroid subjects were treated with radio-iodine to normalize their serum TSH. Thus, abnormal values of serum TSH concentrations might not only reflect a subtle change in the pituitary–thyroid feedback, but also a more widespread thyroid hormone effect at the tissue level, such as the heart.

Several explanations of these findings was hypothesized (18). Most evidently, thyroid hormones may directly affect expression and secretion of BNP in cardiac myocytes. At this regard, Kohno et al. (16) found a dose-dependent stimulation of BNP induced by both T4 and T3 on cultured rat ventricle myocytes. Furthermore, Liang et al. (17) demonstrated that *in vitro* T3 in rat ventricle myocytes increased BNP mRNA and BNP promoter activity, which was accompanied by an increase in myocytes size and protein synthesis. Therefore, the increased NT-proBNP concentrations may also be a direct result of hyperthyroidism. Mean heart rate was significantly higher in hyperthyroid patients than in control subjects. There was a positive correlation between serum NT-proBNP concentrations and heart rate. Heart rate, which reflects sympathetic activity that is stimulated by β-adrenergic activation, may increase BNP mRNA levels. Specific cardiac β-adrenergic receptors in heart muscle are up-regulated and the sympathetic system is activated in hyperthyroidism (23, 24). This activated adrenergic system may affect serum NT-proBNP concentrations (25, 26). These results imply that increased sympathetic activity may affect NT-proBNP concentrations in hyperthyroid patients.

CONCLUSIONS

Data on the association between natriuretic peptides and thyroid disfunction are rather weak. Certainly, natriuretic peptide concentrations are influenced by thyroid function with reduced levels in hypothyroidism and elevated levels in hyperthyroidism. BNP expression and secretion seems to be stimulated by thyroid hormones and, when using this assay in clinical practice, clinicians should be aware of both overt and subclinical hyperthyroidism as a cause of elevated concentrations. Mild elevations in BNP or NT-proBNP concentrations should, therefore, always be accompanied by a thyroid function screening test.

REFERENCES

1. Costello-Boerrigter LC, Boerrigter G, Redfield MM, et al. Aminoterminal pro-B-type natriuretic peptide and B-type natriuretic peptide in the general community. J Am Coll Cardiol 2006;47:345-53.
2. Mueller C, Scholer A, Laule-Kilian K, et al. Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea. N Engl J Med 2004;350:647-54.
3. McCullough PA, Nowak RM, McCord J, et al. B-type natriuretic peptide and clinical judgment in emergency diagnosis of heart failure: analysis from Breathing Not Properly (BNP) Multinational Study. Circulation 2002;106:416-22.
4 Hess G, Moecks J, Zdunek D. N-Terminal-proBNP (NT-proBNP) as an indicator of cardiac dysfunction. A study in patients presenting with suspected cardiac disorders. Z Kardiol 2005;94:247-54.
5. Hunt PJ, Richards AM, Nicholls MG, et al. Immunoreactive amino-terminal pro-brain natriuretic peptide (NT-PROBNP): a new marker of cardiac impairment. Clin Endocrinol 1997;47:287-96.
6. Hammerer-Lercher A, Neubauer E, Müller S, et al. Head-to-head comparison of N-terminal pro-brain natriuretic peptide, brain natriuretic peptide and N-terminal pro-atrial natriuretic peptide in diagnosing left ventricular dysfunction. Clin Chim Acta 2001;310:193-7.
7. Richards AM, Doughty R, Nicholls MG, et al. Plasma N-terminal pro-brain natriuretic peptide and adrenomedullin. Prognostic utility and prediction of benefit from carvedilol in chronic ischemic left ventricular dysfunction. J Am Coll Cardiol 2001;37:1781-7.
8. Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002;347:161-7.
9. Morrison LK, Harrison A, Krishnaswamy P, et al. Utility of a rapid B-natriuretic peptide assay in differentiating congestive heart failure from lung disease in patients presenting with dyspnea. J Am Coll Cardiol 2002;39:202-9.
10. Nielsson JC, Groenning BA, Nielsen G, et al. Left ventricular remodelling in the first year after acute myocardial infarction and the predictive value of N-terminal pro brain natriuretic peptide. Am Heart J 2002;143:696-702.
11. Leskinen H, Vuolteenaho O, Ruskoaho H. Combined inhibition of endothelin and angiotensin II receptors blocks volume load-induced cardiac hormone release. Circ Res 1997;80:114-23.
12. Skvorak JP, Nazian SJ, Dietz JR. Endothelin acts as a paracrine regulator of stretch-induced atrial natriuretic peptide release. Am J Physiol 1995;269:R1093-8.
13. Richards AM, Lainchbury JG, Troughton RW, et al. Clinical applications of B-type natriuretic peptides. Trends Endocrinol Metab 2004;15:170-4.
14. Christ-Crain M, Morgenthaler NG, Meier C, et al. Pro-A-type and N-terminal pro-B-type natriuretic peptides in different thyroid function states. Swiss Med Wkly 2005; 135:549–54.
15. Wei T, Zeng C, Tian Y, et al. B-type natriuretic peptide in patients with clinical hyperthyroidism. J Endocrinol Invest 2005;28:8-11.
16. Kohno M, Horio T, Yasunari K, et al. Stimulation of brain peptide release from the heart by thyroid hormone. Metabolism 1993;42:1059-64.
17. Liang F, Webb P, Marimuthu A, et al. Triiodothyronine increases brain natriuretic peptide (BNP) gene transcription and amplifies endothelin-dependent BNP gene transcription and hypertrophy in neonatal rat ventricular myocytes. J Biol Chem 2003;278:15073-83.
18. Schultz M, Faber J, Kistorb C, et al. N-Terminal-pro-B-type natriuretic peptide (NT-pro-BNP) in different thyroid function states. Clin Endocrinol 2004;60:54-9.
19. Arikan S, Tuzcu A, Gokalp D, et al. Hyperthyroidism may affect serum N-terminal pro-B-type natriuretic peptide levels independently of cardiac dysfunction. Clin Endocrinol 2007;67:202-7.
20. Klein I, Levey GS. The cardiovascular system in thyrotoxicosis. In: Braverman LE, Utiger RU, eds. Werner and Ingbar's the Thyroid. Philadelphia: Lippincott, 2000;596-604.
21. Dörr M, Wolff B, Robinson DM, et al. The association of thyroid functions with cardiac mass and left ventricular hypertrophy. J Clin Endocrinol Metab 2005;90:673-7.
22. Manuchehri AM, Jayagopal V, Kilpatrick ES, et al. The effect of thyroid dysfunction on N-terminal-pro-B-type natriuretic peptide concentrations. Ann Clin Biochem 2006;43:184-8.
23. Shimoike H, Iwai N, Kinoshita M. Different regulation of natriuretic peptide genes in infarcted rat hearts. Clin Exp Pharmacol Physiol 1997;24:23-30.
24. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. N Engl J Med 2001;344:501-9.
25. Passino C, Severino S, Poletti R, et al. Aerobic training decreases B-type natriuretic peptide expression and adrenergic activation in patients with heart failure. J Am Coll Cardiol 2006;47:1835-9.
26. Hartmann F, Kurowski V, Maghsoudi A, et al. Plasma catecholamine and N-terminal proBNP in patients with acute myocardial infarction undergoing primary angioplasty. Relation to left ventricular function and clinical outcome. Z Kardiol 2003;92:73-81.