Detection of left ventricular enlargement and impaired systolic function with plasma N-terminal pro brain natriuretic peptide concentrations

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Background Brain- and N-terminal pro brain natriuretic peptide (NT-proBNP) have been identified as promising markers for heart failure. However, previous studies have revealed that they may hold insufficient diagnostic power for implementation into clinical practice because of a significant overlap in the range of plasma levels between healthy subjects and subjects with heart failure. We hypothesized that imprecision of the reference method (ie, the echocardiographic evaluation of left ventricular [LV] function) may have affected results from those earlier studies. We therefore wanted to investigate the diagnostic potential of NT-proBNP with magnetic resonance imaging as the reference method for the cardiac measurements.

Methods Forty-eight patients with stable symptomatic heart failure in New York Heart Association functional classifications II to IV were examined once with blood samples and magnetic resonance imaging along with 20 age-matched and gender-matched healthy control subjects.

Results NT-proBNP was associated with LV end-diastolic ($r = 0.69$; $P < .0001$) and end-systolic ($r = 0.73$; $P < .0001$) volume indices, LV mass index ($r = 0.69$; $P < .0001$), and LV ejection fraction ($r = -0.75$; $P < .0001$). Receiver operating characteristic curves were calculated for the ability of NT-proBNP to detect LV end-diastolic volume index (>105 mL $\cdot$ m^{-2}[cut-off]; sensitivity/specificity, 82%/87%), LV end-systolic volume index (>35 mL $\cdot$ m^{-2}; sensitivity/specificity, 86%/86%), LV mass index (>152 g $\cdot$ m^{-2}; sensitivity/specificity, 85%/86%), and LV ejection fraction (<58%; sensitivity/specificity, 84%/85%) deviating more than 2 standard deviations from control values.

Conclusion NT-proBNP is a powerful marker for LV dimensions and systolic function in patients with heart failure and discriminates well between healthy subjects and subjects with impaired LV systolic function or increased LV dimensions. (Am Heart J 2002;143:923-9.)

Congestive heart failure is a major public health problem in Western countries. The incidence and prevalence rates of systolic heart failure in the population are high,[1,2] and despite considerable advancement in the treatment of heart failure in the past 20 years, largely the result of introduction of angiotensin-converting enzyme inhibitors,[3] β-blockers,[4] and spironolactone,[5] mortality rate remains high.[3-5] Undertreatment because of underdiagnosis is a significant problem,[2] and currently, diagnosis of systolic heart failure relies mainly on an echocardiographic evaluation of left ventricular ejection fraction (LVEF).[6] In an attempt to bypass this time-consuming and cost-consuming diagnostic step, biochemical markers have been suggested as alternative indicators of disease. Efforts have focused on the natriuretic peptides, among which brain natriuretic peptide (BNP)[7-9] and its aminoterminal portion N-terminal pro BNP (NT-proBNP),[10] which may hold advantages because of greater stability,[11] have proven especially promising. Elevated concentrations of BNP and NT-proBNP have been shown to be associated with left ventricular (LV) systolic dysfunction and increased myocardial mass in patients with heart failure,[9] and community studies have pointed to BNP as a promising marker for the clinical diagnosis of heart failure[12] and for asymptomatic LV systolic dysfunction.[13,14] However, in previous studies, overlaps in the natriuretic peptide plasma levels between healthy subjects and subjects with impaired LV

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performance have been reported, to some degree limiting the potential diagnostic value of the neurohumoral marker in the individual patient. We hypothesized that imprecision in the echocardiographic evaluation of LV function as the reference method may have affected results from earlier studies and wanted to investigate the diagnostic potential of NT-proBNP with high-accuracy magnetic resonance imaging (MRI) for the cardiac measurements.[15]

Methods

Patients

A total of 48 patients with heart failure from mixed causes were consecutively included from 7 Danish hospital-based outpatient heart failure clinics. Both male and female patients with impaired LV systolic function (with routine echocardiography within 3 months before the examination) and symptomatic heart failure (New York Heart Association functional classifications II to IV) for 3 months or more before examination in the study were eligible. In addition, a stable clinical condition, defined as no worsening of dyspnea or peripheral edema or need for drug adjustments for at least 2 weeks before the study, was required. Exclusion criteria were acute myocardial infarction or unstable angina within 28 days before the examination, valvular heart disease, uncontrolled hypertension, and heart failure caused by systemic disease or alcohol abuse. β-Blocker treatment and severe renal disease (plasma creatinine level > 0.2 mmol $\cdot L^{-1}$) were exclusion criteria in the study because β-blockade in patients with heart failure[16] and elevated plasma levels of creatinine[13] have previously been associated with increased plasma concentrations of BNP. Other exclusion criteria with respect to the MRI examination were atrial fibrillation, implanted pacemaker, implanted mechanical heart valves, implanted insulin pump, and claustrophobia.

In addition to the patients with heart failure, 20 age-matched and gender-matched healthy controls with no history or symptoms of heart disease or other chronic disease were included. The regional ethics committee approved the study, and the patients gave written informed consent.

Study design

Patients and control subjects were examined with blood samples and MRI at the Danish Research Center of Magnetic Resonance. Blood samples were taken immediately before the MRI examination. To obtain comparable measurements regarding potential hormonal circadian rhythm, all subjects were examined between 1 PM and 4 PM.

NT-proBNP analysis

Blood samples for NT-proBNP analysis were taken after 20 minutes rest. NT-proBNP was measured with a novel specific immunoassay on the basis of a sandwich format with unextracted ethylenediamine tetraacetic acid plasma. The sensitivity of the assay was <3.0 pmol $\cdot L^{-1}$ and the intraassay and interassay coefficients of variation were 1.3% and 4.8%, respectively.[17]

Magnetic resonance imaging investigation

All MRI studies were performed on a whole-body MRI scanner (Siemens Impact Magnetom, Siemens AG, Erlangen, Germany), operating at 1.0 T with a phased array chest coil as the receiver coil. Each slice was obtained during 15 heartbeats with an electrocardiograph-triggered breath-hold fast low-angle shot cinematographic pulse sequence, with a temporal resolution of 55 ms. Slice thickness was 10 mm with no interslice gap, field of view was 263×350 mm^2, and matrix size was 126×256. The left ventricle was covered with a stack of 10 to 15 slices in the true short axis plane.[18]

A blind analysis of the MRI examinations was undertaken in 1 batch. In each examination, the number of slices to be included in the covering of the LV in end-diastole and end-systole was decided, and typically, 1 slice less in end-systole than in end-diastole was included because of systolic shortening of the left ventricle. End-systole was chosen at the point where the total LV blood pool was smallest. On each end-diastolic frame, both inner and outer circumferences of the LV myocardium were manually defined. On each systolic frame, the endocardial border of the LV was defined. The papillary muscles were included as part of the myocardium but not as part of the chamber volume.[19] Areas enclosed by the borders marked for LV volumes and myocardium were determined with planimetry, and the corresponding volumes were calculated with multiplication of the slice thickness. Finally, total volumes of the LV were calculated with simple addition of the individual slice volumes in the stack of contiguous slices covering the LV. In this manner, LV end-diastolic volume, LV end-systolic volume, and LVEF were determined. LV myocardial mass was determined as the difference between the inner and outer circumferences of the LV myocardium in end-diastole multiplied by a density factor of 1.05.[20]

Heart rate was measured continuously during the MRI investigation and determined as the average heart rate during the examination. Blood pressure was measured before the examination after 20 minutes rest in a sitting position. In addition, body weight and body height were measured and body surface area was calculated.[21] Subsequently, all MRI variables, apart from LVEF, were indexed with division with body surface area. A simple measure of LV systolic global wall stress (SWS) was calculated with the formula: SWS $=$ $0.133 \times$ systolic blood pressure $\times$ [1 + ($3 \times$ LV end-systolic volume index/LV myocardial mass index)].[22]

Statistics

Verification of normal distribution of data was accomplished with histograms and normal plots. LV volume measures, ejection fraction, myocardial mass, and SWS fit into a normal distribution model, whereas NT-proBNP data showed a logarithmic normal distribution and was consequently logarithmically transformed. Two sample *t* tests between mean values of variables in the 2 groups were performed. Subsequently, correlation analyses were performed between log NT-proBNP and LV volumes, myocardial mass, ejection fraction, and SWS. Finally, receiver operating characteristic (ROC) curves for the ability of NT-proBNP to detect LV volumes and myocardial mass 2 standard deviations (SD) above and LVEF 2 SD below normal control values were calculated, and the optimal combination of sensitivity and specificity,

Table I. Characteristics for heart failure patients and normal controls

	Patients (n = 48)	Controls (n = 20)	P
Mean age (y)	66.2 (63.9-68.6)	67.9 (65.4-70.4)	NS
Male	85%	90%	NS
Ischemic etiology	75%	–	–
Past myocardial infarction	52%	–	–
Hypertension	38%	–	–
Diabetes	10%	–	–
NYHA functional class II	51%	–	–
NYHA functional class III	46%	–	–
NYHA functional class IV	3%	–	–
ACE inhibitors	94%	–	–
Angiotensin II antagonists	6%	–	–
Loop diuretics	96%	–	–
Digitalis	73%	–	–
Aspirin	71%	–	–
Lipid-lowering drugs	52%	–	–
Mean HR (bpm)	79.5 (75.5-83.6)	67.7 (63.8-71.6)	.001
Mean SBP (mm Hg)	136 (128-145)	135 (128-143)	NS
Mean DBP (mm Hg)	76.8 (73.4-80.2)	81.6 (77.0-86.1)	NS
Mean LVEDVI (ml · m^{-2})	154 (136-175)	69.9 (62.1-77.6)	<.0001
Mean LVESVI (ml · m^{-2})	111 (93.2-128)	21.6 (18.7-24.5)	<.0001
Mean LVmassI (g · m^{-2})	178 (164-193)	115 (107-123)	<.0001
Mean LVEF (%)	31.0 (27.5-34.5)	68.8 (66.4-71.3)	<.0001
Mean SWS (mm Hg · ml · g^{-1})	49.0 (45.7-52.3)	28.1 (26.2-30.1)	<.0001
Mean NT-proBNP (pmol · L^{-1})*	130 (92.6-182)	16.4 (11.8-22.7)	<.0001
Mean BSA (m^2)	1.49 (1.44-1.54)	1.54 (1.46-1.62)	NS

Values in parenthesis represent 95% CI. *NYHA*, New York Heart Association functional class; *ACE*, angiotensin-converting enzyme; *HR*, heart rate; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *BSA*, body surface area; *NS*, not significant.
*Geometric mean concentrations.

defined as the point on the ROC curve closest to the upper left corner of the diagram, were derived. All tests were 2-sided, and a significance level of 5% was used. All tests were performed in the Statistical Analysis System (SAS Institute Inc, Cary, NC).

Results

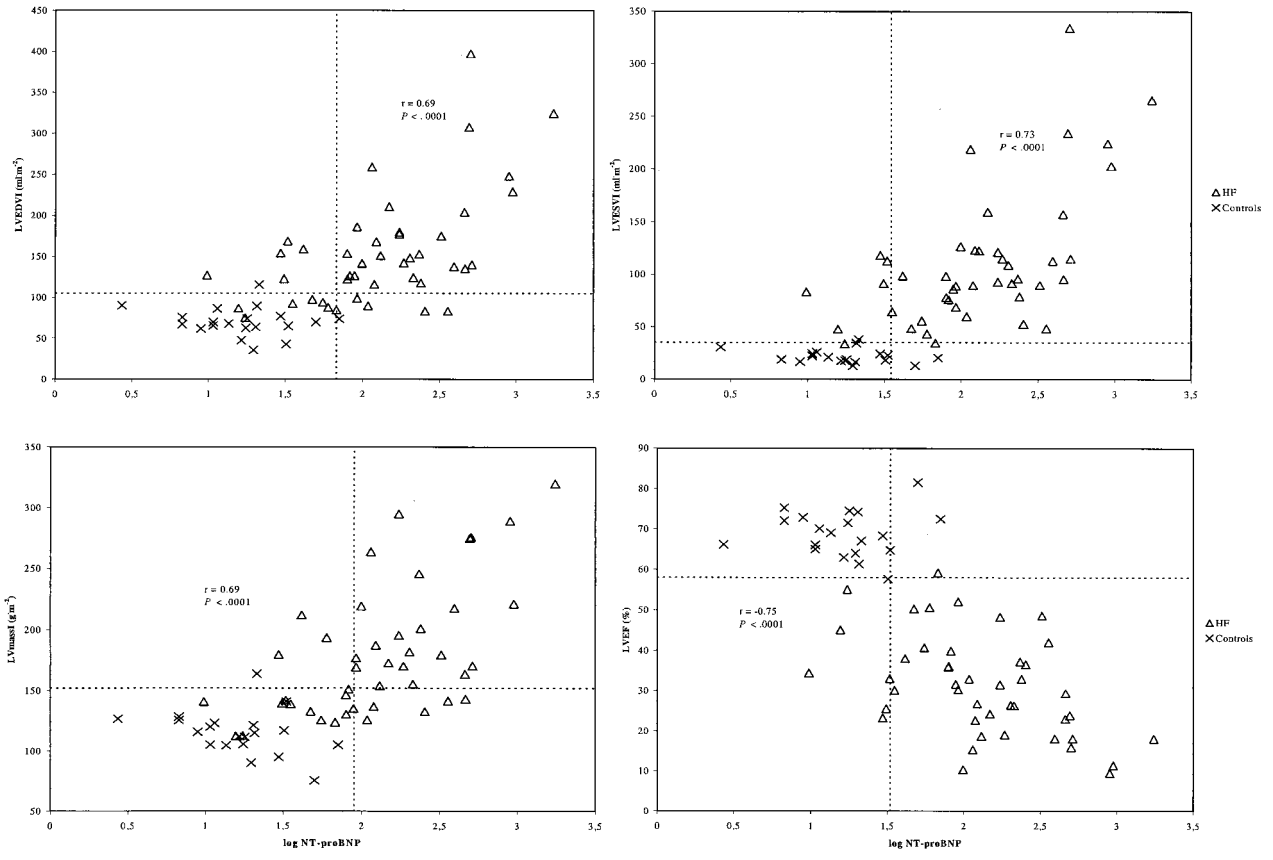
Mean values and 95% confidence intervals for all variables are given in Table I. The groups were matched for age and gender. For body surface area and systolic and diastolic blood pressure, no differences were found between the groups. The heart rate was significantly higher in the patients than in the healthy control subjects. In the patients with heart failure, mean LV end-diastolic volume index (LVEDVI), end-systolic volume index (LVESVI), myocardial mass index (LVmassI), and SWS exceeded control values, and mean LVEF was less than the control value (Table I). The plasma level of NT-proBNP exceeded the control value substantially (Table I). An elevated plasma level of NT-proBNP was associated with high values of LVEDVI ($r = 0.69$; $P < .0001$), LVESVI ($r = 0.73$; $P < .0001$), LVmassI ($r = 0.69$; $P < .0001$), and SWS ($r = 0.58$; $P < .0001$), and a high NT-proBNP level was associated with a low LVEF ($r = -0.75$; $P < .0001$; Figure 1).

Receiver operating characteristic curves

ROC curves were calculated for the ability of NT-proBNP to detect LV measures deviating > 2 SD from the normal control values. For LVEDVI (cut-point: >105 mL · m^{-2}), the point on the ROC curve closest to the upper left corner of the diagram had a sensitivity of 82% and a specificity of 87%, and the corresponding NT-proBNP concentration was 68 pmol · L^{-1}. For LVESVI (cut-point: >35 mL · m^{-2}), a sensitivity of 86% and a specificity of 86% were found, corresponding with an NT-proBNP level of 35 pmol · L^{-1}. For LVmassI (cut-point: >152 g · m^{-2}), a sensitivity of 85% and a specificity of 86% were found, with NT-proBNP of 89 pmol · L^{-1}. For LVEF (cut-point: <58%), a sensitivity of 84% and a specificity of 85% could be derived, corresponding with an NT-proBNP concentration of 33 pmol · L^{-1}.

With demand of a sensitivity of the marker of at least 90%, the following diagnostic ability of NT-proBNP to detect deviations of > 2 SD from control values could be obtained from the ROC curves: LVEDVI (cut-point:

Figure 1



Associations between plasma level of (log_{10}) NT-proBNP and LV dimensions and systolic function. *Horizontal dotted lines* indicate cut-off levels for LV end-diastolic and end-systolic volumes, myocardial mass, and ejection fraction 2 SDs from control values. *Vertical dotted lines* indicate corresponding NT-proBNP levels for optimal combination of sensitivity and specificity of marker to detect LV measures > 2 SDs from control values. *HF,* Patients with heart failure.

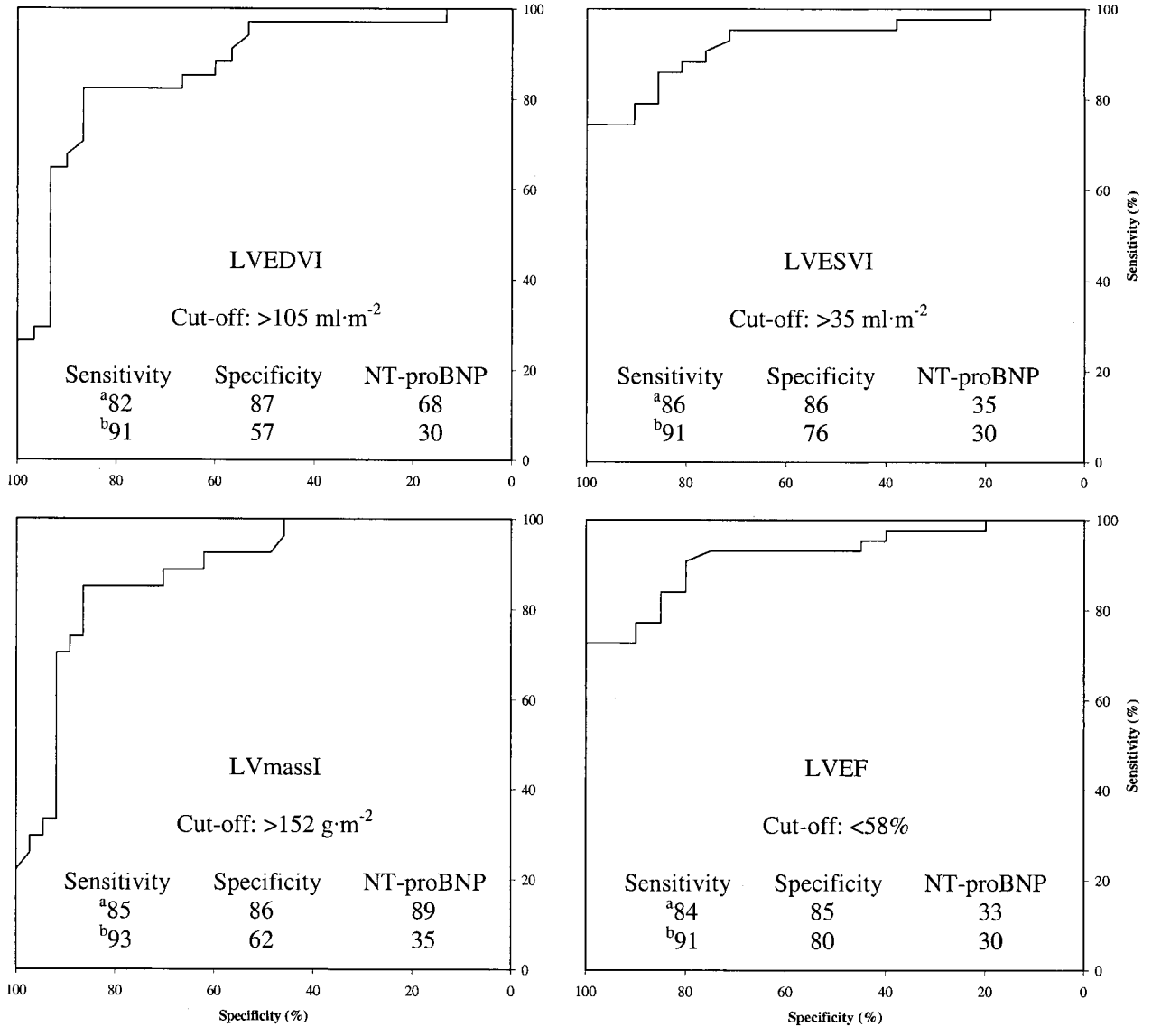
>105 mL · m^{-2}): 91% sensitivity/57% specificity; NT-proBNP = 30 pmol · L^{-1}; LVESVI (cut-point: >35 mL · m^{-2}): 91% sensitivity/76% specificity; NT-proBNP = 30 pmol · L^{-1}; LVmassI (cut-point: >152 g · m^{-2}): 93% sensitivity/62% specificity; NT-proBNP = 35 pmol · L^{-1}; LVEF (cut-point: $<58\%$): 91% sensitivity/80% specificity; NT-proBNP = 30 pmol · L^{-1} (Figure 2).

Discussion

The main finding of our study is that the plasma level of NT-proBNP seems to be a much stronger marker for LV systolic function than could be expected from previous studies with echocardiography as the reference method. Second, this is the first study to show powerful associations between NT-proBNP and LV volumes, myocardial mass, and SWS in patients with heart failure. The consistency of our results strengthens the potential diagnostic role of NT-proBNP in heart failure and suggests that NT-proBNP may be able to detect increased LV dimensions, even in the absence of LV systolic impairment.

Our results support and offer pathophysiologic insight into previous studies with clinical endpoints, which have indicated that natriuretic peptides may be helpful in diagnosis of subjects with symptoms suggestive of heart failure. Previously, BNP has proven useful for detection of asymptomatic LV dysfunction[14] and heart failure in the general population,[23] for discrimination between decompensated heart failure and other causes of breathlessness that lead to hospital admission[24] and for identification of subjects who were subsequently diagnosed with heart failure from a group of patients with symptoms suspected by a general practi-

Figure 2



ROC curves for ability of plasma concentration of NT-proBNP to detect LV dimensions and ejection fraction deviating > 2 SDs from normal control values. [a]Corresponds to point on ROC curve closest to upper left corner of diagram. [b]Demanding sensitivity of at least 90%.

tioner to be caused by heart failure.[12] These findings suggest that analysis for BNP or NT-proBNP or both may have a place as an initial screening tool for patients suspected of heart failure. From this point of view, a high sensitivity of the diagnostic test is essential to miss as few subjects as possible with heart failure, whereas a slightly reduced specificity of the test is acceptable because subjects with false-positive test results are likely to be sent to the hospital for further examination. Previous population-based studies have consistently reported high negative predictive values of the marker for detection of LV systolic dysfunction or heart failure, whereas positive predictive values have been lower.[12-14,23] It should be noted, however, that those patients with false-positive results in terms of exhibiting a normal systolic function may in fact have other cardiac dysfunction, such as LV hypertrophy,[9] isolated diastolic heart failure,[25] or right ventricular failure,[26] all of which are conditions that have previously been associated with increased plasma levels of

BNP. Clearly, this issue warrants further investigation, but we do not see it as an impediment for the introduction of the marker into clinical practice because further examination with echocardiography is well indicated in these patient categories. A fast, low-cost, rule-out screening device of this kind would be of profound importance for the complicated and time-consuming initial diagnosis of this important disease.[6] We have previously shown that the plasma level of NT-proBNP varies with age and gender,[23] which is of special concern for the choice of NT-proBNP cut-off level. The NT-proBNP plasma concentration suggested with the ROC curves in this study may therefore be limited to patients and settings similar to ours.

Study limitations

Our study was not community-based but reflects the ability of NT-proBNP to distinguish between LV morphology and function in consecutively included patients from hospital-based heart failure clinics and age-matched and gender-matched healthy volunteers. This is evidently a weakness, but, as can be seen with Figure 1, LV dimensions and systolic function overlapped between the 2 groups, approaching a realistic and clinically relevant setting for the study.

The use of drug therapy in the heart failure group is a potential problem but is not likely to have biased the results in favor of the diagnostic ability of NT-proBNP because, if anything, treatment with angiotensin-converting enzyme inhibitors and loop diuretics lower the plasma level of NT-proBNP, making it more difficult for the marker to distinguish between the groups.[27]

Conclusion

Our morphologic results support previous studies with clinical endpoints, which have indicated that NT-proBNP will be useful for diagnostic screening for impaired LV systolic function in patients with symptoms suggestive of heart failure, only remitting patients with elevated values for further diagnostic evaluation.

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Effects of the thromboxane synthetase inhibitor and receptor antagonist terbogrel in patients with primary pulmonary hypertension

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Background Circulating mediators, including thromboxane A2, the vasoconstrictor, platelet aggregant, and smooth muscle mitogen, may contribute to the progression of vascular narrowing in primary pulmonary hypertension (PPH).

Methods To further understand the contribution of thromboxane and to provide novel therapy for PPH, we administered the potent orally active thromboxane synthetase inhibitor and thromboxane receptor antagonist terbogrel for 12 weeks to patients with New York Heart Association functional classification II and III PPH. The study had a multicenter randomized placebo-controlled design. The primary endpoint was a change in the distance walked during 6 minutes. The pharmacologic effects of terbogrel on thromboxane and prostacyclin metabolism also were studied.

Results Although the planned enrollment was 135 patients, the study was halted after only 71 patients had been randomized because of the unforeseen side effect of leg pain, which occurred almost exclusively in patients with terbogrel treatment. Only 52 patients completed the 12-week study, and only 22 patients (31%) were fully compliant with the study medication. The leg pain confounded the primary endpoint of walking distance. On an intention-to-treat analysis, no improvements in 6-minute walk distance or in hemodynamics in patients with terbogrel treatment were seen. However, terbogrel was effective from a pharmacologic standpoint, reducing thromboxane metabolites by as much as 98% ($P <$ .0001), with a modest but statistically insignificant (39%) rise in prostacyclin metabolites.

Conclusion Inhibition of thromboxane with an orally active agent is feasible in PPH, but the incidence of severe leg pain with terbogrel precludes its use in this disorder. Similar therapeutic efforts, with other thromboxane inhibitors, should be considered. (Am Heart J 2002;143:923-23.)

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