Impact of Hemoglobin on Plasma Pro-B-Type Natriuretic Peptide Concentrations in the General Population

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Background: Age, sex, and renal function contribute to variations in plasma concentrations of B-type natriuretic peptide (BNP) and its molecular precursor (proBNP). Recent studies indicate that anemia may also affect proBNP concentrations in patients with heart failure or stroke. However, the impact of hemoglobin status on proBNP concentrations has not been established in the general population.

Methods: In the 4th examination in the Copenhagen City Heart Study, we performed a nested case-control study of 6238 individuals from a Danish general population. Of these, 3497 randomly selected participants also underwent an echocardiographic examination. The population was stratified into groups depending on health and hemoglobin status. Correlations between hemoglobin and proBNP concentrations were examined by simple and multiple regression analyses, adjusted for variables known to influence the proBNP plasma concentration.

Results: The mean proBNP concentration was increased 1.7-fold in the group with anemia vs the nonanemic group [mean (SD) 42 (45) pmol/L vs 25 (29) pmol/L, P <0.0001, n = 5892]. Multiple regression analysis confirmed an independent effect of hemoglobin on proBNP concentrations. In a selected subgroup without signs or symptoms of heart disease (n = 2855), lower hemoglobin concentrations, defined as <120 g/L in women and <130 g/L in men, were associated with increased circulating proBNP concentrations, but the contribution to the overall variation in proBNP concentrations was modest.

Conclusions: Because moderate anemia is associated with a 1.7-fold increase in proBNP concentrations, hemoglobin concentrations should be taken into consideration in patients with nonspecific symptoms of heart disease and increased proBNP concentrations.

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ProBNP measurement, perhaps most frequently for elderly patients, in whom diffuse symptoms (discomfort, shortness of breath, fatigue) can be signs of both anemia and cardiac disease. We examined the relationship between hemoglobin and proBNP concentrations in the general population (n = 5892). In addition, we assessed the association between proBNP concentrations and hemoglobin status in selected individuals (n = 2855) with healthy left ventricular systolic function and without a history of heart disease.

Materials and Methods

Study Population

This was a nested case-control study within a prospective general population study, the Copenhagen City Heart Study (16, 17). A random sample of 19329 citizens living in a defined area of Copenhagen City was drawn from the Danish Central Population Register and invited to take part in the first examination in 1976-1978. The sample was stratified by sex and age (5-year strata from the age of 20 years) with the main emphasis on the age group from 35 to 69 years. At the 4th examination (2001–2003), the study population consisted of participants from the previous examinations (n = 11600), supplemented by a random sample of individuals from the younger age strata (n = 1000). A total of 12600 individuals were invited and 6238 participated (49.5%); of these, 3497 (56.1%) randomly selected participants underwent an echocardiographic examination. The population was evaluated in 2 different settings: First, all participants with a history of ischemic heart disease, cancer, or diabetes were excluded; the remaining participants were then analyzed as population 2. The study was performed in accordance with the 2nd Helsinki Declaration and approved by the Danish Ethical Committee (no. 100.2039/91). All participants gave informed consent.

Health Examination

We measured blood pressure with a sphygmomanometer on the left upper arm of seated patients after they had rested for 5 min while seated. We obtained information on ischemic heart disease and diabetes; ischemic heart disease was defined as either major ischemic electrocardiogram alterations (defined by Minnesota codes 1.1–3) or a history of hospital admission due to acute coronary artery occlusion, percutaneous coronary intervention, or coronary artery bypass grafting. Diabetes was defined as self-reported disease, use of antidiabetic medicine, or a nonfasting plasma glucose concentration ≥11.1 mmol/L. Body mass index (BMI) was calculated as weight divided by height squared. Anemia was defined according to the WHO guidelines as blood hemoglobin <120 g/L for women and <130 g/L for men (18). Anemia in chronic disease (ACD) was defined as anemia in individuals with known chronic disease (e.g., cancer) or a plasma C-reactive protein concentration >30 mg/L (19). IDA was defined as a transferrin saturation ratio <0.15 (20). Anemia of unknown cause was defined as anemia without any of the above criteria.

Echocardiography

Three experienced echo technicians using GE Vingmed Ultrasound’s Vivid Five with a 2.5-MHz probe (GE Vingmed Ultrasound) performed all echocardiographic examinations as described (4). All echocardiograms were examined offline by 1 expert using the EchoPAC software version 6.4.3f1 (GE Medical). The 16 standard segments, as suggested by the American Society of Echocardiography (21), were used for evaluation of left ventricular ejection fraction (22–24).

Laboratory Analyses

We obtained nonfasting blood samples for measurement of plasma creatinine, hematologic features, and proBNP. Hematologic features, including erythrocyte mean corpuscular volume and mean corpuscular hemoglobin concentration, were measured by use of an Advia 120 (Bayer). Creatinine was analyzed on a Kone 60 (ILS). Blood samples for measurement of plasma proBNP were collected in EDTA-containing vacutainers and immediately centrifuged. The plasma was stored at −70 °C until analysis. ProBNP was measured with a processing-independent assay as described previously (25). This assay quantifies both the N-terminal proBNP (NT-proBNP) 1–76 fragment and the intact precursor (proBNP 1–108) with equimolar affinity. All measurements were performed in duplicate. The interassay imprecision (CV) was 23% at 38 pmol/L, 11% at 76 pmol/L, and 7% at 152 pmol/L (n = 62) (4). Comparison of the processing-independent proBNP assay with the commercial Roche Modular NT-proBNP method (n = 385) revealed correlation data of $r^2 = 0.91$ and $P < 0.0001$, with a mean 1.7-fold difference in molar concentrations.

Statistical Analysis

Plasma proBNP concentrations were positively skewed and logarithmically ($\log_{10}$) transformed before analysis. We performed comparisons between groups by use of independent sample t-test using the Levene test for equality of variances and comparison between age groups by use of ANOVA. We examined associations with covariates by linear regression analysis. We used Pearson correlation coefficients to estimate correlation of proBNP concentrations with covariates. For evaluation of the association between different variables and the proBNP concentration, we performed multiple regression analysis using a model including sex, age, creatinine, BMI, systolic and diastolic blood pressure, and hemoglobin. The percentage of contribution to the variation in proBNP con-
centrations was calculated on the basis of the sum of squares from an ANOVA. P values <0.05 on 2-sided tests were used as the level of significance. The statistical analysis was performed with SPSS 13.0 and STATA 9.2.

**Results**

Of the 6238 individuals who entered the study, 5892 were in population 1 and 2855 were in population 2. Population 1 was divided by hemoglobin status into the following groups: ACD (n = 61), IDA (n = 74), anemia of unknown cause (n = 208), and no anemia (n = 5549). The characteristics of the subgroups are shown in Table 1. Individuals with ACD and anemia of unknown cause were older than the individuals in the other groups (P <0.0001). The group with IDA had lower hemoglobin concentrations, mean corpuscular volume values, and iron content compared with the other anemic groups. Creatinine concentrations were higher in individuals with anemia of unknown cause. As shown in Fig. 1, plasma proBNP concentrations were 1.7-fold higher in the group with anemia compared with the nonanemic group (1.8-fold in ACD, 1.6-fold in IDA, and 1.7-fold in anemia of unknown cause; all P <0.0001). In general, proBNP concentrations increased exponentially with age, but when stratified according to age, proBNP concentrations for the anemic subgroups were still slightly increased compared with the nonanemic group (Fig. 2). Pearson correlation coefficients showed that all parameters were significantly correlated to plasma proBNP concentrations in the nonanemic population (Table 2). In the anemic subgroups, correlations were significant for age, creatinine (not ACD), and systolic blood pressure as expected, whereas the hemoglobin concentration did not correlate with proBNP concentrations because of preselection associated with this parameter.

Multiple regression analysis in the adjusted model showed that all factors known to influence plasma proBNP concentration, including hemoglobin concentration, were significant effectors in the nonanemic population (Table 3). In the anemic group, only age (all anemic subgroups), diastolic blood pressure in the group with ACD, and creatinine in the group with anemia of unknown cause significantly affected the proBNP concentration. Sums of squares showed that age contributed most to the variation in proBNP, but creatinine (3.7% in the group with anemia of unknown cause) and diastolic blood pressure (8.8% in the group with ACD) also contributed significantly. Hemoglobin status contributed significantly in the nonanemic group (0.4%).

Population 2 comprised 1627 women and 1228 men. Hemoglobin concentrations were 135 (9) g/L in women and 148 (9) g/L in men (P <0.0001). Iron status parameters (iron, transferrin, mean corpuscular hemoglobin concentration) differed significantly between men and women, but differences in absolute values were small (Table 1). ProBNP concentrations were 25 (25) pmol/L in women and 19 (27) pmol/L in men (P <0.0001). Overall, plasma proBNP concentrations correlated with age for both sexes (P <0.0001). The population was divided

<p>| Table 1. Characteristics of the population by hemoglobin status and sex.(^a) |
|-------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>n</th>
<th>Healthy women</th>
<th>Healthy men</th>
<th>P (women vs men)</th>
<th>No anemia</th>
<th>ACD</th>
<th>IDA</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>1627</td>
<td>1228</td>
<td>0.01</td>
<td>58.8 (19.3)</td>
<td>70.5 (13.1)</td>
<td>56.7 (17.9)</td>
<td>67.2 (18.4)</td>
</tr>
<tr>
<td>Hemoglobin, g/L</td>
<td>57.2 (17.2)</td>
<td>55.6 (16.0)</td>
<td>0.01</td>
<td>142 (11)</td>
<td>118 (11)</td>
<td>111 (11)</td>
<td>119 (8)</td>
</tr>
<tr>
<td>proBNP, pmol/L</td>
<td>135 (9)</td>
<td>148 (9)</td>
<td>&lt;0.0001</td>
<td>25 (29)</td>
<td>46 (46)</td>
<td>40 (49)</td>
<td>41 (44)</td>
</tr>
<tr>
<td>MCV, fl</td>
<td>25 (25)</td>
<td>19 (27)</td>
<td>&lt;0.0001</td>
<td>90 (5)</td>
<td>89 (8)</td>
<td>83 (8)</td>
<td>91 (6)</td>
</tr>
<tr>
<td>MCHC, mmol/L</td>
<td>90 (5)</td>
<td>90 (5)</td>
<td>0.98</td>
<td>21.1 (0.7)</td>
<td>20.6 (0.9)</td>
<td>20.2 (0.9)</td>
<td>20.9 (0.7)</td>
</tr>
<tr>
<td>Reticular fraction, %</td>
<td>21.0 (0.6)</td>
<td>21.3 (0.7)</td>
<td>&lt;0.0001</td>
<td>14.3 (0.44)</td>
<td>1.47 (0.44)</td>
<td>1.46 (0.45)</td>
<td>1.47 (0.63)</td>
</tr>
<tr>
<td>Transferrin, mg/L</td>
<td>30.2 (11.3)</td>
<td>27.6 (7.2)</td>
<td>&lt;0.0001</td>
<td>15.9 (5.2)</td>
<td>17.3 (5.7)</td>
<td>16.6 (5.4)</td>
<td>11.2 (5.3)</td>
</tr>
<tr>
<td>Iron, mg/L</td>
<td>3.1 (5.9)</td>
<td>2.7 (4.4)</td>
<td>0.91</td>
<td>8.01 (14.0)</td>
<td>80.1 (15.7)</td>
<td>77.9 (18.9)</td>
<td>89.8 (31.8)</td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td>74.4 (11.9)</td>
<td>86.5 (15.0)</td>
<td>&lt;0.0001</td>
<td>74.4 (11.9)</td>
<td>86.5 (15.0)</td>
<td>74.4 (11.9)</td>
<td>86.5 (15.0)</td>
</tr>
</tbody>
</table>

\(^a\) Values are mean (SD). AUC, anemia of unknown cause; hsCRP, high-sensitivity C-reactive protein.

\(^b\) P <0.0001 vs the group without anemia.
according to age (≥ 50 years) for both sexes, and linear regression analysis of concentrations of proBNP and hemoglobin led to low $R^2$ values for all groups (0.012 for women <50 years of age; 0.017 for women ≥50 years of age; 0.001 for men <50 years of age; 0.042 for men ≥50 years of age). However, when patient data were divided into 3 age groups: <50 years, ≥50 and ≥70 years, as recently reported (4), Pearson correlation coefficients showed that the proBNP concentrations were correlated to hemoglobin in all 3 age strata (data not shown).

Multiple regression analysis in the adjusted model showed that the plasma proBNP concentration was significantly correlated with the hemoglobin concentration as well as to variables already known to affect the proBNP concentration (Table 4). Overall, proBNP concentrations were approximately 2 pmol/L higher when the hemoglobin concentration decreased approximately 10 g/L, corresponding to a 0.6% contribution to the overall variation in proBNP concentration. For comparison, the proBNP concentration increased 5 pmol/L per age decade (a 6.3% contribution to the overall variation).

**Discussion**

In this study, we identified a significant correlation between hemoglobin status and proBNP concentrations in the general population, with a 1.7-fold increase in proBNP concentrations in anemic individuals. In the overall population, however, hemoglobin concentration contributed

| Table 2. Correlation ($r^2$) of confounders with proBNP concentrations in the general population (population 1). |
|-----------------|--------|--------|--------|--------|--------|--------|
|                 | No anemia | $P$    | ACD    | $P$    | IDA    | $P$    |
| n               | 5549   |        | 61     |        | 74     |        |
| Age, years      | 0.38   | <0.0001 | 0.32   | 0.01   | 0.55   | <0.0001 |
| Creatinine, μmol/L | 0.08   | <0.0001 | 0.15   | 0.25   | 0.37   | 0.001  |
| BMI, kg/m²      | 0.04   | 0.004  | 0.09   | 0.49   | 0.12   | 0.30   |
| Systolic blood pressure, mmHg | 0.24   | <0.0001 | 0.08   | 0.55   | 0.17   | 0.14   |
| Diastolic blood pressure, mmHg | 0.04   | 0.009  | −0.31  | 0.02   | −0.07  | 0.56   |
| Hemoglobin, g/L | −0.13  | <0.0001 | −0.13  | 0.32   | 0.07   | 0.54   |

Bars represent mean (SE) values.

Fig. 2. Plasma proBNP concentrations and cause-related hemoglobin status: (A), ACD; (B), IDA; (C), anemia of unknown cause; and (D), no anemia.
Table 3. Impact of known confounders on proBNP concentration in the general population (population 1).

<table>
<thead>
<tr>
<th></th>
<th>Contribution to proBNP variation, %</th>
<th>β coefficient</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No anemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex, female/male</td>
<td></td>
<td>-4.97</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td>0.57</td>
<td>0.0001</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td></td>
<td>0.57</td>
<td>0.0001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td></td>
<td>0.23</td>
<td>0.0001</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td></td>
<td>-0.17</td>
<td>0.0001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td></td>
<td>0.17</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hemoglobin, g/L</td>
<td></td>
<td>-1.27</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Anemia is associated with increased mortality in the elderly (26) and is an independent predictor of mortality in patients with heart failure (27, 28), renal disease (29), and stroke (7). Studies have shown that oxygen extraction in ischemic tissue reaches its upper limit at hemoglobin concentrations of approximately 100 g/L (30). Rapidly progressing anemia thus may induce local hypoxia at the most vulnerable regions. Previous studies have shown that myocardial hypoxia per se can induce expression of the BNP gene (natriuretic peptide precursor B) through activation of the transcription factor HIF-1α (31, 32). Increased cardiac BNP expression could therefore be a direct result of severe or rapidly progressing anemia. In our study, we established a correlation between anemia and circulating proBNP concentrations. In this context, it is noteworthy that the individuals in our cohort did not suffer from severe anemia, and because they were not hospitalized rapidly progressing anemia was unlikely. Therefore, our results are applicable only for hemoglobin concentrations in the midrange, which accounts for the majority of anemic patients in primary care. Patients with lower hemoglobin values are often admitted to hospitals, and the influence of hemoglobin status on proBNP concentration could be more pronounced in these patients.

We tried to define causes of anemia to examine whether alternate causes would differently affect the secretion of natriuretic peptides. However, we could not detect differences between the anemic subtypes. Unfortunately, by far the largest group was the individuals with anemia of unknown cause. The only explanation possible in this context was suggested by the high creatinine concentration in anemia of unknown cause, which indicated that anemia could potentially be a result of renal dysfunction. Previous studies concerning anemia and BNP/proBNP concentrations have included patients seeking medical care owing to cardiac illness or a medical emergency. The results from these studies could therefore also be due to coexisting illness affecting proBNP concentrations. However, 2 studies conducted in “healthy populations” (33, 34) should not introduce this bias. In a study by Muscari et al. (33), the \( r^2 \) value was comparable to our findings, indicating that the correlation of hemoglobin status with the proBNP concentration was relatively small in their study (\( r^2 = 0.046 \)). Furthermore, only one-fifth of the included patients were echocardiographically examined, so some of the individuals could have had cardiac dysfunction. In a study by Kanda et al. (34), none of the participants were examined by echocardiography. Whether this feature of the study explains the relatively high \( R^2 \) value is uncertain, but it is nevertheless the highest reported correlation. Otherwise, the highest values are found in studies examining patient cohorts,
that strongly suggest a comorbid condition affecting the cardiac natriuretic system.

The present study used a processing-independent assay for proBNP quantification (25). This assay measures both intact proBNP 1–108 and the 1–76 fragment NT-proBNP. This approach consequently bypasses potential analytical pitfalls from disease-related changes in post-translational propeptide processing, because both N-terminal fragments and the intact precursor molecule are quantified with equimolar potency (35). The recent reports of intact proBNP in heart failure plasma suggest that increased cardiac BNP gene expression can supersede the biosynthetic capacity for proBNP maturation and lead to secretion of unprocessed precursor peptide (36,37). The commercial NT-proBNP method by Roche is calibrated with NT-proBNP 1–76, which may partly explain some of the 1.7-fold difference in plasma concentrations with this method compared to the processing-independent method. Recently, other proBNP-derived fragments have also been shown to circulate, including a truncated proBNP 3–108 form as well as glycosylated proBNP (38,39). Although we cannot directly extrapolate our findings to other methods, we believe that our results reflect biological changes in plasma proBNP concentrations, which also will affect NT-proBNP concentrations. Notably, the molecular shift from processed fragments (NT-proBNP and BNP) to the immature precursor peptide (proBNP) is reported in plasma from severe heart failure patients, who were excluded from our study in population 2.

Potential limitations of this study include selection bias, misclassification, and confounding. The study population was selected using the Danish Central Population Register and represented a random sample from the Danish adult general population for which we did not have prior knowledge of hematological status or proBNP concentration. Owing to the limited information on cause of anemia, some study participants could potentially have been misclassified into a wrong anemia subgroup, which in turn have affected the accuracy of the subgroup analyses. During data analysis, known confounders were included in all analyses, but unidentified confounders could potentially influence the results. Finally, the results from this study are applicable only to whites, because no other ethnicity was included in the Copenhagen City Heart Study.

In conclusion, mild-to-moderate anemia in the general population is associated with a 1.7-fold increase in proBNP concentrations. Hemoglobin status must therefore be taken into consideration in individuals with non-specific symptoms and increased proBNP concentrations.

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References

the Breathing Not Properly (BNP) Multinational Study. Am J Hema-
9. Willis MS, Lee ES, Grenache DG. Effect of anaemia on plasma
P, et al. Predictors of elevated B-type natriuretic peptide concen-
trations in dyspneic patients without heart failure: an analysis
from the Breathing Not Properly multinational study. Ann Emerg
11. Tsuji H, Nishino N, Kimura Y, Yamada K, Nukui M, Yamamoto S,
et al. Haemoglobin level influences plasma brain natriuretic
12. Wold Knudsen C, Vik-Mo H, Omland T. Blood haemoglobin is an
independent predictor of B-type natriuretic peptide (BNP). Clin Sci
13. Milman N, Agger OA, Nielsen OJ. Iron supplementation during
pregnancy: effect on iron status markers, serum erythropoietin
and human placental lactogen. A placebo controlled study in 207
14. DeMaeyer E, Adiels-Tegman M. The prevalence of anaemia in the
anaemia in geriatrics: a systematic review of the literature. Am J
Copenhagen City Heart Study. A book of tables with data from the
first examination (1976–78) and a five-year follow-up (1981–83).
19. Cook JD. Diagnosis and management of iron-deficiency anaemia.
Suppl 2006;101:S4–8.
21. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R,
Feigenbaum H, et al. 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
22. Berning J, Steensgaard-Hansen F. Early estimation of risk by
echocardiographic determination of wall motion index in an un-
selected population with acute myocardial infarction. Am J Cardiol
1990;65:567–76.
23. Berning J, Rokkedal Niels J, Laumbjerg J, Fogh J, Mickley H,
Andersen PE. Rapid estimation of left ventricular ejection fraction
in acute myocardial infarction by echocardiographic wall motion
echocardiographic method for selecting high risk patients shortly
after acute myocardial infarction for inclusion in multi-centre
studies (as used in the TRACE study). TRAndolapril Cardiac
25. Goetze JP, Kastrup J, Pedersen F, Rehfeld JF. Quantification of
pro-B-type natriuretic peptide and its products in human plasma by
use of an analysis independent of precursor processing. Clin
et al. A prospective study of anaemia status, hemoglobin concen-
tration, and mortality in an elderly cohort: the Cardiovascular
27. Ezekowitz JA, McAlister FA, Armstrong PW. Anaemia is common
in heart failure and is associated with poor outcomes: insights from
a cohort of 12065 patients with new-onset heart failure. Circula-
28. Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Borenstein
J. Anaemia is associated with worse symptoms, greater impairment
in functional capacity and a significant increase in mortality in
patients with advanced heart failure. J Am Coll Cardiol 2002;39:
1780–6.
29. Collins AJ. Influence of target hemoglobin in dialysis patients on
30. Dexter F, Hindman BJ. Effect of hemoglobin concentration on brain
oxygenation in focal stroke: a mathematical modelling study. Br J
31. Goetze JP, Gore A, Moller CH, Steinbruchel DA, Rehfeld JF,
Nielsen LB. Acute myocardial hypoxia increases BNP gene expres-
et al. A constitutively active HIF-1α/VP16 hybrid factor activates
expression of the human B-type natriuretic peptide gene. Mol Phar-
33. Muscaria A, Berzigotti A, Bianchi G, Giannoni C, Ligabue A, Maga-
lotti D, et al. Non-cardiac determinants of NT-proBNP levels in the
elderly: relevance of haematocrit and hepatic steatosis. Eur J
Heart Fail 2005;8:468–76.
34. Kanda H, Kita Y, Okamura T, Kadowaki T, Yoshida Y, Nakamura Y,
et al. What factors are associated with high plasma B-type
natriuretic peptide levels in a general Japanese population? J
35. Rehfeld JF, Goetze JP. The post-translational phase of gene
expression: new possibilities in molecular diagnosis. Curr Mol
36. Giuliani I, Rieunier F, Larue C, Delagneau JF, Granier C, Pau B,
et al. Assay for measurement of intact B-type natriuretic peptide
37. Liang F, O’Rear J, Schellenberger U, Tai L, Lasecki M, Schreiner
GF, et al. Evidence for functional heterogeneity of circulating
38. Lam CS, Burnett JC Jr, Costello-Boerrigter L, Rodeheffer RJ,
Redfield MM. Alternate circulating pro-B-type natriuretic peptide
and B-type natriuretic peptide forms in the general population. J
NS. The precursor to B-type natriuretic peptide is an O-linked