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Association between anaemia and N-terminal pro-B-type natriuretic peptide (NT-proBNP): Findings from the Heart and Soul Study

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Abstract

Background: Anaemia is associated with elevated levels of natriuretic peptides. Whether the association of anaemia with natriuretic peptides is independent of other cardiovascular risk factors is unclear.
Methods: This was a cross-sectional study of 809 ambulatory patients with coronary heart disease (CHD) and no history of heart failure (HF). We evaluated the extent to which the relationship between haemoglobin and N-terminal pro-B-type natriuretic peptide (NT-proBNP) was explained by differences in cardiovascular risk factors, inflammation, and kidney dysfunction.
Results: Of the 809 participants, 189 (23%) had anaemia (haemoglobin <13 g/dL). Haemoglobin (as a continuous variable) was inversely associated with log NT-proBNP (beta coefficient −.28, $p<.0001$). This association was considerably attenuated after accounting for cardiovascular risk factors, C-reactive protein, and kidney dysfunction. However, haemoglobin remained independently associated with log NT-proBNP even after adjustment for these variables (beta coefficient −.11, $p=0.0003$). Each 1 g/dL decrease in haemoglobin was associated with a 20% greater odds of having NT-proBNP in the highest quartile.
Conclusions: The relationship between anaemia and NT-proBNP is largely explained by differences in cardiovascular risk factors, ventricular function, myocardial ischaemia, inflammation, and kidney function. Nonetheless, haemoglobin appears to be inversely associated with NT-proBNP even after adjustment for these risk factors.
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Keywords: Anemia; Natriuretic peptide

1. Introduction

Over 5 million Americans have heart failure (HF), and over a half million new cases are diagnosed annually [1–4]. Anaemia is an independent predictor of incident HF, and of adverse outcomes in patients with established HF[5–14]. In the absence of clinical HF, patients with anaemia have elevated levels of natriuretic peptides, suggesting that anaemia may lead to subclinical ventricular dysfunction [15–18]. However, it is unknown whether the association of anaemia with natriuretic peptides is explained by differences in cardiovascular risk factors, systolic or diastolic function, inflammation, or chronic kidney disease in patients without HF.

Natriuretic peptides are secreted mainly from the cardiac atria in response to pressure and volume overload. They appear to play an important physiologic role in reducing

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intravascular volume by promoting natriuresis, diuresis, vasodilatation, and suppressing the sympathetic nervous system [19,20]. Pro-B-Type Natriuretic Peptide is secreted by myocardial cells in response to increased volume and pressure. This precursor molecule is cleaved to form the active B-Type Natriuretic Peptide (BNP) and the inactive N-terminal pro-B-type natriuretic peptide (NT-proBNP). Elevations in NT-proBNP concentrations signal disruptions in processes designed to maintain normal homeostasis for optimal cardiovascular functioning. Plasma levels of NT-pro BNP are increased in patients with ventricular dysfunction and strongly predict morbidity and mortality in patients with and without heart failure [21,22].

It is unclear why anaemia is associated with elevations in NT-proBNP and increased risk of HF. One possibility is that the increased cardiac workload associated with anaemia may cause stretching of the myocardium leading to ventricular dysfunction. Another possibility is that the presence of anaemia may exacerbate underlying coronary heart disease (CHD), leading to inflammation or ischaemic damage in the myocardium. Yet another possibility is that the association of anaemia with elevated levels of NT-proBNP is confounded by greater impairment in kidney function.

To identify the pathways of association between anaemia and BNP, we measured haemoglobin and NT-proBNP in a cross-sectional study of 809 patients with CHD who had no clinical history of HF. We quantified the extent to which the inverse association of haemoglobin with NT-proBNP was explained by differences in cardiovascular risk factors, systolic or diastolic dysfunction, myocardial ischaemia, inflammation, and kidney dysfunction.

2. Methods

2.1. Study participants

The Heart and Soul Study is a prospective cohort study designed to investigate the influence of psychosocial factors on the outcomes of patients with CHD. Detailed methods have been described previously [22,23]. Between September 2000 and December 2004, we recruited 1024 participants with CHD who were identified from administrative databases at two Department of Veterans Affairs Medical Centers (San Francisco and Palo Alto) and at one university-based medical centre (University of California, San Francisco). Eligible participants had a history of myocardial infarction, angiographic evidence of $\geq 50\%$ stenosis in 1 or more coronary vessels, history of coronary revascularization, or evidence of exercise-induced ischaemia by treadmill or nuclear testing. Patients were excluded if they reported hospitalization for an acute coronary event ≤ 6 months previously, were unable to walk 1 block or were planning to move from the local area within 3 years. The institutional review board at each of the sites approved this protocol, and all participants provided written informed consent. For this cross-sectional study, we excluded 178 participants who reported a history of HF, and 37 participants without measurements of haemoglobin or NT-pro BNP, yielding 809 subjects for the analysis.

2.2. Predictor variable: haemoglobin

Prior to the study appointment, participants completed an overnight fast except for taking their regularly prescribed medications. Venous blood samples were drawn via 21-gauge butterfly needles into chilled tubes containing ethylenediamine-tetra-acetic acid (EDTA). The Beckman Coulter LH 750 (Fullerton, California) yielded the haemoglobin (Hgb) values with an inter-assay coefficient of 0.4%. The laboratory technicians who determined Hgb levels were blinded to the results of the echocardiogram. We examined haemoglobin both as a continuous variable and as a dichotomous variable, with anaemia defined as Hgb < 13 g/dL [24,25].

2.3. Outcome variable: NT-pro BNP

EDTA plasma was frozen at -80 °C for up to 4 years. We measured plasma NT-pro BNP levels from thawed samples using a commercially available immunoassay (Elecsys proBNP, Roche Diagnostics). The assay range is 5 to 35,000 pg/mL. The intra-assay and inter-assay coefficients of variation ranged respectively from 1.8% and 2.3% (at NT-pro BNP concentrations of 4962 pg/mL) to 2.7% and 3.2% (NT-pro BNP 175 pg/mL).

2.4. Other measurements

Self-reported age, sex, ethnicity, lifestyle habits, and medical history were determined by questionnaire. Serum creatinine, total cholesterol, and C-reactive protein were measured after the overnight fast. We measured height and weight to calculate body mass index, and assessed blood pressure using a standard sphygmomanometer. We assessed kidney function using 3 different measures: (1) 24-hour urinary creatinine clearance [26], (2) cystatin C [27], and (3) estimated glomerular filtration rate (eGFR) calculated by the Modification of Diet in Renal Disease (MDRD) Study formula: $\text{eGFR} = 186 \times (\text{serum creatinine}^{-1.154}) \times (\text{age}^{-0.203}) \times (0.742 \text{ if female}) \times (1.21 \text{ if black})$ [28].

All participants underwent resting echocardiography using an Acuson Sequoia Ultrasound System (Mountain View, California) with a 3.5 MHz transducer. A complete resting two-dimensional echocardiogram, including imaging and Doppler in all standard views and subcostal imaging of the inferior vena cava, was performed. We obtained standard two-dimensional parasternal short-axis and apical 2- and 4-chamber views during held inspiration; these were planimetered using a computerized digitization system to determine end-diastolic and end-systolic left ventricular volume and ejection fraction (EF). We categorized participants as having diastolic dysfunction if they had LVEF $\geq 50\%$ and a velocity time integral in their pulmonary vein that was greater during diastole than during systole [25]. Left ventricular mass was indexed to height and

Table 1
Characteristics of 809 study participants with coronary heart disease and no history of heart failure

Variable	Hgb<13 g/dL	Hgb≥13 g/dL	*p* value
	N=189	*N*=620	
Demographic characteristics			
Age (years)	70±12	66±11	<.0001
Sex (% male)	126(67)	534(86)	<.0001
Race			
White	92(49)	393(64)	.0001
Black	47(25)	78(13)	<.0001
Other	50(26)	148(24)	.48
Body Mass Index (kg/m^2)	28±6	28±5	.82
Lifestyle/habits			
Current smoker	28(15)	126(20)	.09
Physically active	103(55)	416(67)	.001
Regular alcohol use	52(28)	195(32)	.29
Medical history			
Diabetes	62(33)	130(21)	.0008
Hypertension	133(70)	423(68)	.60
Myocardial infarction	97(52)	307(50)	.61
Angioplasty	65(35)	236(38)	.38
CABG	55(24)	205(33)	.34
Cardiac function			
LV ejection fraction	.63±.09	.63±.08	.78
Diastolic dysfunction	38(20)	66(11)	.0007
LA volume index	35.6±13	30.9±10.1	<.0001
Mitral deceleration time	236±61	246±65	.06
E/A ratio	1.1±.51	1.04±.42	.14
LV mass index (g/m^2)	98±24.6	94±23.8	.048
Inducible ischaemia	46(26)	118(21)	.11
Angina weekly or more	35(19)	104(17)	.59
Resting heart rate	68±12	68±12	.93
SBP (mm Hg)	135±22	133±21	.26
DBP (mm Hg)	72±10	76±11	<.0001
Other measurements			
Total cholesterol (mg/dL)	171.2±38.7	181±43.1	.005
Creatinine clearance (mL/min)	70.5±27.5	85.6±27.3	<.0001
Estimated GFR	72.4±27	79±21	.0004
Cystatin C	1.4±.81	1.1±.33	<.0001
C-reactive protein	5.9±10	3.7±5.5	<.0001

analyzed as grams/m^2. We measured LA volume using transthoracic echocardiography (using biplane method of disks in apical 2- and 4-chamber views) and calculated Left Atrial volume index as left atrial end systolic volume divided by body surface area. We also measured mitral deceleration time and mitral flow E/A ratios of peak velocities at early rapid filling (E) and late filling due to atrial contraction (A).

To determine the presence of myocardial ischaemia, participants underwent full exercise treadmill testing using a standard Bruce protocol with continuous 12-lead electrocardiographic monitoring. An echocardiogram was performed just prior to and immediately following exercise. Inducible ischaemia was defined as the presence of a new wall motion abnormality observed at peak exercise that was not present at rest.

2.5. Statistical analysis

We compared differences in baseline characteristics between participants with and without anaemia using chi-squared tests for dichotomous variables and *t*-tests (or non-parametric equivalent) for continuous variables. For the continuous analyses, we log-transformed NT-proBNP values, because they were not normally distributed. To determine the independent association between anaemia and NT-proBNP, we used linear regression analyses with haemoglobin entered as a continuous or dichotomous (<13 g/dL) variable as the primary predictor and log NT-pro BNP as the outcome. We sequentially adjusted for demographic and lifestyle factors, medical history, systolic and diastolic function, ischaemia, inflammation and creatinine clearance. We also used logistic regression to determine the association of each 1-point decrease in haemoglobin with having NT-proBNP in the highest quartile. We tested for interactions of anaemia with creatinine clearance, cystatin C, eGFR, left ventricular ejection fraction, diastolic dysfunction, and inducible ischaemia. All analyses were performed using Statistical Analysis Software (Version 9, SAS Institute, Inc.).

3. Results

Of the 809 participants, 189 (23%) had anaemia (Hgb<13 g/dL). Subjects with anaemia were older, less likely to be male or white, more likely to be black, and less likely to be physically active, compared with subjects who did not have anaemia (Table 1). Subjects with anaemia were more likely to have diabetes, diastolic dysfunction, higher left atrial end systolic volume, and left ventricular hypertrophy. They also had lower diastolic blood pressure, cholesterol and creatinine clearance, but higher C-reactive protein than those without anaemia.

Lower haemoglobin was linearly associated with higher mean levels of log NT-proBNP (Fig. 1). This association was considerably attenuated after accounting for demographic and lifestyle factors, medical history, cardiac function, and C-reactive protein (Table 2). Adjusting for creatinine clearance alone resulted in a 27% further decrease in the

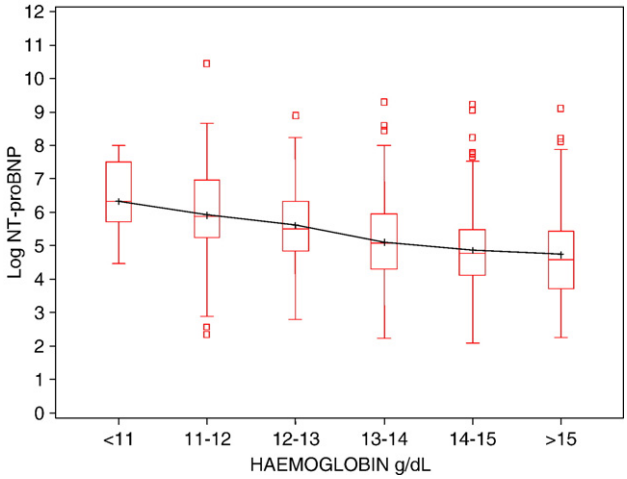

Fig. 1. Mean (95% confidence interval) concentrations of log NT-proBNP by haemoglobin level (p<0.001 for trend).

beta coefficient (from −.15 to −.11), but haemoglobin was independently associated with NT-proBNP after adjustment for all of the above variables.

Although we excluded participants who reported a history of clinical heart failure, a total of 68 participants had a LVEF ≤50% and 104 had diastolic dysfunction. After excluding these participants with LVEF ≤50% or diastolic dysfunction, haemoglobin remained associated with log-NT-proBNP in a fully adjusted model (*B* coefficient −.12±.03; $p<.0001$).

Sex was not significantly associated with NT-proBNP in the model adjusted for demographic and lifestyle factors (Table 2). However, to verify that sex was not responsible for the association of haemoglobin with NT-proBNP, we forced sex into the final model. After adjustment for sex, age, physical activity, history of myocardial infarction, coronary artery bypass grafting, LV ejection fraction, diastolic dysfunction, LV mass index, inducible ischaemia, heart rate, systolic and diastolic blood pressure, cholesterol, CRP, and creatinine clearance, haemoglobin remained inversely associated with log NT-proBNP (*B* coefficient −.09±.03; $p<.0001$).

Of the 189 individuals with anaemia, 38% (72/189) had NT-proBNP levels in the highest quartile (>367 pg/ml), compared with 16% (99/620) of those without anaemia ($p<.0001$). Each 1-point decrease in haemoglobin was associated with 50% greater odds of having high NT-proBNP. Although this association was largely attenuated after adjustment for cardiovascular risk factors and kidney function, each 1-point decrease in haemoglobin remained independently associated with 20% greater odds of having high NT-proBNP (Table 3). We found no evidence for any interaction of haemoglobin with LV ejection fraction, diastolic dysfunction, inducible ischaemia, creatinine clearance, cystatin C, or eGFR (all *p* values for interaction ≥0.2).

Table 2
Association of haemoglobin as a continuous variable with log NT-proBNP as a continuous variable by linear regression

Model	B coefficient±SE for haemoglobin	*p* value
Unadjusted	−.28±.03	<.0001
Adjusted*		
Demographic factors+lifestyle/habits †	−.25±.03	<.0001
Above+medical history‡	−.22±.03	<.0001
Above+cardiac function§	−.20±.03	<.0001
Above+cholesterol and CRP‖	−.15±.03	<.0001
Above+CrCl¶	−.11±.03	.0003
Above+eGFR but not CrCl	−.14±.02	<.0001
Above+cystatin C but not CrCl or eGFR	−.12±.02	<.0001

CrCl creatinine clearance, eGFR estimated glomerular filtration rate.
*Each model adjusted for all Table 1 variables associated with NT-proBNP from previous step. Other variables associated with NT-proBNP (at $p<0.05$) were:
†Age, race and physically active.
‡Age, race, physically active, history of hypertension, myocardial infarction, and coronary artery bypass grafting.
§Age, race, physically active, history of myocardial infarction, coronary artery bypass grafting, LV ejection fraction, diastolic dysfunction, LV mass index, inducible ischaemia, heart rate, and systolic and diastolic blood pressure.
‖Age, race, physically active, history of myocardial infarction, coronary artery bypass grafting, LV ejection fraction, diastolic dysfunction, LV mass index, inducible ischaemia, heart rate, systolic and diastolic blood pressure, cholesterol and CRP.
¶Age, physically active, history of myocardial infarction, coronary artery bypass grafting, LV ejection fraction, diastolic dysfunction, LV mass index, inducible ischaemia, heart rate, systolic and diastolic blood pressure, choles terol, CRP, and creatinine clearance.

Table 3
Association of each 1-point decrease in haemoglobin with having NT-proBNP in the highest quartile among 809 patients with coronary disease and no history of heart failure

Model	Odds ratio (95% CI)	*p* value
Unadjusted	1.5 (1.3–1.7)	<.0001
Adjusted*		
Demographic factors+lifestyle/habits†	1.5 (1.3–1.7)	<.0001
Above+medical history‡	1.5 (1.3–1.7)	<.0001
Above+cardiac function§	1.6 (1.3–2.0)	.0001
Above+cholesterol and CRP‖	1.3 (1.1–1.6)	.001
Above+CrCl¶	1.2 (1.0–1.4)	.05
Above+eGFR but not CrCl	1.3 (1.1–1.6)	.007
Above+cystatin but not eGFR or CrCl	1.2 (1.03–1.5)	.02

CrCl creatinine clearance, eGFR estimated glomerular filtration rate.
*Each model adjusted for variables associated with NT-proBNP (at $p<0.05$) from previous step. Other variables associated with NT-proBNP were:
†Age, race and physically active.
‡Age, race, physically active, history of hypertension, myocardial infarction, and coronary artery bypass grafting.
§Age, race, physically active, history of myocardial infarction, coronary artery bypass grafting, LV ejection fraction, diastolic dysfunction, LV mass index, inducible ischaemia, heart rate, and systolic and diastolic blood pressure.
‖Age, race, physically active, history of myocardial infarction, coronary artery bypass grafting, LV ejection fraction, diastolic dysfunction, LV mass index, inducible ischaemia, heart rate, systolic and diastolic blood pressure, cholesterol and CRP.
¶Age, physically active, history of myocardial infarction, coronary artery bypass grafting, LV ejection fraction, diastolic dysfunction, LV mass index, inducible ischaemia, heart rate, systolic and diastolic blood pressure, cholesterol, CRP, and creatinine clearance.

4. Discussion

We found that anaemia was inversely associated with circulating levels of NT-proBNP in 809 outpatients with known CHD and no clinical history of HF. The association between anaemia and elevated NT-pro BNP was considerably attenuated after accounting for greater systolic dysfunction, diastolic dysfunction, CHD severity, inflammation, and kidney dysfunction in patients with anaemia. Adjustment for these variables explained approximately 2/3 of the association. However, even after adjustment for all of these factors, anaemia remained independently predictive of NT-proBNP.

Our findings indicate that, clinical ventricular dysfunction, ischaemia, inflammation and kidney dysfunction are largely responsible for the association of anaemia with NT-proBNP. However, even after adjustment for these risk factors, anaemia remains independently predictive of

elevated NT-proBNP concentrations. One prior study of 234 patients with suspected CHD and no history of HF demonstrated that the association of anaemia with BNP was independent of left ventricular ejection fraction, left ventricular end diastolic pressure, extent of CHD, and estimated creatinine clearance [16]. Our study extends these findings by demonstrating that the association of anaemia with natriuretic peptides is also independent of inducible ischaemia and C-reactive protein. These results raise the possibility that anaemia may be associated with increased ventricular pressure and myocardial strain even before evidence of clinical ventricular dysfunction can be detected.

The relation between anaemia and HF may be caused by activation of the renin–angiotensin–aldosterone system, hyperactivity of the sympathetic nervous system, or poor oxygen carrying capacity, resulting in increased workload on the heart [29,30]. Three primary factors determine the amount of oxygen delivered to an organ: blood flow and its distribution, the blood's oxygen-carrying capacity, and oxygen extraction [31]. When the oxygen-carrying capacity is diminished as in chronic anaemia, the primary haemodynamic mechanism that compensates is an increase in cardiac output, mediated by lower after-load and consequentially increased preload. Tissue hypoxia, enhanced nitric oxide activity, and lower blood viscosity yield vasodilation and decreased vascular resistance. In response, venous return and left ventricular filling increase, resulting in an increased left ventricular end-diastolic volume and maintenance of high stroke volume.

Greater left ventricular stress may also stem from an anaemia-associated increase in plasma catecholamines or other haemodynamic factors. Over time, such haemodynamic alterations may result in increased workload, cardiac enlargement, and left ventricular hypertrophy. These compensatory mechanisms are most prominent with very low haemoglobin concentrations. However, an ischaemic heart is more sensitive than a normal heart to even smaller drops in haemoglobin, yielding worsening of ischaemia and cardiac function [32]. In our study population with known CHD and no history of HF, the finding of anaemia-associated elevated NT-pro BNP levels, reflective of increased ventricular filling pressures, may suggest an increased sensitivity and attempted cardiac compensation for anaemia. This may also explain why haemoglobin is not as strongly correlated with log natriuretic peptides in patients who have dyspnoea from pulmonary problems rather than from CHD [17].

Understanding the mechanisms of association between anaemia and NT-proBNP may improve our understanding of cardiac pathophysiology, and help target potential therapies to prevent the development and progression of HF. Apart from triggering existent cardiac adaptation, anaemia may also independently cause hormonal and metabolic effects that influence cardiac function. Toxic metabolic effects such as retention of salt and water, decreased renal blood flow, and neurohormonal activation have been noted in chronic severe anaemia [33]. Such effects may cause cardiac strain, and neurohormonal activation may potentiate NT-pro BNP production. However, the role of metabolic and hormonal effects in milder anaemia has not been extensively studied.

Strengths of our study include its large sample size and comprehensive measurement of potential mechanisms, including systolic function, diastolic function, myocardial ischaemia, inflammation, and creatinine clearance. However, a number of limitations should be considered when interpreting our results. First, the cross-sectional design of our analysis precludes determining the causal direction of association between anaemia and NT-proBNP. It is plausible that NT-proBNP is the result of subclinical ventricular dysfunction that may also decrease perfusion to the kidney leading to decreased erythropoietin production and anaemia. Second, it is possible that low haemoglobin concentration may reflect haemodilution, and that increases in natriuretic peptides may be due to volume overload rather than to true anaemia [34]. However, none of our participants had a clinical history of heart failure, and all blood samples were drawn in a fasting state, making it unlikely that lower haemoglobin concentrations were due to volume overload. Third, our cohort predominantly consists of men, and as natriuretic peptide levels may vary by sex, our results may not generalize to women [17]. Finally, our sample was restricted to patients with known CHD, and the association of anaemia with NT-proBNP may differ in patients without CHD.

In summary, we observed a strong relationship between lower haemoglobin levels and elevated concentrations of NT-proBNP in patients with CHD and no history of HF. This association was largely explained by difference in cardiovascular risk factors, inflammation and kidney dysfunction. Nonetheless, anaemia remained independently associated with NT-proBNP even after adjustment for these risk factors.

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