Carotid-femoral pulse wave velocity is associated with N-terminal pro-B-type natriuretic peptide level in patients with atrial fibrillation

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ABSTRACT

Objective To determine the extent to which conduit artery stiffness is associated with plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) in patients with atrial fibrillation (AF).

Design Cross-sectional study.

Setting National University Hospital, Singapore.

Patients Cases (n=117) were patients with AF onset <65 years of age without heart failure or structural heart disease. Controls (n=274) were patients without AF who were seen at the general cardiology clinic.

Interventions Transthoracic echocardiography, carotid-femoral pulse wave velocity (CFPWV) measured using applanation tonometry and blood draw for plasma NT-proBNP at enrolment for all patients.

Main outcome measures Plasma NT-proBNP.

Results In patients with AF, CFPWV was associated with NT-proBNP after adjusting for hypertension and factors that were univariately associated with NT-proBNP: age at enrolment, type of AF, body mass index, left ventricular mass index, left atrial volume index, mitral E/E′, mitral deceleration time and use of β-blockers (β=0.234; 95% CI 0.100 to 0.367; p=0.001). In contrast, CFPWV was not associated with NT-proBNP in controls. In patients with AF, the adjusted mean NT-proBNP level in the highest quartile of CFPWV (350 pg/ml; 95% CI 237 to 517 pg/ml) was fivefold higher than the lowest quartile (69 pg/ml; 95% CI 47 to 103 pg/ml) (p=0.001).

Conclusions CFPWV is associated with NT-proBNP level in AF. Since elevated NT-proBNP is a marker of adverse cardiovascular outcomes, arterial stiffness may be associated with worse prognosis in patients with AF.

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a neurohormonal marker that is secreted by cardiomyocytes in response to ventricular volume and pressure overload[1] and thus is elevated in chronic heart failure (CHF).[2] For reasons that are not entirely clear, NT-proBNP is also elevated in atrial fibrillation (AF) patients with[3] and without structural heart disease.[4 5] Of note, elevated NT-proBNP predicts adverse cardiovascular outcomes such as cardiovascular death, non-fatal myocardial infarction, CHF and stroke.[6–9] Therefore, a better understanding of the determinants of NT-proBNP level in patients with AF may help refine risk prediction of adverse cardiovascular outcomes in patients with AF.

Previous studies have investigated the role of left ventricular (LV) diastolic wall stress on NT-proBNP elevation in patients with AF. In a cohort of patients with lone AF, left atrial (LA) volume index, pulmonary artery systolic pressure and mitral E/E′ were found to be independent predictors of NT-proBNP levels.[10] In chronic AF patients with preserved LV systolic function, independent predictors of NT-proBNP included LA volume index, LV mass index and duration of AF.[11] Collectively, these findings suggest that among other factors, increased LV diastolic wall stress might contribute to NT-proBNP elevation in AF patients. On the basis that increased arterial stiffness correlates with LV diastolic dysfunction,[12 13] we hypothesised that conduit arterial stiffness is associated with NT-proBNP level in AF patients. To test this hypothesis, we explored the relationship between NT-proBNP level and carotid-femoral pulse wave velocity (CFPWV) in a cohort of patients with AF and controls.

MATERIAL AND METHODS

Study population

Consecutive patients referred to the heart rhythm clinic of the National University Hospital in Singapore with AF onset <65 years of age were identified and invited to participate in the study after obtaining informed, written consent. Consecutive patients without AF or other arrhythmias, who were <65 years age and evaluated at the general cardiology clinic of the National University Hospital in Singapore were enrolled as controls. The National University Hospital is a tertiary medical centre that accepts referrals from all private general practitioner clinics, government community clinics and other tertiary hospitals in Singapore. Patients seen at the National University Hospital are representative of the Singapore general population in terms of age, gender and ethnic distribution.

AF was defined as replacement of sinus P waves by rapid oscillations or fibrillatory waves that varied in size, shape and timing and were associated with an irregular ventricular response when atrioventricular conduction was intact. Documentation of AF on an ECG, rhythm strip, event monitor or Holter monitor recording was required. Patients were excluded from the study if they had structural or valvular abnormalities including moderate or severe valvular regurgitation, mitral stenosis of any severity, LF ejection fraction <50% and atrial septal defect. Patients were also excluded if they had a history of coronary artery disease, CHF, primary

Table 1 Baseline characteristics of AF cases and controls

Characteristic	AF (n=117)	Controls (n=274)	p
Clinical			
Age at diagnosis (years)	48.5±10.9	NA	NA
Age at enrolment (years)	53.7±10.5	50.9±10.0	0.012
Brachial pulse pressure (mm Hg)	57.6±11.5	52.3±12.9	<0.001
Duration of AF (years)	5.3±6.7	NA	NA
Male gender	96 (82.1)	172 (62.8)	<0.001
Body mass index (kg/m^2)	26.9±4.8	25.7±4.4	0.014
Type of AF			
Paroxysmal	75 (64.1)	NA	NA
Persistent	41 (35.0)	NA	NA
Hypertension	74 (63.2)	129 (47.1)	<0.001
NT-proBNP (pg/ml)	156.0 (50.0–548.0)	28.0 (15.0–53.0)	<0.001
Log NT-proBNP (pg/ml)	5.0±1.5	3.3±1.0	<0.001
Arterial tonometry			
CFPWV (m/s)	8.8±2.2	8.1±3.4	0.010
Echocardiography			
LV ejection fraction (%)	65.0 (60.0–70.0)	66.0 (63.0–70.0)	<0.001
LA volume index (ml/m^2)	34.2±12.9	22.7±5.7	<0.001
LV mass (g)	166.4±38.6	139.2±39.3	<0.001
LV mass index (g/m^2)	90.0±18.8	78.3±18.8	<0.001
Mitral E velocity (m/s)	76.5±20.7	71.4±17.0	0.019
Mitral E′ velocity (m/s)	8.8±2.4	8.1±2.1	0.002
Mitral E/E′	10.1±5.7	9.3±3.6	0.204
Mitral DT (ms)	182 (162–207)	192 (174–220)	0.002
Log mitral DT (ms)	5.2±0.3	5.3±0.4	0.191
IVRT (ms)	78.3±21.4	79.0±22.0	0.755
Medications			
β-Blockers	50 (42.7)	32 (11.7)	<0.001
Calcium channel blockers	26 (22.2)	46 (16.8)	0.007
Class 1C antiarrhythmics	19 (16.2)	0 (0.0)	<0.001
Amiodarone	13 (11.1)	0 (0.0)	<0.001
Sotalol	34 (29.1)	0 (0.0)	<0.001

Categorical variables are presented as number (%); normally distributed continuous variables are presented as mean±SD, skewed data are presented as median (IQR).
AF, atrial fibrillation; CFPWV, carotid-femoral pulse wave velocity; DT, deceleration time; IVRT, isovolumic relaxation time; LA, left atrial; LV, left ventricular; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

cardiomyopathy, myocardial infarction, hyperthyroidism or permanent AF. Paroxysmal AF was defined as AF lasting more than 30 s that terminated spontaneously. AF was classified as persistent when it lasted more than 7 days and required either pharmacologic therapy or electrical cardioversion for termination. AF that was completely refractory to cardioversion or was allowed to continue was classified as permanent.[14]

Clinical and echocardiographic evaluation

All patients were screened comprehensively by a review of medical records and systematic measurement of risk factors such as blood pressure, fasting plasma glucose and thyroid function. Additionally, each patient filled out a structured questionnaire under the supervision of a research nurse. The questionnaire included items pertaining to demographics, symptoms, family history, other comorbid illnesses and AF treatment (drugs, pacemaker and catheter ablation). Patients were classified as having hypertension if their blood pressure was >140/90 mm Hg on two previous occasions (as documented in the medical record), or if they were on anti-hypertensive medications for blood pressure control at enrolment.[15]

Detailed two-dimensional and Doppler transthoracic echocardiographic studies were performed to measure indexes of LA and LV size, LV systolic and diastolic function, and to exclude structural heart and valvular abnormalities. All AF patients were in sinus rhythm for at least a month before echocardiographic studies were performed. LA volume was obtained by the biplane area–length method and indexed to body surface area as previously described.[16] Doppler echocardiographic variables were averaged from at least five cardiac cycles.

Measurement of CFPWV

CFPWV was measured in the supine position using the SphygmoCor system (AtCor, Sydney, Australia) during sinus rhythm. All AF patients were in sinus rhythm for at least a month before CFPWV was measured. The SphygmoCor system uses applanation tonometry to determine the time delay between the rapid upstroke of the feet of sequentially recorded pulse waves in the carotid and femoral arteries. At each site, triplicates of 10 waveforms were acquired (ie, total of 30) and a mean time delay was obtained. The distance between the recording sites over the carotid and femoral arteries was measured with a tape ruler. CFPWV was calculated as the distance to transit time ratio and expressed in metres per second (m/s). Left- and right-sided measurements were obtained for each patient; an average of both was calculated and used for analysis.

Measurement of NT-proBNP

Five millilitres of whole blood was collected by venipuncture from each patient at enrolment. All AF patients were in sinus rhythm for at least a month before venipuncture was performed. Blood samples were analysed within 2 h by the Roche NT-proBNP electrochemiluminescent assay and testing was performed on a Cobas analyser (Roche Diagnostics, Mannheim, Germany). Assay prediction, analytical sensitivity, interferences and stability were previously described.[17]

Statistical analysis

For normally distributed variables, summary data are presented as mean±SD; for skewed distributions, data are summarised as median (IQR). Categorical variables are presented as number (%). Because NT-proBNP and mitral deceleration time (DT) were positively skewed, log-transformed values were used for analyses. Associations between log NT-proBNP and continuous clinical, echocardiographic and tonometry variables were first assessed by using simple linear regression. Multiple linear regression analysis was subsequently used to identify independent predictors of log NT-proBNP level and adjust for possible confounders. Variables that univariately associated with NT-proBNP level or were known to biologically affect NT-proBNP level were considered in the multiple regression analysis. Multivariable models were constructed using the backward elimination method. Adjusted mean NT-proBNP levels were estimated for increasing quartiles of CFPWV in AF patients. Statistical analysis was performed using Stata version SE 9.2 (StataCorp). All p values reported were two-sided and statistical significance was evaluated at the 5% level.

Informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Institutional Review Board of the National University of Singapore. The research protocol and questionnaire were approved by the Institutional Review Board of the National University of Singapore. The authors have full access to and take responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Table 2 Univariate associations between baseline independent variables and log-transformed plasma N-terminal pro-B-type natriuretic peptide in patients with AF and controls

	AF (n=117)			Controls (n=274)		
Variable	**Coefficient (95% CI)**	**p**	**R^2 (%)**	**Coefficient (95% CI)**	**p**	**R^2 (%)**
Age at diagnosis (years)	0.054 (0.030 to 0.077)	<0.001	15.04	–	–	–
Age at enrolment (years)	0.074 (0.049 to 0.099)	<0.001	23.22	0.022 (0.010 to 0.034)	<0.001	4.78
Brachial pulse pressure (mm Hg)	0.002 (−0.020 to 0.023)	0.841	0.04	0.011 (0.0009 to 0.022)	0.033	1.66
Duration of AF (years)	0.049 (0.005 to 0.093)	0.028	4.12			
Male gender	−0.230 (−0.997 to 0.538)	0.554	0.30	−0.669 (−0.905 to −0.432)	<0.001	10.23
Body mass index (kg/m^2)	−0.076 (0.016 to 0.136)	0.013	5.23	−0.041 (−0.068 to −0.013)	0.004	3.05
Type of AF		<0.001	21.54	–	–	–
Paroxysmal	0.00	–	–	–	–	–
Persistent	1.279 (0.538 to 2.021)	0.001	–	–	–	–
Hypertension	0.356 (−0.240 to 0.953)	0.239	1.21	−0.138 (−0.379 to 0.103)	0.262	0.46
Carotid-femoral pulse wave velocity (m/s)	0.267 (0.158 to 0.376)	<0.001	18.11	−0.004 (−0.039 to 0.031)	0.803	0.02
LV ejection fraction (%)	−0.018 (−0.058 to 0.022)	0.376	0.68	0.030 (0.003 to 0.057)	0.079	1.75
LA volume index (ml/m^2)	0.070 (0.058 to 0.094)	<0.001	37.47	0.041 (0.020 to 0.062)	<0.001	5.30
LV mass (g)	0.006 (−0.001 to 0.014)	0.112	2.18	−0.003 (−0.006 to 0.000)	0.080	1.71
LV mass index (g/m^2)	0.011 (−0.005 to 0.027)	0.164	1.68	0.000 (−0.006 to 0.007)	0.919	0.00
Mitral E velocity (m/s)	0.083 (0.001 to 0.165)	0.050	3.22	0.011 (0.004 to 0.018)	0.002	3.39
Mitral E′ velocity (m/s)	0.056 (−0.052 to 0.163)	0.307	0.85	0.022 (−0.036 to 0.079)	0.462	0.20
Mitral E/E′	0.031 (0.018 to 0.044)	<0.001	16.38	0.023 (−0.011 to 0.056)	0.179	0.66
Log mitral DT (ms)	−1.469 (−2.539 to −0.400)	0.008	6.10	−0.065 (−0.399 to 0.270)	0.703	0.05
IVRT (ms)	−0.012 (−0.026 to 0.002)	0.082	2.61	0.001 (−0.005 to 0.006)	0.787	0.03
Use of β-blockers	0.810 (0.267 to 1.353)	0.004	7.06	0.342 (0.119 to 0.564)	0.003	3.26
Use of calcium channel blockers	0.328 (−0.340 to 0.995)	0.333	0.82	−0.230 (−0.478 to 0.018)	0.069	1.21
Use of Class 1C antiarrhythmics	−0.823 (−1.988 to 0.342)	0.165	1.67	–	–	–
Use of amiodarone	−0.500 (−1.760 to 0.759)	0.433	0.54	–	–	–
Use of sotalol	−0.411 (−1.294 to 0.472)	0.359	0.73	–	–	–

AF, atrial fibrillation; DT, deceleration time; IVRT, isovolumic relaxation time; LA, left atrial; LV, left ventricular; (–), not applicable.

RESULTS

Participants

Between January 2006 and June 2008, 117 AF patients (82% men; mean age at enrolment: 53.7±10.5 years) and 274 controls (63% men; mean age at enrolment: 50.9±10.0 years) were recruited into the study. Baseline characteristics of the two groups are summarised in table 1. At enrolment, based on transthoracic echocardiography, none of the patients had evidence of structural or valvular abnormalities. Of note, patients with AF had higher NT-proBNP and CFPWV than controls.

Univariate analysis

Because NT-proBNP distribution was skewed, univariate and multivariate analyses were performed by using natural logarithmic transformed values. The following were found to be associated with higher NT-proBNP in AF patients: older age at diagnosis and age at enrolment, longer duration of AF, lower body mass index (BMI), persistent AF, higher CFPWV, LA volume index, mitral E velocity, mitral E/E′, shorter log mitral DT and use of β-blockers (table 2). Of these univariate associations, six had an R^2>15% (ie, each of these predictors individually explained more than 15% of the variability in NT pro-BNP): age at diagnosis, age at enrolment, type of AF, CFPWV, LA volume index and mitral E/E′. The associations of LA volume index, mitral E velocity, mitral E/E′ and log mitral DT with NT-proBNP suggest the important role of LV diastolic dysfunction in the elevation of NT-proBNP in AF patients.

In controls, older age at enrolment, higher brachial pulse pressure, female gender, lower BMI, higher LA volume index and mitral E velocity, and use of β-blockers were associated with higher NT-proBNP. Of note, CFPWV was not associated with NT-proBNP in controls.

Table 3 Multivariable model for prediction of log-transformed plasma N-terminal pro-B-type natriuretic peptide in patients with atrial fibrillation*

Variable	Coefficient (95% CI)	p
Type of atrial fibrillation		0.007
Paroxysmal	–	–
Persistent	0.745 (0.174 to 1.316)	0.011
Carotid-femoral pulse wave velocity (m/s)	0.203 (0.117 to 0.288)	<0.001
Left atrial volume index (ml/m^2)	0.054 (0.037 to 0.072)	<0.001

*Final model: R^2=53.3%.

Multivariate analysis

In multivariate analysis for AF patients, the following variables were considered for inclusion in the model: type of AF, CFPWV, LA volume index, age at enrolment, BMI, hypertension, LV mass index, mitral E/E′, log mitral DT and use of β-blockers. These covariates were considered on the basis of either significant univariate association with NT-proBNP level or biological relevance, or both. Although age at diagnosis, duration of AF and mitral E velocity were univariately associated with NT-proBNP, they were not included in the multivariable model because of possible collinearity with age at enrolment, type of AF and mitral E/E′, respectively. CFPWV was significantly associated with NT-proBNP level after adjusting for type of AF, LA volume index, age at enrolment, BMI, hypertension, LV mass index, mitral E/E′, log mitral DT and use of β-blockers (β=0.234; 95% CI 0.100 to 0.367; p=0.001). In the multivariable model, only type of AF, CFPWV and LA volume index were found to be

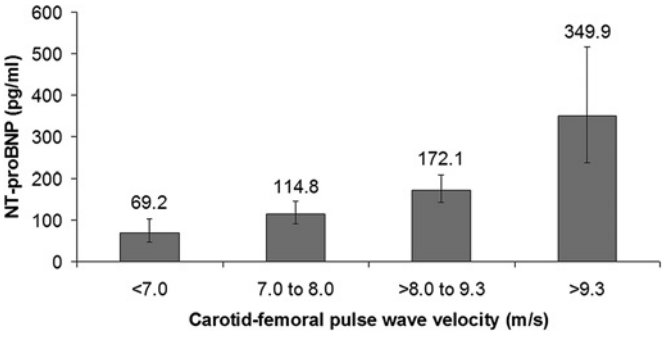

Figure 1 Adjusted mean N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels with increasing quartiles of carotid-femoral pulse wave velocity in patients with atrial fibrillation. Covariates adjusted for include type of atrial fibrillation, left atrial volume index, age at enrolment, body mass index, hypertension, left ventricular mass index, mitral E/E′, log mitral deceleration time and use of β-blockers. The numbers above the bar charts represent point estimates; error bars indicate 95% CIs.

significantly associated with NT-proBNP (table 3). This parsimonious model accounted for 53% of the variability in NT-proBNP.

The adjusted mean NT pro-BNP levels for increasing quartiles of CFPWV in patients with AF are shown in figure 1. The adjusted mean NT pro-BNP level in the highest quartile of CFPWV (349.9 pg/ml; 95% CI 236.8 to 517.1 pg/ml) was fivefold higher than the lowest quartile (69.2 pg/ml; 95% CI 46.7 to 102.5 pg/ml) (p=0.001).

In multivariate analysis for controls, the following variables were considered for inclusion in the model: CFPWV, LA volume index, age at enrolment, gender, brachial pulse pressure, BMI, hypertension, LV mass index, mitral E velocity and use of β-blockers. These covariates were considered on the basis of either significant univariate association with NT-proBNP level, biological relevance or both. In the multivariable model, only age at enrolment, female gender and mitral E velocity were found to be significantly associated with NT-proBNP (table 4). This parsimonious model accounted for 16% of the variability in NT-proBNP.

In patients with AF, CFPWV was univariately associated with the following indexes of LV diastolic function: LA volume index, LV mass index, mitral E′ velocity and mitral E/E′.

DISCUSSION

Previous studies have reported echocardiographic and clinical variables as independent predictors of NT-proBNP level in patients with AF, but none of them have evaluated indexes of arterial stiffness. In this study, we report that after adjustment for age and clinical covariates, CFPWV was associated with plasma NT-proBNP level in patients with AF. This association, however, was not found in controls. Compared with patients in the lowest quartile of CFPWV, patients in the highest quartile of CFPWV had a fivefold higher NT-proBNP level. Since NT-proBNP elevation is associated with adverse cardiovascular outcomes,[6–9] conduit arterial stiffness may be a marker of worse prognosis in patients with AF.

Consistent with previous studies,[10 11] we also found significant univariate associations between LA volume index, mitral E velocity, mitral E/E′ and log mitral DT with NT-proBNP, supporting the contribution of LV diastolic dysfunction to NT-proBNP elevation.[18] In addition, we found that CFPWV was univariately associated with indexes of LV diastolic function (LA volume index, LV mass index, mitral E′ velocity and mitral E/E′). Therefore, the association of arterial stiffness with NT-proBNP level may be partially mediated by LV diastolic dysfunction.

This study had several strengths. First, to minimise the effect of potential confounding factors, we restricted our analysis to patients who developed AF at a young age (<65 years) in the absence of LV systolic dysfunction, CHF, structural or valvular heart abnormalities. Second, to minimise the haemodynamic effect of acute AF on NT-proBNP elevation, plasma NT-proBNP level was measured in AF patients after maintenance of 1 month of sinus rhythm without AF recurrence. Third, we included controls as a comparison group to demonstrate that the association between CFPWV and NT-proBNP is present in patients with AF and absent in individuals without AF. Thus, this association is unique to AF.

Our study had several limitations. First, this study being cross-sectional was suitable for assessing associations but not for determining causation. However, the findings of this study provide the basis to evaluate prospectively the contribution of arterial stiffness to NT-proBNP level in patients with AF. Second, we are using NT-proBNP as a surrogate of adverse cardiovascular outcomes. Again, the data from this study provide the basis to determine prospectively the extent to which arterial stiffness predicts worse outcomes in patients with AF.

Table 4 Multivariable model for prediction of log-transformed plasma N-terminal pro-B-type natriuretic peptide in controls*

Variable	Coefficient (95% CI)	p
Age at enrolment	0.029 (0.016 to 0.042)	<0.001
Male gender	−0.596 (−0.828 to −0.364)	<0.001
Mitral E′ velocity (m/s)	0.085 (0.024 to 0.147)	0.007

*Final model: R^2=16.2%.

CONCLUSION

Our findings suggest that CFPWV is independently associated with NT-proBNP in patients with AF. Since NT-proBNP elevation is a marker of adverse cardiovascular outcomes, conduit arterial stiffness may be associated with a worse prognosis in patients with AF.

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Competing interests None

Ethics approval This study was conducted with the approval of the National University of Singapore Institutional Review Board.

Provenance and peer review Not commissioned; externally peer reviewed.

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