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N-terminal proatrial natriuretic peptide correlates with systolic dysfunction and left ventricular filling pattern in patients with idiopathic dilated cardiomyopathy

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Abstract

***Objective*—To investigate the diastolic Doppler filling pattern in patients with idiopathic dilated cardiomyopathy and its relation to N-terminal pro-atrial natriuretic peptide (NT-pro-ANP).**

***Methods*—32 patients (26 male, six female) with idiopathic dilated cardiomyopathy were investigated. All were in sinus rhythm. Conventional M mode echocardiography and Doppler echocardiography was done in each patient. Pulsed wave Doppler inflow signals were obtained and the following variables were measured: maximum E wave, maximum A wave, E/A ratio, E wave deceleration time, A wave deceleration time. NT-pro-ANP was measured using radioimmunoassay.**

***Results*—Mean (SD) left ventricular ejection fraction was 34 (7)% and mean left ventricular end diastolic diameter on M mode echocardiography was 69 (7) mm. Left ventricular filling indices were as follows: maximum E wave velocity, 0.86 (0.22) m/s; maximum A wave velocity, 0.71 (0.24) m/s; E/A ratio, 1.41 (0.65). Mean E wave deceleration time was 140 (50) ms; mean A wave deceleration time was 100 (20) ms. In a stepwise forward regression model, NT-pro-ANP correlated significantly with left atrial diameter ($r = 0.603$; $p < 0.001$), left ventricular ejection fraction ($r = -0.758$; $p < 0.001$), and Doppler derived E/A ratio ($r = 0.740$; $p < 0.001$).**

***Conclusions*—In patients with idiopathic dilated cardiomyopathy there is a relation between NT-pro-ANP and both systolic and diastolic variables. In a multivariate model NT-pro-ANP correlated with left atrial diameter, left ventricular ejection fraction, and Doppler derived E/A ratio on transmitral inflow.**

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Keywords: idiopathic dilated cardiomyopathy; transmitral Doppler filling; N-terminal pro-ANP; atrial natriuretic factor

Diastolic dysfunction is thought to be responsible for signs and symptoms of heart failure in many disease entities.[1] It has been shown earlier that in patients with chronic heart failure caused by systolic dysfunction the degree of exercise limitation is closely correlated with left ventricular filling pressures.[2] More recently, several studies have suggested that left ventricular filling pressures can be estimated by transmitral Doppler flow velocity curves. Indices that can be used for this purpose include the E/A ratio (ratio of peak early to atrial filling velocity) and the deceleration time of both the E wave and the A wave.[3–7] Moreover, it has been shown that Doppler derived diastolic filling variables may play an important role in predicting cardiac mortality in patients with dilated cardiomyopathy and congestive heart failure. In particular, the restrictive filling pattern—characterised by a high E wave, a low A wave, a high E/A ratio, and a shortened deceleration time of the E wave—is a powerful predictor of increased mortality in patients with congestive heart failure and dilated cardiomyopathy.[8–11]

Atrial natriuretic factor (atrial natriuretic peptide, ANP) is a cardiac hormone that exists as a pro-ANP molecule and is stored as a 126 amino acid prohormone within atrial granules. In response to atrial stretch, pro-ANP is cleaved by a membrane protease and released into the circulation as a 28 amino acid C-terminal peptide and a 98 amino acid N-terminal peptide.[12] Plasma concentrations of atrial natriuretic factor are low and fluctuate rapidly. In contrast, concentrations of the inactive fragment N-terminal pro-ANP (NT-pro-ANP) are more stable and their concentration is at least 10 times higher than that of C-terminal ANP, mainly because of its slower elimination. The major known stimulus for secretion of atrial peptides is increased atrial wall stress, usually described as increased atrial stretch.[13] High concentrations of atrial natriuretic factor as well as of NT-pro-ANP are associated with a poor long term prognosis in patients with congestive heart failure and after myocardial infarction.[13–15]

In this study we were interested in determining whether there is a relation between NT-pro-ANP and indices of left ventricular filling obtained from Doppler echocardiography, a simple diagnostic tool for measuring diastolic dysfunction.

Methods

STUDY POPULATION

Fifty six patients with idiopathic dilated cardiomyopathy were screened for this study. The diagnosis was made according to the usual criteria in the presence of a depressed left ventricular ejection fraction (less than 45% by both echocardiography and coronary angiography) and in the absence of significant coronary artery disease and other specific heart muscle disease.[11 16 17] During routine diagnostic procedures all patients underwent right and left heart catheterisation as well as coronary angiography. Patients were included in the study not earlier than six months after a definitive diagnosis had been established to allow stabilisation on treatment. Patients were not eligible if they were more than 80 years old or had any of the following: atrial fibrillation; echocardiographic images and mitral Doppler tracings of insufficient quality for analysis; severe valvar disease requiring operation; significant chronic renal failure (serum creatinine > 159 μmol/l); and cancer or other systemic disease that might substantially shorten survival. Ultimately, 32 patients met the entry criteria for the study. The patients' symptoms were assessed by a functional classification. Asymptomatic patients were assigned to functional class I, mildly symptomatic patients to class II, moderately symptomatic patients to class III, and severely symptomatic patients with minimal activity or at chair-ridden to class IV, as previously described.[18]

ECHOCARDIOGRAPHY

Complete M mode and cross sectional echocardiography and Doppler ultrasound examination was performed in all patients using standard equipment (GE Vingmed 800, General Electrics Ultrasound Europe, Horten, Norway). Diastolic flow velocity at the left ventricular inflow tract was recorded by pulsed wave Doppler echocardiography using a 3.25 MHz transducer, as previously described.[9 19] In the apical four chamber view, the pulsed wave Doppler sample volume was placed in the middle of the left ventricular inflow tract, 1 cm below the plane of the mitral annulus between the tips of the mitral leaflets, where maximum flow velocity in early diastole was recorded.[9 18 19] Images were stored digitally on a magneto-optical cartridge.

MEASUREMENTS

The following diastolic variables were measured: peak early mitral valve filling velocity (E wave), peak atrial filling velocity (A wave), ratio of peak early and atrial filling velocity (E/A), deceleration time of the E wave, and deceleration time of the A wave. The deceleration time was taken as the time from the peak E velocity to the point at which the deceleration of flow was extrapolated to the baseline. Deceleration time of the A wave was measured in the same manner. The E/A ratio was calculated. For further analysis the mean of at least three measurements from each patient was used.[5 7 9 20]

BLOOD SAMPLES

Venous blood samples were collected from an antecubital vein immediately after echocardiographic investigation. Patients had to be at rest for at least 15 minutes before blood sampling. Blood was collected into chilled tubes containing EDTA. The blood samples were placed immediately on ice and promptly centrifuged at 4°C (2131 ×*g* for 10 minutes) and then stored at −70°C until final analysis. Blood samples were analysed blindly by laboratory physicians.

N-terminal proatrial natriuretic peptide (NT-pro-ANP) was measured in plasma using a radioimmunoassay without extraction (Biotopoy, Oulu, Finland, distributed by Immundiagnostik GmbH, Bensheim, Germany). The minimum detectable NT-pro-ANP concentration with this kit is 0.03 nmol/l; normal values range from 0.11 to 0.60 nmol/l.

STATISTICAL ANALYSIS

Statistics were done using a statistical software package (SigmaStat 2.0). Data are given as mean (SD). Correlations of neurohumoral indices and Doppler echocardiographic variables were examined using simple linear regression analysis and by forward stepwise regression analysis. Statistical significance was defined as $p < 0.05$.

Results

The study population consisted of 32 patients (26 male, six female; mean age 55 (13) years). All but one were treated with an angiotensin enzyme converting enzyme (ACE) inhibitor (97%), 29 (91%) were on diuretics, 27 (84%) on digitalis, eight (25%) were on β blocking agents, and four (13%) on long acting nitrates. Nine patients were in functional class I and II, 10 in class III, and four in class IV.

CONVENTIONAL AND ECHO-DOPPLER INDICES

Echocardiography revealed no significant valvar malfunction in any patient in the study population. Left ventricular end diastolic diameter was 69 (7) mm; left atrial diameter was 45 (8) mm; and left ventricular ejection fraction (LV-EF) was 34 (7)%. Indices of left ventricular filling were as follows: maximum E wave velocity was 0.86 (0.22) m/s; maximum A wave velocity was 0.71 (0.24) m/s; the E/A ratio was 1.41 (0.65); mean E wave deceleration time was 140 (50) ms; mean A wave deceleration time was 100 (20) ms.

PLASMA CONCENTRATIONS OF NT-pro-ANP

Plasma concentrations of NT-pro-ANP for the entire study population ranged from 0.234 to 4.906 nmol/l (mean 1.320).

RELATION BETWEEN NEUROHUMORAL AND ECHOCARDIOGRAPHIC VARIABLES

In a univariate analysis we found no correlation between NT-pro-ANP and heart rate, age, or afterload (that is, blood pressure). Table 1 shows the univariate analysis of echocardiographic and Doppler indices from the entire study population. There was a significant correlation between NT-pro-ANP and left atrial diameter, left ventricular end diastolic diameter, and left ventricular ejection fraction. Furthermore, NT-pro-ANP correlated significantly with all Doppler derived indices of transmitral inflow. Figure 1 shows the correlation between NT-pro-ANP and the E/A ratio ($r = 0.740$; $p < 0.001$).

Table 1 Correlation between N-terminal pro-ANP and echocardiographic and Doppler indices in all patients

	r Value	*p Value*
Left atrial diameter	0.603	< 0.001
Left ventricular end diastolic diameter	0.587	< 0.001
Left ventricular ejection fraction	−0.587	< 0.001
Doppler indices		
E wave (m/s)	0.501	0.003
A wave (m/s)	0.501	0.003
E/A ratio	0.740	< 0.001
E wave deceleration time (ms)	−0.535	0.002
A wave deceleration time (ms)	−0.525	0.002

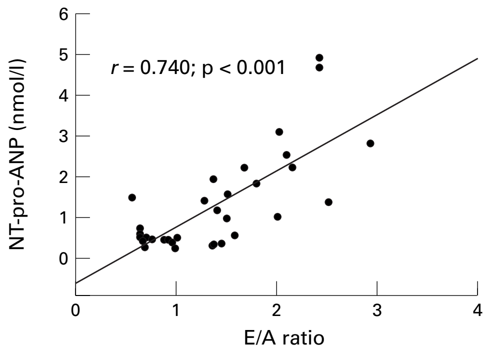

Figure 1 Univariate analysis of the correlation between the E/A ratio (ratio of peak early and atrial filling velocity) and NT-pro-ANP in our study population.

In a forward stepwise regression model that included the variables of the univariate analysis left ventricular end diastolic diameter lost its ability to predict NT-pro-ANP, while both left atrial diameter and left ventricular ejection fraction remained significant (left atrial diameter: $r = 0.603$; $p < 0.001$; left ventricular ejection fraction: $r = -0.758$; $p < 0.001$).

Doing the same analysis with Doppler indices, only the E/A ratio remained significant ($r = 0.740$; $p < 0.001$); all the other variables where eliminated.

Discussion

Our study showed that in patients with systolic dysfunction from idiopathic dilated cardiomyopathy there is a wide range of NT-pro-ANP concentrations. The values showed a good correlation with left atrial diameter, left ventricular ejection fraction, and the Doppler derived E/A ratio.

CONVENTIONAL AND DOPPLER INDICES IN PUBLISHED REPORTS

It is well known from previous studies that heart rate, mean left atrial diameter, and ventricular diameter increase, while left ventricular ejection fraction decreases, when patients become more symptomatic.[20] Yu *et al* reported on patients with a restrictive filling pattern whose left ventricular systolic function was more depressed than in patients with abnormal relaxation.[17] Recently our group was able to show that functional impairment in patients with idiopathic dilated cardiomyopathy correlates with left ventricular filling pattern.[21 22] Furthermore, in patients with left ventricular systolic dysfunction, restriction to filling is associated with a worse functional class.[23]

It is well known from previous Doppler studies that high E wave velocities, low A wave velocities, and high E/A ratios (usually termed a “restrictive filling pattern”) are associated with raised left ventricular filling pressures.[5 9 20 23 24] Extended work on this topic showed that there are further Doppler indicators of increased filling pressures. Shortened deceleration times of both the E wave and the A wave are non-invasive markers of a raised end diastolic pressure.[5-7] Furthermore, Giannuzzi and coworkers[18] showed earlier that the deceleration time in patients who died from progressive heart failure was significantly shorter than in patients who died suddenly.

DIFFERENT FINDINGS IN STUDIES ON NT-pro-ANP

Both atrial natriuretic factor and its stable precursor N-terminal pro-ANP correlate with left ventricular filling pressure.[17] Concentrations of these peptides are markedly increased in patients with a depressed left ventricular ejection fraction, regardless of symptoms.[12 26] There is, however, ongoing discussion over the role of atrial natriuretic factor in symptomatic and in asymptomatic patients.[17 27] NT-pro-ANP is now under investigation as a screening tool for patients with left ventricular dysfunction in the general population.[28] Atrial shear stress, usually described as atrial enlargement, is the most powerful trigger for secretion of NT-pro-ANP. It is therefore not surprising that patients with chronically enlarged left atria show raised plasma concentrations of NT-pro-ANP.

It was reported earlier that there is no correlation between NT-pro-ANP and age.[17 29] We also found no correlation between age and NT-pro-ANP. Univariate analysis showed good correlations between NT-pro-ANP and various echocardiographic indices, as shown earlier.[17] When putting these variables into a forward stepwise regression model, only left atrial diameter, left ventricular ejection fraction, and Doppler derived E/A ratio were able to predict NT-pro-ANP levels in the entire study population.

To our knowledge we are the first to demonstrate a correlation between natriuretic peptides (in our investigation, NT-pro-ANP) and diastolic filling. This is of particular interest as diastolic dysfunction is becoming increasingly recognised as a cause of symptoms. Furthermore, we were able to show that patients with high concentrations of natriuretic peptides can easily be identified by measuring ventricular diameter and diastolic dysfunction. This finding, however, can contribute further to elucidating the connection between diastolic function and neurohumoral activation, which itself is known to be a marker of poor prognosis.

LIMITATIONS OF OUR STUDY

The major limitation of our investigation is that we did not measure pulmonary venous blood flow. We believe that inclusion of this variable is unlikely to have influenced our results because it is well known that pulmonary venous flow is closely correlated with mitral flow.[6] It is, however, more difficult to record from the precordium and, like mitral flow, it is dependent on a combination of several factors. In placing the sample volume between the tips of mitral leaflets, Doppler signals of high quality can be obtained from study patients. Furthermore, diagnosing a restrictive filling pattern does not require measurement of pulmonary venous blood flow—it can also be diagnosed from a combination of the E/A ratio and the deceleration time of the E wave.[9 11 17 18 23]

CONCLUSIONS

Patients with idiopathic dilated cardiomyopathy show a relation between NT-pro-ANP and both systolic and diastolic indices. In a multivariate model NT-pro-ANP shows a significant correlation with left atrial diameter, left ventricular ejection fraction, and Doppler derived E/A ratio on transmitral inflow.

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