Natriuretic peptides in patients with diastolic dysfunction due to idiopathic dilated cardiomyopathy


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Aims The degree of systolic dysfunction does not always correlate with functional impairment in patients with congestive heart failure. In contrast, diastolic dysfunction correlates well with functional impairment. In heart failure, both elevation of N-terminal proatrial natriuretic peptide and B-type natriuretic peptide are markers of a poor prognosis.

Methods We investigated 32 patients (26 male, 6 female; mean age 55 ± 2 years) with dilated cardiomyopathy and sinus rhythm. M-mode echocardiography and 2D-echocardiography were carried out in each patient. Pulsed-wave Doppler inflow signals were obtained and the following parameters were measured: maximal E wave and maximal A wave velocity, E/A ratio, E wave deceleration time, A wave deceleration time. Immediately after echocardiography blood samples were collected from patients in the supine position. N-terminal proANP and brain natriuretic peptide were measured using a radioimmuno assay.

Results The left ventricular ejection fraction was 34 ± 1%, the left ventricular end-diastolic diameter on M-mode echocardiography was 68 ± 1 mm, while left atrial diameter was 45 ± 1 mm. Univariate analysis revealed a significant correlation between both left atrial diameter and ejection fraction and N-terminal proANP and brain natriuretic peptide. All transmitral Doppler parameters showed a significant correlation with N-terminal proANP and brain natriuretic peptide. On forward stepwise regression analysis, left atrial diameter and ejection fraction were able to predict both N-terminal proANP and brain natriuretic peptide. However, of the diastolic parameters only the E/A ratio remained significant. Mildly symptomatic patients differed significantly from severely symptomatic patients in all Doppler parameters. Mildly symptomatic patients had significantly lower levels of N-terminal proANP (0.571 ± 0.079 vs 2.282 ± 0.340 nmol . l⁻¹; P < 0.001) and brain natriuretic peptide (51 ± 14.8 vs 474.2 ± 86.8 pg . ml⁻¹; P < 0.001).

Conclusion There is a close relationship between natriuretic peptides and diastolic Doppler parameters of left ventricular filling in patients with dilated cardiomyopathy. There is also a significant difference between patients with mild and severe functional impairment regarding both natriuretic peptides and transmitral Doppler parameters.

Key Words: Idiopathic dilated cardiomyopathy, functional impairment, transmitral Doppler filling, natriuretic peptides.

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Introduction

Signs and symptoms of heart failure are closely related to the degree of diastolic dysfunction in many disease entities such as left ventricular hypertrophy or hypertrophic obstructive cardiomyopathy[1]. It has been shown earlier, in patients with chronic systolic dysfunction, that the degree of exercise limitation correlates closely 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. Parameters that can be used for this are the E/A ratio and deceleration times of both the E and the A wave[3–7]. It has also 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, characterized by a high E wave, a low A wave, a high
E/A ratio and a shortened E wave deceleration time, is a powerful predictor of increased mortality in patients with congestive heart failure and dilated cardiomyopathy [8–11].

Natriuretic peptides are hormones that are produced within the heart and released into the circulation in response to stretch. Therefore, atrial natriuretic peptide and brain natriuretic peptide are both related to left ventricular filling pressure [12]. High levels of both atrial natriuretic peptide and its inactive fragment N-terminal proANP, as well as high levels of brain natriuretic peptide give prognostic information: elevated levels of natriuretic peptides are associated with poor long-term prognosis in patients with congestive heart failure and in survivors of an acute myocardial infarction [13–16]. Recently, it has been shown that plasma levels of N-terminal proANP are significantly related both to parameters of systolic dysfunction (LVEF) and diastolic dysfunction (E/A ratio) [17–19]. Therefore, efforts have been made to use natriuretic peptides as a screening tool for heart failure in the general population [20, 21].

Recently we were able to demonstrate that different classes of functional impairment (New York Heart Association — NYHA) reveal different types of transmitral Doppler filling pattern [22, 23]. Patients in higher NYHA classes show a restrictive filling pattern with high E waves, low A waves, supernormal E/A ratios and short deceleration times. Patients in NYHA classes I and II show either a normal transmitral Doppler profile or impaired relaxation characterized by a low E wave, a high A wave, low E/A ratios and prolonged deceleration times. In the present study our interest focused on the question of whether mildly and severely impaired patients with dilated cardiomyopathy differ in plasma levels of N-terminal proANP and brain natriuretic peptide. We also wanted to find out which echocardiographic parameters correlate with N-terminal proANP and brain natriuretic peptides in patients with left ventricular dysfunction due to idiopathic dilated cardiomyopathy who were stable on their current regimens.

Methods

Characteristics of the study population

Fifty-five patients with idiopathic dilated cardiomyopathy were screened for this study. The diagnosis of idiopathic dilated cardiomyopathy was made 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, 12, 24]. All patients underwent right and left heart catheterization as well as coronary angiography. Patients were included in the study not earlier than 6 months after establishing the definite diagnosis to allow stabilization 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 valvular disease requiring operation, significant chronic renal failure (serum creatinine level \( \geq 2.0 \text{ mg} \cdot \text{dl}^{-1} \)), cancer or other systemic disease that might substantially shorten survival. Finally 32 patients were suitable for the study. Patients’ symptoms were assessed according to functional classification. Asymptomatic patients were assigned to functional class I, mildly symptomatic patients to class II, those moderately symptomatic to class III and those severely symptomatic with minimal activity or at rest to class IV, as previously described [25].

Echocardiography

Complete M-mode and two-dimensional echocardiography and Doppler ultrasound examination were performed in all patients from the precordium using standard equipment (GE Vingmed 800, General Electrics Ultrasound Europe). Diastolic flow velocity at the left ventricular inflow tract was recorded with pulsed wave Doppler echocardiography using a 3·25 MHz transducer, as previously described [9, 26]. 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 maximal flow velocity in early diastole was recorded [9, 25, 26]. Images were stored digitally on a magneto-optical cartridge.

Measurements

Diastolic parameters were measured as follows: peak early transmitral filling velocity (E wave), peak atrial filling velocity (A wave), ratio of peak early and atrial filling velocity (E/A), deceleration time of both the E wave and 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. The deceleration time of the A wave was measured accordingly. For further analysis the mean of at least three measurements from each patient was used [5, 7, 9, 27]. Heart rate was measured during echocardiography.

Blood samples

Venous blood samples were collected from an antecubital vein after echocardiographic investigation. Patients had to be at rest for at least 15 min 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 (4000 rpm for 10 min) and then stored at −70 °C until final analysis.

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Blood samples were analysed blindly by laboratory physicians who were not aware of the patients’ clinical classification. No neurohumoral parameter was available to the clinician and did not influence patient management either with regard to medication or timing of heart transplantation.

N-terminal proatrial natriuretic peptide was measured in plasma using a radioimmunoassay without extraction (Biotopoy, Oulu, Finland, distributed by Immundiagnostik GmbH, Bensheim, Germany). The minimal detectable (NT-ANP) concentration with this kit is 0·03 nmol . l$^{-1}$; normal values range from 0·11–0·60 nmol . l$^{-1}$.

Brain natriuretic peptide was measured in plasma using a solid phase radioimmunoassay without extraction (Shionogi, Osaka, Japan, distributed by Biocis, Vienna, Austria). BNP-levels up to 18·4 pg . ml$^{-1}$ are normal when using this kit.

**Statistical analysis**

Statistics were done using a statistical software package (SigmaStat® 2.0). According to clinical presentation patients were divided into two groups: those with no or only minimal limitations at exercise (NYHA functional classes I and II) and those with marked limitations at low levels of exercise or at rest (NYHA functional classes III and IV). Normally distributed variables were tested using the t-test, not normally distributed variables were tested using the Mann–Whitney Rank Sum test. Correlations of neurohumoral parameters and Doppler echocardiographic variables were examined using simple linear regression analysis and by forward stepwise regression analysis. Data are given as mean value ± standard error of the mean (SEM). Statistical significance was defined as $P<0·05$.

**Results**

The study population consisted of 32 patients (26 male, 6 female; mean age 55 ± 2 years). All but one were treated with an ACE inhibitor, 29 were on diuretics, 27 on digitalis, eight patients were on beta-blocking agents and four on long-acting nitrates. Nine patients were in functional classes I and classes II, respectively, ten in class III and four in class IV. Patients in classes I and II were group A, those in classes III and IV group B.

**Treatment differences between groups A and B**

Patients in both groups had comparable doses of ACE inhibitors for treatment of left ventricular dysfunction. The daily dose of captopril in group A was 96 ± 2 mg, in group B it was 94 ± 1 mg (ns). Enalapril was used in group A at a dosage of 20 ± 1 mg . day$^{-1}$ while in group B it was 19 ± 1 mg . day$^{-1}$ (n.s.). The daily dose of lisinopril in group A was 19 ± 2 mg and 18 ± 1 mg in group B (ns).

Daily doses of diuretics (frusemide) were markedly different between groups A and B: patients in group A had a daily dose of 31 ± 3 mg of frusemide while patients in group B had a daily dose of 53 ± 4 mg ($P=0·001$).

**Echocardiography**

The study cohort revealed a left ventricular end-diastolic diameter of 68 ± 1 mm and a left ventricular ejection fraction of 34 ± 1%. Mean heart rate, conventional echocardiographic parameters and diastolic Doppler parameters for both groups A and B are given in Table 1. All patients in group B had severely dilated ventricles;
in group A two patients had a left ventricular end-
diastolic diameter within the upper limit of normal
although they also had impaired systolic function. There
was no significant valvular malfunction in any study
patient.

**Natriuretic peptides**

Plasma levels of N-terminal proANP ranged from 0·234
to 4·906 nmol . l$^{-1}$ (mean 1·320). There was a significant
difference between mildly and severely symptomatic
patients: group A had a mean N-terminal proANP level
of 0·571 ± 0·079 nmol . l$^{-1}$ while group B had a mean
level of 2·282 ± 0·340 nmol . l$^{-1}$ ($P<0·001$, Fig. 1).

Brain natriuretic peptide values ranged from 0·1 to
1160·9 pg . ml$^{-1}$ (mean 247·5). Mildly symptomatic
patients differed significantly from severely symptomatic
patients: group A revealed a mean brain natriuretic
peptide level of 51·0 ± 14·8 pg . ml$^{-1}$ while group B had
a mean of 474·2 ± 86·8 pg . ml$^{-1}$ ($P<0·001$, Fig. 2).
There was a significant correlation between plasma
levels of N-terminal proANP and brain natriuretic
peptide: $r=0·942$, $P<0·001$ (Fig. 3).

**Correlation analysis**

When doing a univariate analysis of echocardiographic
and Doppler parameters, we found several correlations
that were statistically significant. These data are given in
Table 2. In a forward stepwise regression model left
ventricular end-diastolic diameter lost its ability to pre-
dict N-terminal proANP, while both the left atrial
diameter and left ventricular ejection fraction remained
significant (left atrial diameter: $P<0·001$; left ventricular
ejection fraction: $P<0·001$). The same analysis with
Doppler parameters revealed that only the E/A ratio
remained significant ($P<0·001$) while all other
parameters where eliminated.

The forward stepwise regression model for brain
natriuretic peptide revealed similar results: both left
atrial diameter and left ventricular ejection fraction were
able to predict brain natriuretic peptide at a highly
significant level (left atrial diameter: $P=0·002$; left ven-
tricular ejection fraction: $P<0·001$). All Doppler pa-
rameters that were significant in the univariate analysis
lost their ability to predict brain natriuretic peptide,
except the E/A ratio which remained highly significant
($P<0·001$).

**Follow-up**

During a follow-up period of 24 ± 4 months there
were several deaths as well as heart transplantations.
With the exception of maximal E wave velocity, sur-
vivors and non-survivors/transplant patients differed in
all parameters obtained. Further details are given
in Table 3.

**Discussion**

Our study demonstrates that mildly and severely
impaired patients with dilated cardiomyopathy reveal
significant differences in transmitral Doppler filling pa-
rameters. The differences, however, are closely related to
the differences in plasma levels of both N-terminal
proANP and brain natriuretic peptide. Forward step-

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*Figure 1* Patients in NYHA classes I and II (group A) show significantly lower
levels of N-terminal proANP (NT-ANP) than patients in NYHA classes III and
IV (group B).
wise regression analysis revealed a significant correlation between echocardiographic parameters of systolic dysfunction (left atrial diameter and left ventricular ejection fraction) and both N-terminal proANP and brain natriuretic peptide. Furthermore, there is a significant correlation between echocardiographic parameters of diastolic dysfunction, such as the transmitral E/A ratio and these natriuretic peptides. Although our study cohort was much too small to relate the findings to mortality, we found that patients who underwent heart transplantation or died during follow-up had markedly higher levels of N-terminal proANP and brain natriuretic peptide than survivors.

**Conventional and Doppler parameters**

Patients in higher NYHA classes (group B) had higher mean resting heart rates than mildly symptomatic...
patients (group A). Their mean left atrial and ventricular diameters were significantly greater and their ejection fraction was lower. Recently Rihal and co-workers[27] reported that patients with no or mild symptoms (NYHA I/II) have higher ejection fractions than those with moderate or severe symptoms (NYHA III/IV). Furthermore, Yu et al. reported on patients with restrictive filling patterns whose left ventricular systolic function was more depressed than those of patients with an abnormal relaxation[12]. One can conclude from these reports that progression of congestive heart failure is accompanied by a further impairment of both systolic and diastolic dysfunction.

Our group reported recently[22,23] that functional impairment in patients with idiopathic dilated cardiomyopathy correlates with the diastolic Doppler filling pattern. Those with a restrictive filling pattern on transmural Doppler echocardiography are more likely to be in high NYHA classes than those with abnormal relaxation. In patients with left ventricular systolic

<table>
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<th>Table 2</th>
<th>Univariate and multivariate predictors of N-terminal proANP (NT-ANP) and brain natriuretic peptide (BNP) in 32 patients with dilated cardiomyopathy</th>
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<tr>
<td></td>
<td>Univariate</td>
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<td>Chi-square</td>
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<tr>
<td>NT-ANP</td>
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<tr>
<td>E/A ratio</td>
<td>36-24</td>
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<td>Left atrial diameter</td>
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<td>Left ventricular ejection fraction</td>
<td>15-73</td>
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<td>A wave deceleration time</td>
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<td>10-53</td>
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<td>E wave velocity</td>
<td>10-01</td>
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<tr>
<td>Left ventricular end-diastolic diameter</td>
<td>3-97</td>
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<tr>
<td>BNP</td>
<td></td>
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<tr>
<td>E/A ratio</td>
<td>27-37</td>
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<tr>
<td>Left atrial diameter</td>
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<tr>
<td>Left ventricular end-diastolic diameter</td>
<td>3-97</td>
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<th>Table 3</th>
<th>Differences in echocardiography and in natriuretic peptides between survivors and those patients who died or underwent heart transplantation</th>
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<tr>
<td></td>
<td>Survivors</td>
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<td></td>
<td>(n=22)</td>
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<tr>
<td>Echo-parameters</td>
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<tr>
<td>LVEDD (mm)</td>
<td>67 ± 1</td>
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<tr>
<td>LAD (mm)</td>
<td>42 ± 2</td>
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<tr>
<td>LVEF (%)</td>
<td>36 ± 1</td>
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<td>Doppler parameters</td>
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<td>E wave (m. s⁻¹)</td>
<td>0-82 ± 0-05</td>
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<td>A wave (m. s⁻¹)</td>
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<tr>
<td>E/A ratio</td>
<td>1-2 ± 0-13</td>
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<tr>
<td>E wave deceleration time (ms)</td>
<td>151 ± 10</td>
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<tr>
<td>A wave deceleration time (ms)</td>
<td>102 ± 10</td>
</tr>
<tr>
<td>Natriuretic peptides</td>
<td></td>
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<tr>
<td>NT-ANP (nmol . l⁻¹)</td>
<td>0-828 ± 0-141</td>
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<tr>
<td>BNP (pg . ml⁻¹)</td>
<td>116 ± 34-5</td>
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<tr>
<td>Follow-up</td>
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<tr>
<td>Sudden unexpected death (n=)</td>
<td>0</td>
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<td>Death from progressive heart failure (n=)</td>
<td>0</td>
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<tr>
<td>Heart transplantation (n=)</td>
<td>0</td>
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</tbody>
</table>

LVEDD=left ventricular end-diastolic diameter; LAD=left anterior diameter; LVEF=left ventricular ejection fraction; NT-ANP=N-terminal proatrial natriuretic peptide; BNP=brain natriuretic peptide.
dysfunction, a restriction to filling is associated with a worse functional class\(^{(20)}\).

It is well known from previous Doppler studies that high E wave velocities, low A wave velocities and high E/A ratios (usually termed ‘restrictive filling pattern’) are associated with elevated left ventricular filling pressures\(^{(5,9,27,28,29)}\). Extended work on this topic revealed that there are further Doppler indicators of elevated filling pressures. Both a shortened E wave deceleration time and a shortened A wave deceleration time are non-invasive markers of an elevated end-diastolic pressure\(^{(5,6,7,30)}\). Giannuzzi and co-workers\(^{(25)}\) demonstrated earlier that the deceleration time of patients who die from progressive heart failure is significantly shorter than that of patients who die suddenly, a fact that we also found in our study population.

**Different findings in studies on N-terminal proANP and brain natriuretic peptide**

Both N-terminal proANP and brain natriuretic peptide are elevated in patients with depressed left ventricular ejection fraction regardless of symptoms\(^{(17,18)}\). Recently, Yu and co-workers reported that patients in higher NYHA classes have significantly higher levels of both atrial natriuretic peptide and brain natriuretic peptide\(^{(12)}\). Our results are consistent with these since we found markedly elevated levels of N-terminal proANP and brain natriuretic peptide in patients with severe functional impairment while asymptomatic patients revealed lower or even normal levels of natriuretic peptides.

Recently, it has been shown that plasma levels of N-terminal proANP are significantly related both to systolic (left ventricular ejection fraction) and diastolic parameters (E/A ratio)\(^{(17-19)}\). Although patients in these earlier studies had higher left ventricular ejection fractions than patients in our investigation the findings on N-terminal proANP are similar. All but one patient in our investigation was treated with an ACE inhibitor, while this drug was used rarely in the earlier investigations\(^{(17-19)}\). ACE-inhibitors, however, are known to lower circulating levels of brain natriuretic peptide in patients after myocardial infarction\(^{(31)}\). Therefore, it is questionable whether natriuretic peptides should be used as a tool for screening asymptomatic patients with heart failure who are being already treated with an ACE inhibitor since asymptomatic or mildly symptomatic patients often reveal normal levels of N-terminal proANP, as shown in our study. On the other hand, one can speculate that natriuretic peptides are useful in monitoring therapeutic advances in patients with congestive heart failure since they are normal or nearly normal in low NYHA functional classes.

We reported recently that the functional status and transmitial Doppler filling pattern are closely related\(^{(22,23)}\). Those with severe functional impairment (NYHA class III and IV) show a restrictive filling pattern, while patients with little or no symptoms reveal normal diastolic filling or impaired relaxation. In our recent study we were able to demonstrate that both elevation of N-terminal proANP and brain natriuretic peptide can be predicted from a large left atrial diameter, a low left ventricular ejection fraction and markers of a restrictive filling pattern, predominantly a high E/A ratio. Contrary to previous investigators\(^{(12)}\) our recent study shows good correlations between natriuretic peptides and various echocardiographic parameters. On stepwise forward regression analysis both left atrial diameter and left ventricular ejection fraction were able to predict plasma levels of N-terminal proANP and brain natriuretic peptide.

Recently it has been reported, that both N-terminal proANP and brain natriuretic peptide are elevated in patients with severe impairment of functional capacity compared to patients with no or mild symptoms of congestive heart failure\(^{(12,21)}\), a finding that is consistent with our results.

In clinical routine, patients with severely impaired left ventricular function and advanced functional impairment are considered candidates for heart transplantation. Those patients who underwent transplantation or died more often had a restrictive diastolic filling pattern than those who survived. Restrictive diastolic filling, however, is accompanied by a marked elevation of both N-terminal proANP and brain natriuretic peptide which itself is known to be an independent marker for a poor prognosis after myocardial infarction\(^{(13-16)}\). In this context, however, it is interesting that although we investigated patients with idiopathic dilated cardiomyopathy our study suggested that both hormones are prognostic markers in this disease as well. This suggestion needs to be investigated in further studies.

**Limitations of our study**

1. Our study population had only a few patients in functional class IV. In order to increase the statistical power we pooled patients with no or mild symptoms into one group and compared them with a group of patients with moderate or severe symptoms, as described by other investigators\(^{(10,12)}\). This procedure is comparable to clinical routine when patients are classified as mildly or severely impaired.

2. We did not measure pulmonary venous blood flow. In our opinion, inclusion of this parameter 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, is dependent on the 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 pulmonary venous blood flow
but can be diagnosed by combining the E/A ratio and the deceleration time of the E wave \cite{10,11,12,25,28}.

**Conclusion**

To our knowledge this is the first study to demonstrate that there is a significant diastolic and diastolic Doppler parameters of left ventricular pressure. We were able to show that there is a significant difference between patients with mild and severe functional impairment regarding both natriuretic peptides and transmitral Doppler parameters. Further studies are needed to elucidate these connections better.

**References**


