Clinical evaluation of new methods for the assessment of heart failure

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Clinical evaluation of new methods for the assessment of heart failure

Klinische evaluatie van nieuwe methoden ter beoordeling van hartfalen

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1 Introduction

Definition of the subject

Although every physician seems to know the term "heart failure", there is no general agreement on its definition. Due to the complex nature of heart failure and the changing insights into its pathophysiology over time, many different definitions exist.[1-5] Some focus on clinical presentations, while others highlight specific features of heart failure based on physiological concepts. In the studies which constitute this thesis, the clinical definition of heart failure as proposed by the Task Force on Heart Failure of the European Society of Cardiology has been used.[5] In accordance with this definition patients were diagnosed as having heart failure when they had symptoms of heart failure, typically dyspnoea, fatigue or ankle swelling, and objective evidence of left ventricular dysfunction. This diagnosis was considered to be reinforced by an adequate response to treatment directed towards heart failure. It should be noted that patients with heart failure who have responded to treatment may be entirely asymptomatic. In the studies presented in this thesis, these patients were labelled as having asymptomatic left ventricular dysfunction.

Several different adjectives can be used to describe heart failure. These include acute and chronic heart failure, congestive heart failure and systolic and diastolic heart failure. In its acute form, heart failure presents with rapidly developing symptoms and signs, such as dyspnoea, orthopnoea, pulmonary rates or peripheral oedema. Chronic heart failure, on the other hand, develops gradually, the symptoms are aspecific (e.g. fatigue) and the physical signs may be absent despite elevation of ventricular filling pressures.[6] Since many patients with chronic heart failure who are treated with diuretics do not have physical signs of congestion, the term heart failure should be used instead of congestive heart failure. Although heart failure is often assumed to be associated with impaired left ventricular systolic function, diastolic heart failure is increasingly being recognised as a separate clinical entity.[7] This issue, however, is beyond the scope of the present thesis, which focuses on patients with chronic heart failure and left ventricular systolic dysfunction.

Pathophysiology of heart failure

Over the past decade our knowledge of the pathophysiology of heart failure has improved substantially due to intensive research. Traditionally, heart failure has been regarded as a mechanical disorder, but nowadays the development and progression of the syndrome is thought to result from a complex interplay of

hemodynamic and neurohormonal factors.[4] After an injury to the heart (e.g. an acute myocardial infarction or prolonged cardiovascular stress) hemodynamic and neurohormonal mechanisms are activated to compensate for the loss of cardiac function. Changes at the cardiac level, such as ventricular dilatation and myocardial hypertrophy, and changes in the autonomic control of the heart, such as activation of the sympathetic nervous system, provide inotropic support for the heart. Peripheral vasoconstriction and salt and water retention provide further maintenance of systemic blood pressure and tissue perfusion. Heart failure develops when compensatory hemodynamic and neurohormonal mechanisms are overcome of exhausted. The disorder progresses when these mechanisms exert adverse effects.[8]

Objectives of the thesis

These enhanced insights into the pathophysiology of heart failure have altered the management of this disorder.[8,9] At the same time, they have led to the development of new methods that can be used for the assessment of specific aspects of heart failure. In this thesis several of these recently developed methods are evaluated from a clinical point of view. Amongst these are analysis of heart rate variability, measurement of cardiac peptides and Doppler echocardiographic assessment of left ventricular filling. In addition to these rather technical methods, attention is paid to the assessment of quality of life in patients with chronic heart failure.

Outline of the thesis

Analysis of heart rate variability is a non-invasive method to study the autonomic control of the heart. In healthy people, there is a physiological variation in the interval between consecutive heart beats. In patients with heart failure this heart rate variability is reduced. In **Chapter 2** the clinical and prognostic value of the heart rate variability index as simple and robust measure of heart rate variability is studied in patients with chronic heart failure.
Neurohormonal activation plays an important role in the development of heart failure. Increased plasma concentrations of norepinephrine and cardiac peptides have been shown to be early neurohormonal markers of heart failure. **Chapter 3** reports on the relationship between the heart rate variability index and neurohormonal activation in patients with asymptomatic or mildly symptomatic left ventricular dysfunction.

Cardiac peptides are released from the myocardium in response to the wall stretch that occurs with increased filling pressures. Atrial natriuretic peptide and its N-terminal counterpart are mainly released from the atria, whereas brain natriuretic peptide (named after the place of first identification) and N-terminal pro-brain natriuretic peptide are also secreted by the ventricles. In **Chapter 4** the relationship between plasma concentrations of atrial natriuretic peptides and echocardiographic measures of left ventricular systolic and diastolic function in patients with chronic heart failure was studied.

Plasma concentrations of cardiac peptides are sensitive to rapid changes in hemodynamics. In **Chapter 5** the differences in response to exercise between atrial natriuretic peptide, brain natriuretic peptide and their N-terminal counterparts were investigated.

Doppler recordings of mitral flow velocities can be used to assess left ventricular filling and diastolic function. Left ventricular filling abnormalities are common in patients with heart failure. In **Chapter 6** the relationship between left ventricular filling abnormalities and exercise capacity is explored.

Pseudonormalisation of the left ventricular filling pattern complicates the Doppler echocardiographic assessment of left ventricular diastolic function in patients with heart failure. **Chapter 7** describes the potentials and limitations of the Valsalva manoeuvre as a method of differentiating between normal and pseudonormal left ventricular filling patterns.

Assessment of health-related quality of life is considered to be an important factor in the management of patients with heart failure. In addition, there is a growing interest in using quality of life measurements in heart failure research. In **Chapter 8** the validity of the Dutch version of the Minnesota Living with Heart Failure Questionnaire was investigated by testing its relationship to corresponding clinical and psychological measures of health status.

Finally, in **Chapter 9** the results of these studies are discussed and recommendations for further research are provided.

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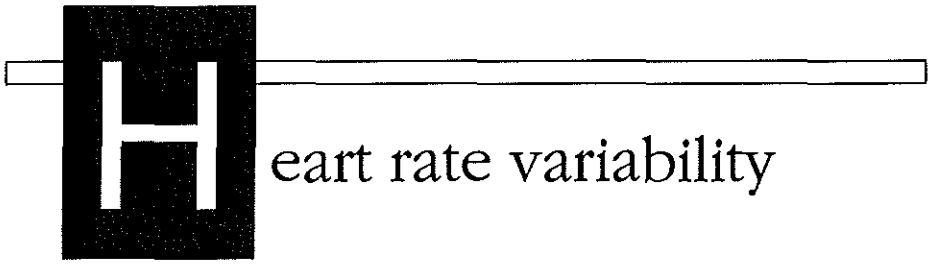

Heart rate variability

2 The heart rate variability index in heart failure: relation to clinical variables and prognosis

Abstract

Background Analysis of heart rate variability has been shown to supply clinically useful information in patients with heart failure. The heart rate variability index is a simple measure of heart rate variability that can be derived from only casually edited electrocardiographic recordings. Because of its robustness, this index overcomes the disadvantage of other heart rate variability measures. The aim of this study was to evaluate the clinical and prognostic value of the heart rate variability index in patients with chronic heart failure.

Methods and results Sixty-four patients with chronic heart failure and sinus rhythm underwent clinical assessment, 24-hour ambulatory electrocardiography and echocardiography. Patients were followed for 6 to 30 months. Cardiac death or heart transplantation constituted the primary endpoint of the study. The heart rate variability index was related to left ventricular ejection fraction ($r = 0.29$, $p = 0.02$) and New York Heart Association class ($p = 0.01$). Patients with a restrictive left ventricular filling pattern had a lower heart rate variability index compared to patients with a non-restrictive pattern (26 ± 11 versus 33 ± 9 units, $p = 0.01$). Patients who died ($n = 11$) or underwent heart transplantation ($n = 4$) had a lower heart rate variability index compared to survivors (21 ± 10 versus 33 ± 9 units, $p < 0.0001$). In multivariate survival analysis, a reduced heart rate variability index was related to survival independent of parameters of left ventricular function.

Conclusion The heart rate variability index provides independent information on clinical status and prognosis in patients with chronic heart failure and may thus be of practical use in the clinical and prognostic assessment of chronic heart failure.

Introduction

Non-invasive assessment of cardiac autonomic status can be achieved by heart rate variability analysis.[1,2] Measures of heart rate variability have been used as prognostic indicators in different groups of patients, in particular after myocardial infarction.[3] In addition, several heart rate variability measures obtained from 24-hour electrocardiographic recordings have been shown to supply clinically useful information in patients with congestive heart failure.[4-7] The disadvantage of most methods used for the analysis of heart rate variability is that the required corrections for ectopic beats, that are known occur frequently in heart failure, together with noise, baseline drift and signal loss, which are inherent to 24-hour electrocardiographic recordings, make the analysis of heart rate variability difficult and time-consuming.[8]

The heart rate variability triangular index is a simple geometrical measure of heart rate variability that can be derived from only casually edited 24-hour electrocardiographic recordings.[9] Because of its robustness, this index overcomes the disadvantage of other heart rate variability measures and might therefore be of practical use in the clinical assessment of patients with heart failure. However, the clinical and prognostic value of the heart rate variability index in patients with heart failure has not been studied so far. For that reason, the relationship between the heart rate variability index and several parameters of severity of heart failure, such as functional classification, left ventricular ejection fraction and left ventricular filling pattern in patients with chronic heart failure was explored. In addition, the prognostic value of the heart rate variability index in these patients was evaluated in a multivariate survival model.

Methods

Study population

Seventy-two patients (61 men, 59 ± 10 years) with chronic heart failure due to coronary artery disease or dilated cardiomyopathy and sinus rhythm were studied. The aetiology of heart failure was established after careful review of clinical history and results of echocardiographic and angiographic examinations. Patients with diabetes mellitus were excluded. All patients underwent 24-hour ambulatory electrocardiography and echocardiography. Fifty-two patients with predominantly mild heart failure underwent cardiopulmonary exercise testing as part of another study protocol. Patients without exercise tests were in a higher

New York Heart Association class and had lower left ventricular ejection fractions, but were of similar age and gender and used similar medication compared to patients with exercise tests.

Holter recordings and heart rate variability analysis

Electrocardiographic recordings were made on 3 channel tape recorders (Oxford MR 4500-3). Morphological classification of QRS complexes was performed in the recorder on raw electrocardiographic data and the results were stored on a digital track on the tape. The classifications were checked manually and corrected if necessary using the Oxford Medilog Excel-2 Holter Management System (software version 7.5). Only a casual editing of the recordings was performed, spending no more than 10 minutes on each recording. Files of digital samples, QRS classifications and RR interval durations were stored on CD-ROM for further analysis. A sample density histogram of all normal RR interval durations measured on a discrete scale with bins of 7.8125 ms (1/128 sec) was constructed for each recording and the heart rate variability index was derived by dividing the total number of all intervals by the height of the histogram.[9] Recordings with less than 18 hours of normal RR intervals were considered to be unsuitable for analysis.[1] In addition, all tapes were analysed for the incidence of ventricular premature beats and ventricular tachycardias. An episode of ventricular tachycardia was defined as ≥ 3 consecutive ventricular premature beats with a rate of $>$ 100/min.

Echocardiographic examinations and measurements

Two-dimensional and Doppler echocardiographic examinations were performed with either a Vingmed CFM-800c or a Toshiba SSA-380a system using 2.5 and 3.5 MHz transducers. Left ventricular ejection fraction was calculated from the apical four-chamber and long-axis views using a biplane disk method.[10] Left ventricular inflow velocities were recorded from the apical four-chamber view using pulsed Doppler echocardiography with the sample volume placed between the tips of the mitral leaflets. Doppler measurements were made by manual tracing of the outermost portion of the velocity contour using an off-line computer, a digitising tablet and a dedicated software program. Parameters of left ventricular filling included peak velocities of both early (E) and atrial (A) diastolic filling, the E/A ratio and deceleration time of peak E to baseline. Mean values were obtained by averaging at least 3 consecutive beats. Heart rate was averaged from the same beats. Since either an increased E/A ratio and a shortened deceleration time are indicative of restrictive physiology,[11,12] both variables were used to subdivide the

study patients into two groups: patients with an E/A ratio ≥ 2 were considered to have a restrictive pattern, whereas patients with an E/A ratio ≤ 1 were considered to have a non-restrictive pattern. In case patients had an E/A ratio between 1 and 2 a deceleration time ≤ 150 msec was defined as restrictive and a deceleration time > 150 msec as non-restrictive.

Cardiopulmonary exercise testing

Symptom-limited exercise was performed on a bicycle ergometer (Lode, Groningen, the Netherlands) at a constant pedalling speed of 60 rpm with workload increments of 10 Watts/min. Heart rate, blood pressure and a 12-lead electrocardiogram were monitored during the test. Both gas volume and gas concentrations were measured continuously using either a breath-by-breath system and a face mask with a digital volume sensor (Oxycon Champion) or a mixing chamber and a mouthpiece with a three-way low resistance valve and a noseclip (Oxycon-4, Mijnhardt Oxycon Systems, Bunnik, the Netherlands). Gas analyses were made by a paramagnetic oxygen and infrared carbon dioxide analyser. Oxygen consumption and carbon dioxide production were recorded every 30 seconds. Predicted maximum oxygen consumption according to age, height, weight and gender was calculated for each patient.[13] Peak oxygen consumption (defined as the maximal value measured at the end of the test) was expressed as percentage of the predicted maximum oxygen consumption.

Follow-up

The patients were followed for 6 to 30 months. The occurrence of either cardiac death or heart transplantation was the primary end point of the study.

Statistical analysis

Comparisons between groups were made by unpaired t tests for continuous data and χ^2 tests for categorical data. The relationships between clinical variables and the heart rate variability index were tested using univariate linear regression analysis. Analysis of variance was used to test the relationship between New York Heart Association class and the heart rate variability index. The effects of individual variables on the occurrence of death or heart transplantation were assessed by univariate proportional hazards regression analysis. Multivariate survival analysis was performed with all variables that had been shown to be significantly related to time to death or heart transplantation in univariate analysis, except for exercise data because these data were not available in all study

Table 1
Baseline clinical and heart rate variability data for all patients, for patients who survived and for patients who died or underwent heart transplantation

	all patients	without event	with event	P value
		survival	death or HTX	
n	*64*	*49*	*15*	
Age (years)	59 ± 10	60 ± 10	58 ± 10	ns
Gender (% male)	86	86	87	ns
Aetiology (% CAD)	63	59	73	ns
Third heart sound (% present)	28	16	67	0.0002
Systolic blood pressure (mm Hg)	129 ± 24	133 ± 20	116 ± 30	0.02
NYHA classification	2.2 ± 0.8	1.9 ± 0.6	3.0 ± 0.8	< 0.0001
Peak VO_2 (%)	66 ± 16	68 ± 15	50 ± 9	0.01
Duration (months)	38 ± 33	40 ± 34	32 ± 30	ns
LVEF (%)	31 ± 8	33 ± 7	25 ± 7	< 0.0001
TMF pattern (% restrictive)	36	24	73	0.0006
Deceleration time (msec)	189 ± 74	202 ± 70	141 ± 70	0.005
Plasma sodium (mmol/L)	140 ± 4	140 ± 3	137 ± 5	0.008
Heart rate (bpm)	76 ± 10	74 ± 9	84 ± 8	< 0.0001
HRV index (-)	30 ± 10	33 ± 9	21 ± 10	< 0.0001
Ventricular premature beats (/hour)	16 (1-375)	15 (1 - 375)	19 (1 - 208)	ns
Ventricular tachycardia (%)	48	47	53	ns
Medication (%)				
ACE inhibitors	92	92	93	ns
Diuretics	78	74	93	ns
Digitalis	58	55	67	ns
Nitrates	34	29	53	ns
β blockers	14	14	13	ns

Data are expressed as mean ± SD, median (range) or percentage of patients; P values are given for comparisons between survivors and patients who died or underwent heart transplantation. HTX = heart transplantation; CAD = coronary artery disease; NYHA = New York Heart Association; VO_2 = oxygen consumption; LVEF = left ventricular ejection fraction; TMF = transmitral flow; HRV = heart rate variability.

subjects and transmitral flow pattern because this was not an independent variable. Receiver operator characteristics curves were constructed to identify the optimum cut-off value (taken as the interception of sensitivity and specificity) of the defined variables. Survival curves were calculated using the Kaplan-Meier method and tested for significance with the log-rank test. Data are presented as mean ± SD unless otherwise specified. Because of the skewed distribution of number of premature ventricular beats, the natural logarithmic transformed value was used in the analyses. All analyses were performed using SPSS for Windows (version 6.1). Statistical significance was defined as $P < 0.05$.

Results

Study population

Eight out of 72 (11%) patients were excluded because they had recordings with less than 18 hours of normal RR intervals due to either frequent ectopic beats or poor data quality. The remaining 64 patients formed the study group. Patients with unsuitable recordings were more symptomatic and had lower left ventricular ejection fractions compared to patients with suitable Holter recordings.

Baseline data and follow-up

Fifteen out of 64 (23%) patients experienced end point events during the follow-up period: 11 patients died and 4 patients underwent heart transplantation because of end-stage heart failure. Baseline data for all patients as well as for patients who survived and patients who died or underwent heart transplantation are presented in Table 1. Patients who died or underwent heart transplantation had more severe heart failure as regards functional classification, findings at physical examination, exercise capacity and left ventricular systolic and diastolic function compared to survivors. In addition, they had lower plasma sodium concentrations, higher heart rates at rest and lower heart rate variability index values.

The heart rate variability index in relation to clinical variables

The heart rate variability index was related to left ventricular ejection fraction ($r = 0.29$, $P = 0.02$), heart rate ($r = -0.37$, $P = 0.003$), deceleration time ($r = 0.38$, $P = 0.002$) and New York Heart Association class ($P = 0.01$). Patients who had a restrictive transmitral flow pattern had lower heart rate variability index values

compared to patients with a non-restrictive transmitral flow pattern (26 ± 11 vs. 33 ± 9 units, P = 0.01). The heart rate variability index was not significantly related to age (r = 0.09, ns), duration of heart failure (r = 0.13, ns), systolic blood pressure (r = 0.20, ns), plasma sodium concentration (r = 0.22, P = 0.08) or peak oxygen consumption (r = 0.27, P = 0.06) and did not differ significantly between males and females (30 ± 10 vs. 30 ± 11 units), patients with and without angiotensin converting enzyme inhibitors (30 ± 9 vs. 30 ± 18 units), patients with and without diuretics (29 ± 10 vs. 34 ± 10 units), patients with and without digitalis (30 ± 11 vs. 31 ± 9 units), patients with and without nitrates (29 ± 10 vs. 31 ± 11 units) and patients with and without β blockers (32 ± 9 vs. 30 ± 11 units). There were no significant differences in the heart rate variability index between patients with heart failure due to coronary artery disease and patients with heart failure due to dilated cardiomyopathy (31 ± 11 vs. 30 ± 10 units).

Survival analysis

In univariate survival analysis, low heart rate variability index, diminished left ventricular ejection fraction, low peak oxygen consumption, low plasma sodium concentration, low systolic blood pressure, increased heart rate at rest, a third heart sound at auscultation, the presence of a restrictive transmitral flow pattern and a shortened deceleration time were significantly related to the occurrence of cardiac death or heart transplantation (Table 2). Age, gender, aetiology and duration of heart failure, frequency of ventricular premature beats, presence of ventricular tachycardia and heart failure medication were also tested but not found to be significant. Multivariate survival analysis showed that low heart rate variability index and diminished left ventricular ejection fraction were the only independent predictors of the occurrence of cardiac death or heart transplantation (Table 2). The optimum cut-off values for the heart rate variability index and left ventricular ejection fraction (as derived from receiver operator characteristics curves) were 26 units and 30%, respectively. A heart transplantation free survival curve was constructed for all possible combinations of heart rate variability index and left ventricular ejection fraction above and below their optimum cut-off value (Figure 1). The difference in survival time between the four groups was statistically significant when evaluated with the log-rank test (χ^2 = 18.6, P < 0.0001). Repetition of the analyses after exclusion of the transplanted patient (n = 4) as well as after exclusion of patients with a left ventricular ejection fraction ≥ 40% (n = 10) did not lead to different results.

Table 2
Time to death or heart transplantation in relation to prognostic variables - univariate and multivariate proportional hazards regression analysis

	univariate analysis			multivariate analysis		
	Hazard Ratio	95% CI	P value	Hazard Ratio	95% CI	P value
HRV index	12.6 *	3.9 - 41.4	<0.0001	11.8 *	3.2 - 43.1	0.0002
LVEF (%)	9.8 *	2.8 - 34.4	0.0004	9.8 *	2.4 - 31.0	0.001
Peak VO_2 (%)	6.3 *	1.3 - 29.9	0.02	-	-	-
Deceleration time (msec)	4.4 *	1.7 - 11.3	0.002	3.9 *	0.9 - 10.1	0.08
Heart rate (bpm)	4.4 **	1.8 - 10.4	0.0008	1.6 **	0.7 - 7.2	0.44
Systolic blood pressure (mm Hg)	4.3 *	1.6 - 11.8	0.005	1.4 *	0.4 - 5.4	0.63
Plasma sodium (mmol/L)	1.7 *	1.2 - 2.3	0.003	1.1 *	0.7 - 1.9	0.60
Third heart sound (present)	2.8	1.7 - 4.9	0.0002	1.2	0.5 - 2.7	0.72
TMF pattern (restrictive)	2.6	1.4 - 4.6	0.001	-	-	-

* Hazard ratio and 95% confidence interval for a decrease to the size of the interquartile difference for the specified variable. ** Hazard ratio and 95% confidence interval for an increase to the size of the interquartile difference for the specified variable. CI = confidence interval; HRV = heart rate variability; LVEF = left ventricular ejection fraction; VO_2 = oxygen consumption; TMF = transmitral flow. Third heart sound was classified as present (n = 18) and not present (n = 46). Transmitral flow pattern was classified as restrictive (n = 23) and non-restrictive (n = 41).

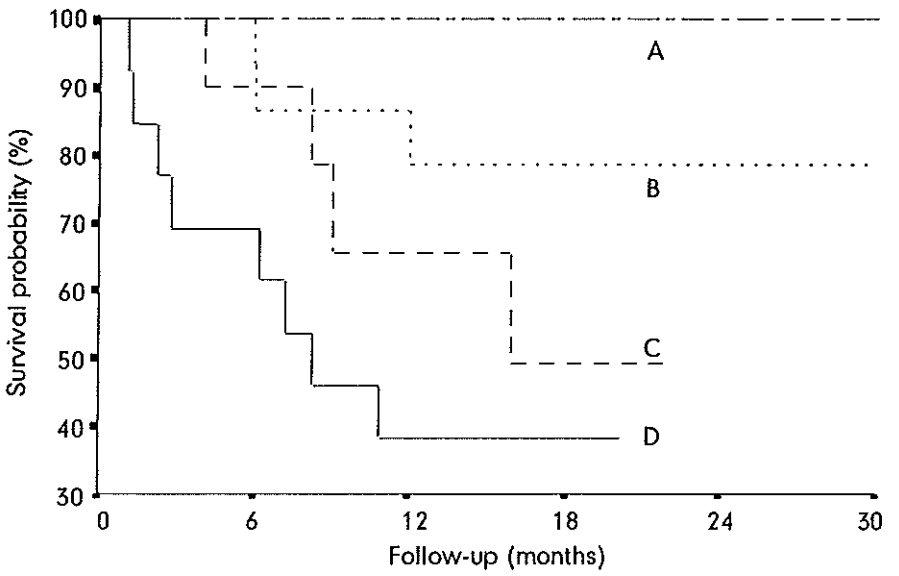

Figure 1
Kaplan-Meier curves for cardiac death or heart transplantation in patients with a heart rate variability index > 26 units and a left ventricular ejection fraction > 30% (line A), patients with a heart rate variability index > 26 units and a left ventricular ejection fraction ≤ 30% (line B), patients with a heart rate variability index ≤ 26 units and a left ventricular ejection fraction > 30% (line C) and patients with a heart rate variability index ≤ 26 units and a left ventricular ejection fraction ≤ 30% (line D).

Discussion

Heart rate variability index, severity of heart failure and prognosis

In the present study, it was shown that in patients with chronic heart failure, the heart rate variability index is significantly related to left ventricular ejection fraction and left ventricular filling pattern. Furthermore, it was demonstrated that in these patients a decreased heart rate variability index is associated with an increased risk of cardiovascular death or heart transplantation. Heart rate variability is known to be reduced in patients with heart failure compared to normal subjects.[14,15] In previous studies, it has been demonstrated that conventional heart rate variability parameters are related to left ventricular systolic function and functional classification.[6,16-19] In addition, several measures of heart rate variability have been shown to have predictive value in patients with advanced heart failure as well as in patients with mild to moderate heart failure.[4-7] The

present finding that the heart rate variability index supplies prognostic information in patients with different stages of heart failure is in conformance with these reports. Indeed decreased heart rate variability is related to severity of left ventricular dysfunction and therefore associated with a poor prognosis, but in multivariate survival analysis it was shown that the heart rate variability index provided prognostic information independent of and additive to left ventricular ejection fraction. Whether this additional predictive value is found because patients with a relatively preserved ejection fraction and decreased heart rate variability have a different mode of death compared to patients with severe left ventricular systolic dysfunction can not be determined from this study.

The relationship between left ventricular filling pattern and heart rate variability has not been studied before. A restrictive left ventricular filling pattern in patients with chronic heart failure has been shown to be associated with elevated filling pressures, more severe disease and a poor prognosis.[20,21] The present finding that a restrictive transmitral flow pattern is associated with depressed heart rate variability supports the notion that patients with severe heart failure have markedly altered sympathetic variability and emphasises the relationship between severity of heart failure and the heart rate variability index.[22]

Study limitations

Differences in medication, resting heart rate and aetiology of heart failure might have affected both heart rate variability and survival. Nevertheless, there was no significant difference in the heart rate variability index between patients with and without concomitant heart failure medication and between patients with coronary artery disease and dilated cardiomyopathy. In addition, neither baseline medication use nor aetiology of heart failure differed significantly between patients who survived and patients who died or underwent heart transplantation. There were differences in heart rate between patients who survived and patients who died or underwent heart transplantation, but, as heart rate was found not to be significant in multivariate survival analysis, these differences are unlikely to have influenced the present results. Finally, the definitions for restrictive and non-restrictive filling patterns can be considered as arbitrary. Nevertheless, the heart rate variability index did not only differ between patients with different filling patterns, but correlated with transmitral deceleration time as well.

Practical implications for the clinical use of the heart rate variability index

Although several prior studies have reported on the clinical and prognostic value of analysis of heart rate variability in the assessment of patients with heart failure,[4-7,16-19] this technique has not been incorporated into clinical practice yet. This might be due to the fact that most methods used for the analysis of heart rate variability require difficult and time-consuming manual editing of computer-recognised series of RR intervals. The heart rate variability index, on the contrary, has been shown to be less sensitive to the analytical quality of electrocardiographic recordings and can therefore be performed on casually edited data.[9] The only requirement for the use of this method is the need for a reasonable number of normal RR intervals to construct the geometrical pattern.[1] From the 72 recordings that were considered for the present study, 8 (11%) had less than 18 hours of normal RR intervals due to ectopic beats or poor data quality and were excluded from analysis. The remaining 64 recordings were analysed without extensive data editing and the resulting heart rate variability index was shown to be related to clinical parameters of severity of heart failure and to provide prognostic information independent of and additive to left ventricular ejection fraction. Therefore, the heart rate variability index as simple and robust measure of heart rate variability may be useful in the clinical and prognostic assessment of chronic heart failure.

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3

Heart rate variability is related to neurohormonal activation in patients with asymptomatic or mildly symptomatic left ventricular systolic dysfunction

Abstract

Background Increased plasma concentrations of norepinephrine and natriuretic peptides have been shown to be early neurohormonal markers of heart failure. This study investigated whether heart rate variability, as non-invasive measure of cardiac autonomic control, is related to neurohormonal activation in patients with early stages of heart failure.

Methods and results Plasma concentrations of norepinephrine, atrial natriuretic peptide, N-terminal pro-atrial natriuretic peptide and brain natriuretic peptide were measured in 45 patients with asymptomatic or mildly symptomatic left ventricular systolic dysfunction. In addition, 24-hour ambulatory electrocardiography was performed. The heart rate variability index, as a simple and robust measure of overall heart rate variability, correlated with plasma norepinephrine ($r = -0.33$, $p = 0.03$), atrial natriuretic peptide ($r = -0.42$, $p = 0.005$), N-terminal pro-atrial natriuretic peptide ($r = -0.45$, $p = 0.002$) and brain natriuretic peptide ($r = -0.46$, $p = 0.001$). Multivariate analysis showed that this was independent of age, functional class, left ventricular ejection fraction and heart rate.

Conclusion The heart rate variability index is related to neurohormonal status in patients with asymptomatic or mildly symptomatic left ventricular systolic dysfunction. Analysis of heart rate variability, as non-invasive method to study cardiac autonomic status, might thus be a useful tool in the early detection of heart failure.

Introduction

Neurohormonal activation plays an important role in the development of heart failure. Plasma concentrations of norepinephrine and natriuretic peptides are not only elevated in patients with severe heart failure, but are also increased in early stages of heart failure.[1-5] Plasma norepinephrine, atrial natriuretic peptide (ANP), N-terminal proANP and brain natriuretic peptide (BNP) are therefore known to be early markers of heart failure.[2-5]

Abnormal autonomic control of the heart is common in patients with congestive heart failure and can be studied non-invasively by analysis of heart rate variability.[6,7] Several heart rate variability measurements obtained from 24-hour electrocardiographic recordings have been shown to be depressed in patients with heart failure.[8-10] The heart rate variability index is a simple geometrical method to assess overall heart rate variability over 24 hours.[11] Recently, this method has been demonstrated to be of clinical and prognostic value in patients with heart failure.[12]

Previous studies have shown that parameters of overall heart rate variability are correlated with plasma norepinephrine concentrations in patients with advanced heart failure.[13,14] This suggests that analysis of heart rate variability provides information on neurohormonal activation and could thus be useful in the early detection of heart failure. However, whether heart rate variability is related to plasma norepinephrine in patients with mild forms of heart failure is not known. Furthermore, the relationship between heart rate variability and plasma natriuretic peptides has not been studied before. In order to gain insight in the neurohormonal correlates of heart rate variability in patients with early stages of heart failure, the present study investigated the relationship between the heart rate variability index and plasma concentrations of norepinephrine, ANP, N-terminal proANP and BNP in patients with asymptomatic or mildly symptomatic left ventricular systolic dysfunction.

Methods

Study population

Within the framework of an outpatient heart failure research project, 69 patients with left ventricular systolic dysfunction due to coronary artery disease or dilated cardiomyopathy underwent several non-invasive cardiovascular tests, among

which echocardiography, 24-hour ambulatory electrocardiography and blood sampling for measurements of plasma neurohormones. Only patients with asymptomatic or mildly symptomatic left ventricular systolic dysfunction (left ventricular ejection fraction < 45% and New York Heart Association functional class I or II) and sinus rhythm were considered to be eligible for the present study. Patients with diabetes mellitus or Holter recordings with less than 18 hours of normal RR intervals due to frequent ectopic beats or poor data quality were excluded. The resulting study population consisted of 45 patients, 40 men and 5 women. Other clinical characteristics are presented in Table 1. In all cases, Holter monitoring was started right after blood sampling.

Holter recordings and heart rate variability analysis

Electrocardiographic recordings were made on 3-channel tape recorders (Oxford MR 4500-3, Oxford Instruments, Oxon, UK). Morphological classification of QRS complexes was performed on raw electrocardiographic data and the results were stored on a digital track on the tape. The classifications were checked manually and corrected if necessary using the Oxford Medilog Excel-2 Holter Management System (software version 7.5). Files of digital samples, QRS classifications and RR interval durations were stored on CD-ROM for further analysis. A sample density histogram of all normal RR interval durations measured on a discrete scale with bins of 7.8125 ms (1/128 sec) was constructed for each recording and the heart rate variability index was derived by dividing the total number of all intervals by the height of the histogram.[11]

Table 1
Clinical characteristics

	n = 45
Age (years)	59 ± 10
NYHA class	
I	10 (22%)
II	35 (78%)
Aetiology	
Coronary artery disease	28 (62%)
Dilated cardiomyopathy	17 (38%)
LVEF (%)	33 ± 6
Heart rate (beats/min.)	74 ± 9
HRV index (-)	33 ± 10
Medication	
ACE inhibitors	41 (91%)
Diuretics	32 (71%)
Digitalis	24 (53%)

Data are presented as mean ± SD or number (%). ACE = angiotensin converting enzyme; HRV = heart rate variability; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

Blood sampling and neurohormone analysis

Venous blood samples were drawn after 30 minutes of supine rest. The tubes were placed on ice and centrifuged within 30 minutes from sampling in a refrigerated centrifuge for 10 minutes at 3000 g.

Plasma was stored at -70°C. Plasma norepinephrine and natriuretic peptide measurements were performed in the Cardiovascular Research Laboratory, University Hospital Rotterdam, The Netherlands. Commercially available kits were used for measurement of ANP (Nichols Institute, Wijchen, The Netherlands) and N-terminal proANP (Biotop, Oulu, Finland).[15] Plasma norepinephrine was measured as described previously.[16] Brain natriuretic peptide measurements were performed in the Institute for Surgical Research, University of Oslo, Norway, using an immunoradiometric assay for human BNP (Shionoria BNP kit, Shionogi & Co. Ltd., Japan).[17]

Echocardiography

Two-dimensional echocardiographic examinations were performed in all patients. Left ventricular ejection fractions were derived from the two-dimensional apical four-chamber and long-axis views using a biplane disk-method.[18] Mean values were obtained by averaging three consecutive beats. Heart rate was averaged from the same beats.

Statistical analysis

Comparisons between patients in New York Heart Association class I and II, between patients with and without concomitant heart failure medication and between patients with coronary artery disease and dilated cardiomyopathy were made by unpaired t tests. Univariate linear regression analysis was used to test the relationship between the heart rate variability index and clinical variables, between the heart rate variability index and neurohormonal values and between neurohormonal values and clinical variables. In order to evaluate the relationship between the heart rate variability index, clinical variables and neurohormonal values, separate multivariate linear regression analyses for each neurohormone were performed. The standardised regression coefficients (β), as representation of the relative contribution of the specified variables to the variations in heart rate variability index, and corresponding P values were presented in tabular form. Because of their skewed distribution, the natural logarithmic transformed values of norepinephrine, ANP, N-terminal proANP and BNP were used in the analyses. Data are presented as mean ± SD unless otherwise specified. All analyses were performed using SPSS for Windows (version 6.1). Statistical significance was defined as $P < 0.05$.

Results

Univariate analysis: Heart rate variability index and clinical variables

The heart rate variability index was significantly related to heart rate (r = - 0.49, P = 0.001), but not to age or left ventricular ejection fraction. Patients in New York Heart Association class I had a higher heart rate variability index than those in class II (39 ± 10 vs. 31 ± 9; P = 0.02). The heart rate variability index did not significantly differ between males and females, patients with and without angiotensin converting enzyme inhibitors, patients with and without diuretics, patients with and without digitalis or between patients with coronary artery disease and patients with dilated cardiomyopathy.

Univariate analysis: Heart rate variability index and plasma neurohormones

Plasma neurohormone concentrations are presented in Table 2. The heart rate variability index was significantly related to norepinephrine (r = -0.33, P = 0.03), ANP (r = -0.42, P = 0.005), N-terminal proANP (r = -0.45, P = 0.002) and BNP (r = -0.46, P = 0.0001) (Figures 1- 4).

Table 2
Neurohormonal data

	n = 45
Norepinephrine (pg/ml)	365 (134 - 949)
ANP (pmol/L)	109 (16 - 358)
N-terminal proANP (nmol/L)	0.67 (0.10 - 2.42)
BNP (pmol/L)	51 (2 - 383)

Data are presented as median (range). ANP = atrial natriuretic peptide; BNP = brain natriuretic peptide.

Univariate analysis: plasma neurohormones and clinical variables

Left ventricular ejection fraction was related to plasma norepinephrine (r = -0.33, P = 0.02), ANP (r = -0.33, P = 0.03), N-terminal proANP (r = 0.35, P = 0.09) and BNP (r = -0.36, P = 0.02). None of the neurohormones were related to age or heart rate, and their plasma concentrations did not significantly differ between patients in New York Heart Association class I and II, males and females, patients with and without angiotensin converting enzyme inhibitors, patients with and without diuretics, patients with and without digitalis or between patients with coronary artery disease and patients with dilated cardiomyopathy.

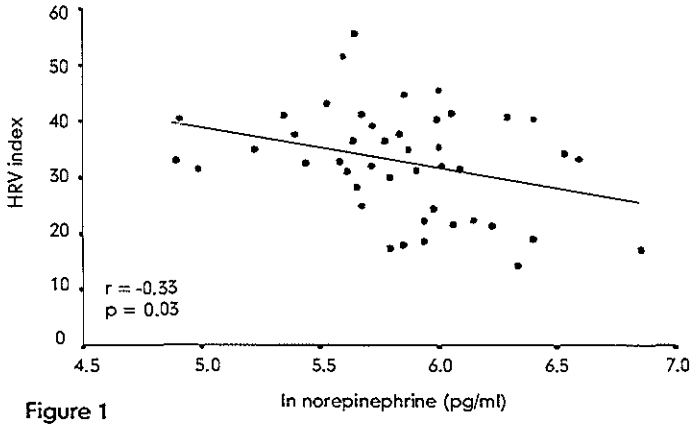

Figure 1
Scatterplot of the relationship between the heart rate variability (HRV) index and plasma norepinephrine.

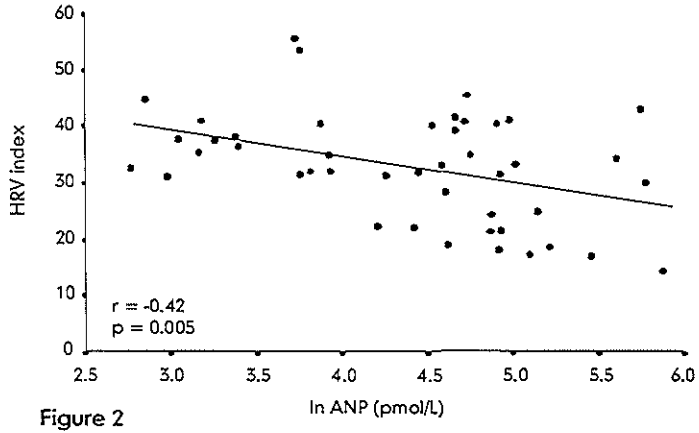

Figure 2
Scatterplot of the relationship between the heart rate variability (HRV) index and plasma atrial natriuretic peptide (ANP).

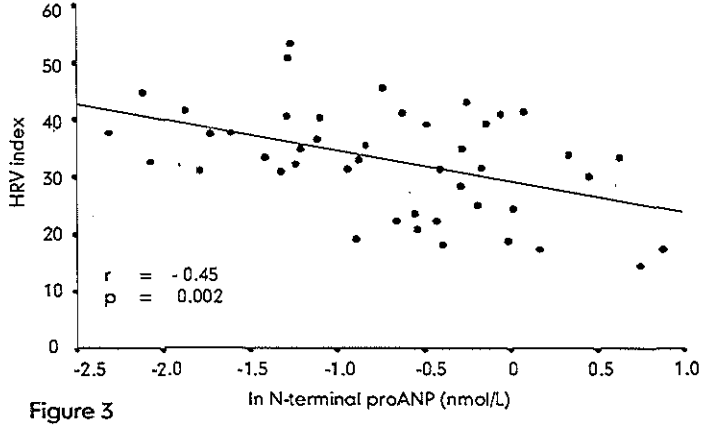

Figure 3
Scatterplot of the relationship between the heart rate variability (HRV) index and plasma N-terminal pro-atrial natriuretic peptide (N-terminal proANP).

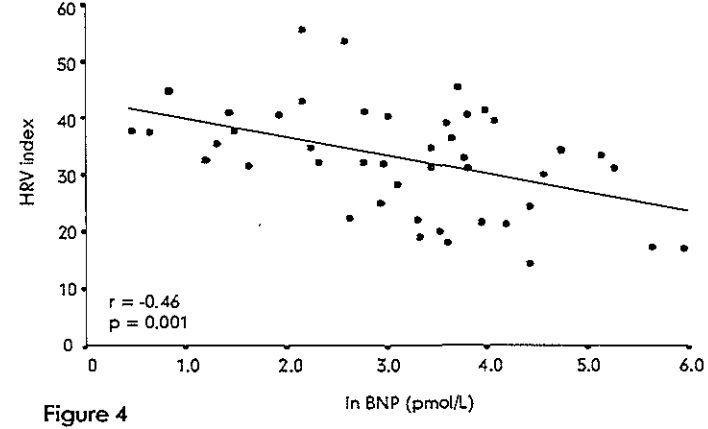

Figure 4
Scatterplot of the relationship between the heart rate variability (HRV) index and plasma brain natriuretic peptide (BNP).

Table 3
Results of multivariate linear regression analyses

	HRV index		HRV index		HRV index		HRV index	
	β	P value	β	P value	β	P value	β	P value
Age (years)	-0.01	ns	-0.07	ns	-0.01	ns	0.01	ns
NYHA class	-0.16	ns	-0.14	ns	-0.13	ns	-0.18	ns
Left ventricular ejection fraction (%)	-0.03	ns	-0.02	ns	-0.02	ns	-0.17	ns
Heart rate (beats/min.)	-0.43	0.005	-0.48	0.003	-0.43	0.003	-0.39	0.007
ln norepinephrine (pg/ml)	-0.31	0.04	-	-	-	-	-	-
ln ANP (pmol/L)	-	-	-0.37	0.008	-	-	-	-
ln N-terminal proANP (nmol/L)	-	-	-	-	-0.42	0.002	-	-
ln BNP (pmol/L)	-	-	-	-	-	-	-0.41	0.002

β = standardized regression coefficient; ln = natural logarithmic transformed. Abbreviations are as in Table 1 and 2.

Multivariate analysis

Four separate multivariate analyses were performed with heart rate variability index as outcome variable and age, New York Heart Association class, left ventricular ejection fraction, heart rate and neurohormonal values (norepinephrine, ANP, N-terminal proANP and BNP, respectively) as explanatory variables (Table 3). Heart rate as well as norepinephrine, ANP, N-terminal proANP and BNP contributed to the variations in heart rate variability index. Together, heart rate and norepinephrine were able to explain 37% (R^2 = 0.37), heart rate and ANP were able to explain 41%, heart rate and N-terminal proANP were able to explain 44% and heart rate and BNP were able to explain 45% of the variations in heart rate variability index. Age, left ventricular ejection fraction and New York Heart Association class did not contribute significantly to variations in heart rate variability index.

Discussion

Heart rate variability and neurohormonal activation

Plasma norepinephrine concentrations are increased and related to severity of left ventricular dysfunction and prognosis in patients with congestive heart failure.[19] The association between indicators of sympathetic activation and measurements of heart rate variability derived from long-term electrocardiographic recordings in patients with moderate to severe heart failure has been reported previously.[13] Moreover, it has been demonstrated that patients with advanced heart failure and complex heart rate variability have increased serum norepinephrine concentrations.[14] Our finding that heart rate variability measured over 24 hours is related to norepinephrine in patients with asymptomatic or mildly symptomatic left ventricular systolic dysfunction does not only support the notion that heart rate variability might provide information on sympathetic activation, but also indicates the potential value of analysis of heart rate variability as a non-invasive method to detect increased sympathetic activity in an early stage of heart failure.

Plasma natriuretic peptides are early markers of heart failure as well.[2-5] Both the active C-terminal ANP and the inactive N-terminal fragment of its prohormone are secreted from the atria in response to atrial stretch and are related to atrial filling pressures.[20,21] The C-terminal BNP is not only secreted from the atria, but also from the ventricles, especially in patients with heart failure.[17] Plasma ANP

has been reported to inhibit cardiac sympathetic activity in normal humans.[22] However, the present study showed a negative correlation between plasma ANP concentrations and heart rate variability, suggesting that severity of the disease is a more powerful determinant of decreased heart rate variability than the effect of ANP on cardiac function itself. This relationship may be due to the fact that increased filling pressures in patients with elevated natriuretic peptide concentrations cause sympathetic activation, which is reflected by reduced overall heart rate variability. In contrast to our results, no direct relationship was found between heart rate variability and other methods to assess sympathovagal balance in two studies in patients with moderate heart failure.[23,24] However, in the first study all methods showed improvement in autonomic balance after physical training, and in the latter study similar changes in plasma norepinephrine and heart rate variability in response to treatment were observed, indicating that analysis of heart rate variability can be used to monitor neurohormonal status in patients with heart failure.[23,24]

Heart rate variability and clinical variables

In previous studies, functional class and left ventricular systolic function have been shown to be related to parameters of heart rate variability.[8-10,25] In the present study, heart rate variability correlated only weakly with New York Heart Association class and was not related to left ventricular ejection fraction. In addition, in multivariate analysis both parameters of severity of heart failure did not play a significant role. Because the study group consisted predominantly of patients with mildly symptomatic left ventricular systolic dysfunction there was not much variation in functional class and left ventricular ejection fraction between the patients and it is possible that for this reason statistical significance was not reached. On the other hand, it should be appreciated that the heart rate variability index provides an approximate assessment of cardiac autonomic status and, although related, neurohormonal activation and deterioration of left ventricular function do not necessarily show simultaneous progression.

Study limitations

Heart rate variability has been shown to be affected by multiple factors, including age, medication and heart rate.[26] Multivariate analyses showed that heart rate did account for a considerable part in the variations in heart rate variability index, but also that the relationships between heart rate variability index and neurohormonal concentrations were independent of heart rate. In addition, neither age nor heart failure medication were found to be related to heart rate variability

index and are therefore not likely to have influenced our results. Finally, only one measure of heart rate variability, the heart rate variability index, was used to show the relationship with plasma neurohormones. Most other measures of heart rate variability, however, require difficult and time-consuming manual editing of computer-recognised series of RR intervals and were therefore considered unsuitable for the analysis of long-term recordings in patients with frequent ectopic beats.

Conclusion

The present study demonstrates that reduced heart rate variability is related to neurohormonal status in patients with asymptomatic or mildly symptomatic left ventricular systolic dysfunction. Neurohormonal activation plays an important role in the development of congestive heart failure and both increased plasma concentrations of norepinephrine and natriuretic peptides have been shown to be early markers of heart failure. Therefore, our result suggests that analysis of heart rate variability, as non-invasive method to study cardiac autonomic status, might be a useful tool in the early detection of heart failure and merits further investigations in this area of research.

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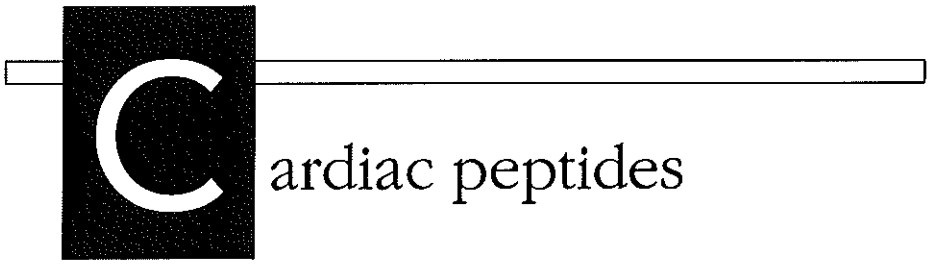

Cardiac peptides

4

Relation of atrial natriuretic peptides to left ventricular systolic and diastolic function in heart failure

Abstract

Background Plasma concentrations of atrial natriuretic peptides are correlated with atrial pressures, as are left ventricular ejection fraction and left ventricular filling abnormalities. This study investigated the relation of atrial natriuretic peptides to both left ventricular systolic and diastolic function in heart failure.

Methods and results Plasma concentrations of atrial natriuretic peptide and N-terminal pro-atrial natriuretic peptide were measured in 63 patients with chronic heart failure and left ventricular systolic dysfunction. According to Doppler transmitral flow measurements, 19 patients had a restrictive and 44 patients had a non-restrictive left ventricular filling pattern. Plasma concentrations of atrial natriuretic peptide and N-terminal pro-atrial natriuretic peptide were higher in patients with a restrictive filling pattern than in patients with a non-restrictive filling pattern (197 vs. 75 pmol/L, $P < 0.0001$ and 1.14 vs. 0.45 nmol/L, $P < 0.0001$). In univariate analysis, atrial natriuretic peptide and N-terminal pro-atrial natriuretic peptide correlated with deceleration time, E/A ratio and left ventricular ejection fraction. In multivariate analysis, both peptides appeared independently related to left ventricular ejection fraction and left ventricular filling pattern.

Conclusion In patients with chronic heart failure, atrial natriuretic peptides provide information on left ventricular systolic as well as diastolic function. This underlines the potential value of determination of plasma atrial natriuretic peptides as simple test for overall cardiac function in the assessment of heart failure.

Introduction

Atrial natriuretic peptide (ANP) and the N-terminal fragment of its prohormone (N-terminal proANP) are known to be released in response to atrial stretch and to be closely correlated with atrial pressures in patients with heart failure.[1,2] Moreover, plasma atrial natriuretic peptide concentrations have been shown to be increased in patients with left ventricular systolic dysfunction and to be related to severity of heart failure.[3-5]

In addition to left ventricular systolic dysfunction, abnormalities of diastolic function are common in patients with heart failure. Impaired relaxation in the presence of normal filling pressures results in reduced early diastolic filling. A restrictive filling pattern, on the other hand, is characterised by a fast, but abruptly ending increase in early filling reflecting diminished ventricular compliance and is associated with increased filling pressures, more severe disease and a poor prognosis.[6-9]

In patients with left ventricular systolic dysfunction, a relationship between restrictive left ventricular filling patterns and elevated natriuretic peptide concentrations has been described.[10] However, whether this association resulted from the evident differences in left ventricular ejection fraction remained undefined. A clear understanding of the determinants of atrial natriuretic peptide concentrations in patients with heart failure is important for a correct interpretation of these markers of severity of the disease. For that reason, we studied the direct relationship between plasma atrial natriuretic peptide concentrations and left ventricular systolic as well as diastolic function in patients with heart failure.

Methods

Study population

Within the framework of a comprehensive out-patient heart failure study protocol, 69 consecutive patients with chronic heart failure and left ventricular systolic dysfunction due to coronary artery disease or dilated cardiomyopathy underwent several non-invasive cardiovascular tests, among which echocardiography and blood sampling for measurement of plasma atrial natriuretic peptide concentrations. For the present study, only patients who were in sinus rhythm were eligible. The study population consisted of 63 patients, 54 men and 9 women, aged 61 ± 9 years. Clinical characteristics are presented in Table 1. Echocardi-

ography and blood sampling were performed on the same day in the late morning, two to three hours after administration of heart failure medication, in order to standardise for diurnal variations of measurement parameters. The investigation conforms to the principles outlined in the Declaration of Helsinki.

Echocardiography

Left ventricular ejection fraction was calculated from the apical four-chamber and long-axis views using a biplane disk-method.[11] Mean values were obtained by averaging 3 consecutive beats. Mitral regurgitation was identified using continuous wave Doppler echocardiography and graded on a scale of one to four.[12] Left ventricular inflow velocities were recorded from the apical four-chamber view using pulsed Doppler echocardiography with the sample volume placed between the tips of the mitral leaflets. Doppler measurements were made by manual tracing of the outermost portion of the velocity contour using an off-line computer, a digitising tablet and a dedicated software program.[13] Parameters of left ventricular filling included peak early (E) and peak atrial (A) filling velocities, the E/A ratio and deceleration time of peak early filling to baseline. Mean values were obtained by averaging 10 consecutive beats. Heart rate was averaged from the same beats. Patients were classified as having a restrictive or a non-restrictive left ventricular filling pattern based on E/A ratio and deceleration time: an E/A ratio ≥ 2 was considered to be restrictive, whereas an E/A ratio ≤ 1 was considered to be non-restrictive. In case the E/A ratio was between 1 and 2, a deceleration time ≤ 150 msec was considered to be restrictive and a deceleration time > 150 msec was considered to be non-restrictive.[14,15]

Atrial natriuretic peptides

Venous blood samples were drawn after 30 minutes of supine rest and collected in pre-chilled polystyrene tubes containing EDTA and aprotinine. The tubes were placed on ice and centrifuged within 30 minutes from sampling in a refrigerated centrifuge for 10 minutes at 3000 g. Plasma was stored in polyethylene tubes at - 70 °C until analysed. All analyses took place in the Cardiovascular Research Laboratory, University Hospital Rotterdam, The Netherlands. Plasma concentrations of ANP were determined with a commercially available radioimmunoassay kit (Nichols Institute, Wijchen, The Netherlands) after extraction from plasma. N-terminal proANP concentrations were measured directly in plasma using a commercially available radioimmunoassay kit from Biotop, Oulu, Finland.[16]

Statistical analysis

Comparisons between patients with restrictive and non-restrictive left ventricular filling patterns were made by unpaired t tests for continuous data and χ^2 tests for categorical data. Univariate linear regression analysis was used to test the relation between atrial natriuretic peptide concentrations and deceleration time, E/A ratio and left ventricular ejection fraction. Multivariate linear regression analysis was used to evaluate the relation of plasma ANP and N-terminal proANP concentrations to left ventricular filling pattern, left ventricular ejection fraction, New York Heart Association functional class, diuretic therapy, heart rate, age and an interaction term between left ventricular filling pattern and age. Because of their skewed distribution, the natural logarithmic transformed values of ANP and N-terminal proANP were used in the analyses. Data are described as mean ± SD unless otherwise specified. All analyses were performed with SPSS for Windows (release 6.1). Statistical significance was defined as $P < 0.05$.

Table 1
Clinical characteristics for all patients and for patients with restrictive and non-restrictive left ventricular filling patterns

	all patients	non-restrictive pattern	restrictive pattern
n	*63*	*44*	*19*
Age (years)	61 ± 10	62 ± 8	58 ± 13
Gender (male/female)	54/9	38/6	16/3
Aetiology (CAD/DCM)	40/23	27/17	13/6
MR (≥ grade 2)	5 (8%)	3 (7%)	2 (10%)
Heart rate (beats/min)	72 ± 11	71 ± 10	75 ± 14
LVEF (%)	32 ± 7	33 ± 6	30 ± 7
NYHA classification	1.9 ± 0.6	1.8 ± 0.6	2.3 ± 0.6 *
Medication			
ACE inhibitors	57 (91%)	40 (91%)	17 (90%)
Diuretics	47 (75%)	29 (66%)	18 (95%) **
Digoxin	31 (49%)	20 (46%)	11 (58%)
Nitrates	20 (32%)	15 (34%)	5 (26%)

Data are expressed as mean ± SD or number (%). * P = 0.003 ** P = 0.02, patients with non-restrictive vs. restrictive left ventricular filling patterns. CAD = coronary artery disease; DCM = dilated cardiomyopathy; MR = mitral regurgitation; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; ACE = angiotensin converting enzyme.

Results

Group characteristics

According to transmitral flow parameters, 19 patients had a restrictive left ventricular filling pattern, whereas 44 patients had a non-restrictive left ventricular filling pattern. Both groups were comparable as regards age, gender, aetiology of heart failure, heart rate, left ventricular ejection fraction, presence of more than mild mitral regurgitation (≥ grade 2) on echocardiography and use of angiotensin converting enzyme inhibitors, digoxin and nitrates. However, patients with a restrictive left ventricular filling pattern were more symptomatic and were using diuretics more frequently than patients with a non-restrictive pattern (Table 1).

Univariate analysis

Plasma concentrations of ANP and N-terminal proANP were higher in patients with a restrictive filling pattern compared to patients with a non-restrictive filling pattern (Figure 1). Median (and range) for ANP (pmol/L) in patients with a restrictive vs. patients with a non-restrictive pattern were 197 (83 - 358) vs. 75 (16 - 197) ($P < 0.0001$) and for N-terminal proANP (nmol/L) 1.14 (0.52 - 2.42) vs. 0.45 (0.10 - 1.26) ($P < 0.0001$). For the whole group, ANP correlated well with N-terminal proANP ($r = 0.89$, $P < 0.0001$). In univariate linear regression analysis, ANP correlated with deceleration time ($r = - 0.52$, $P < 0.0001$) (Figure 2A), E/A ratio ($r = 0.50$, $P < 0.0001$) (Figure 3A) and left ventricular ejection fraction ($r = - 0.37$, $P = 0.003$). Similarly, N-terminal proANP was related to deceleration time ($r = - 0.48$, $P = 0.0001$) (Figure 2B), E/A ratio ($r = 0.48$, $P = 0.0001$) (Figure 3B) and left ventricular ejection fraction ($r = - 0.38$, $P = 0.002$).

Multivariate analysis

In order to evaluate the relationship between atrial natriuretic peptide concentrations, left ventricular filling pattern and left ventricular systolic function, separate multivariate linear regression analyses were performed for each peptide. Since age influences atrial natriuretic peptide concentrations[17] as well left ventricular filling[18], both age and an interaction term between age and left ventricular filling pattern (derived by multiplying age by filling pattern) were included in the analyses.

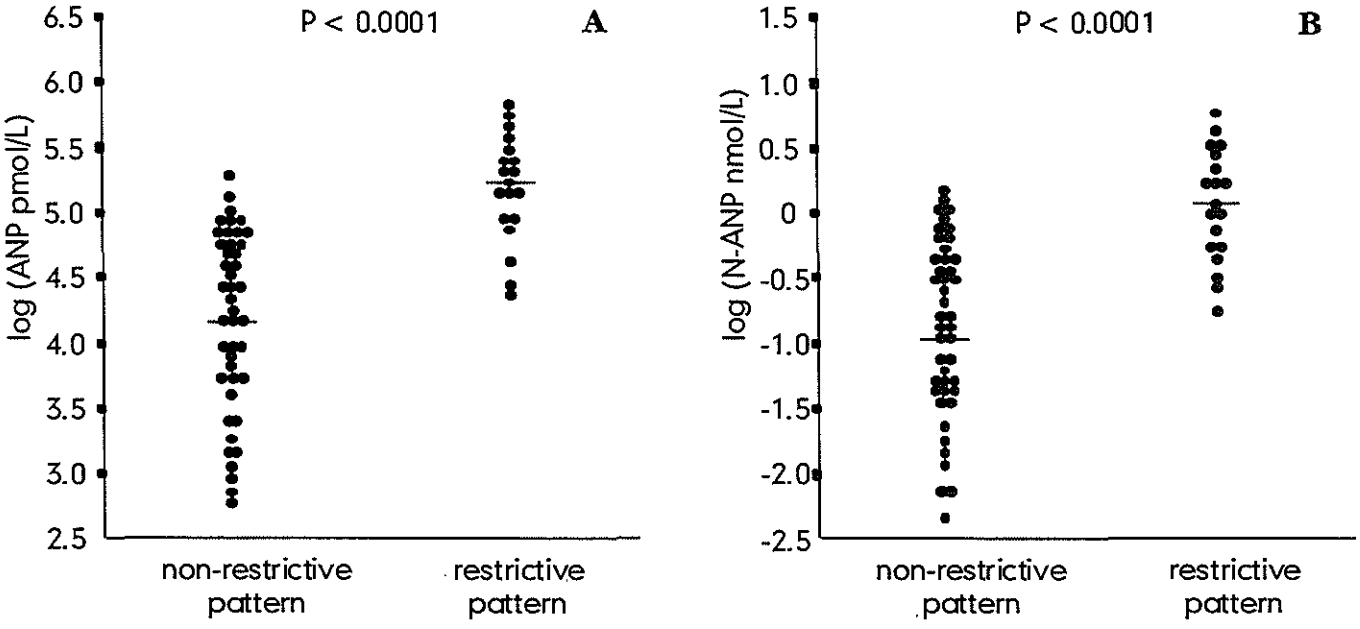

Figure 1
Plasma concentrations of (A) atrial natriuretic peptide (ANP) and (B) N-terminal proANP according to left ventricular filling pattern.

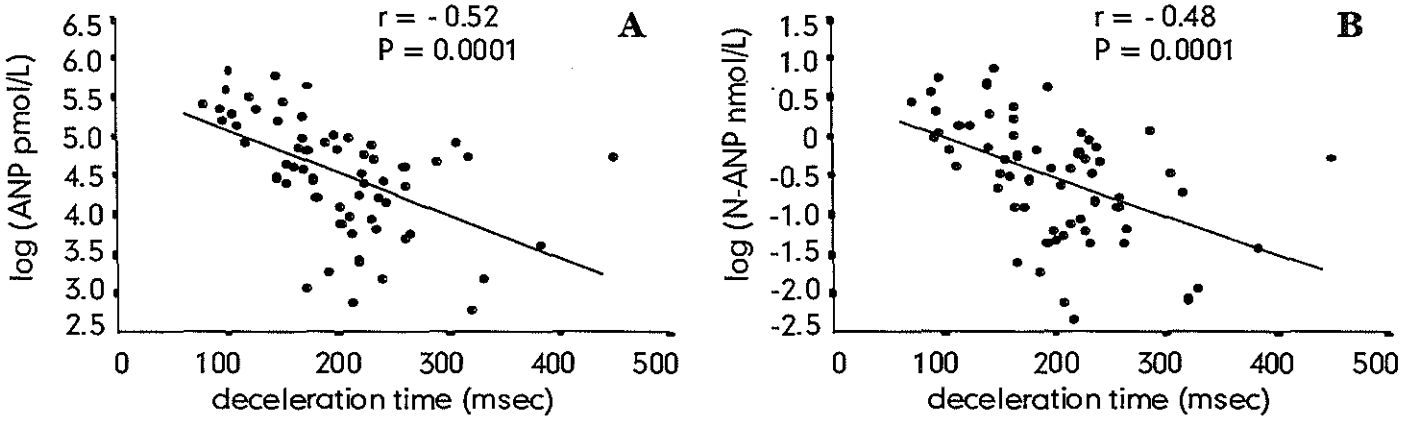

Figure 2
Correlation between plasma concentrations of (A) atrial natriuretic peptide (ANP) and (B) N-terminal proANP and deceleration time.

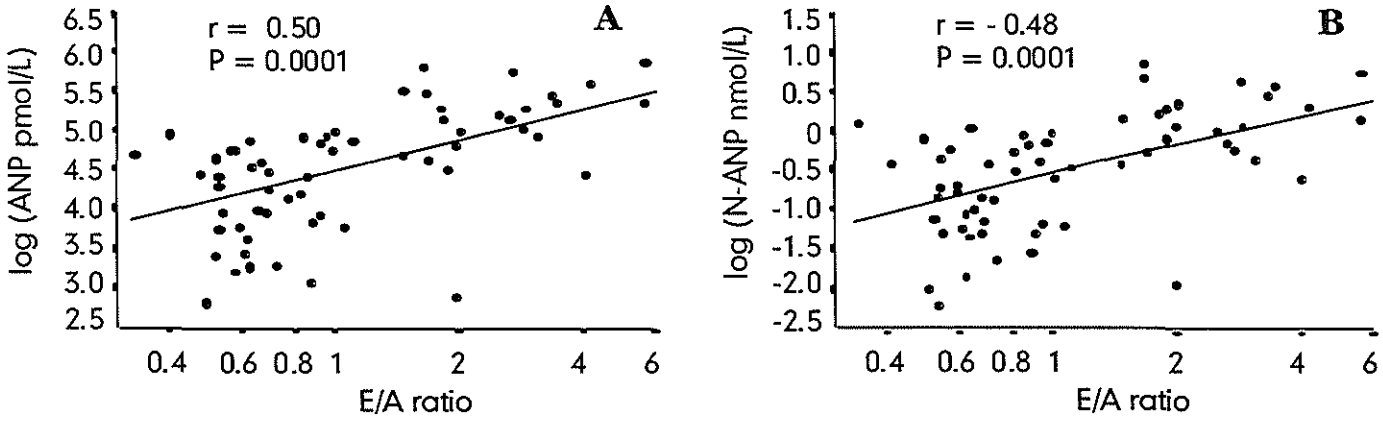

Figure 3
Correlation between plasma concentrations of (A) atrial natriuretic peptide (ANP) and (B) N-terminal proANP and E/A ratio.

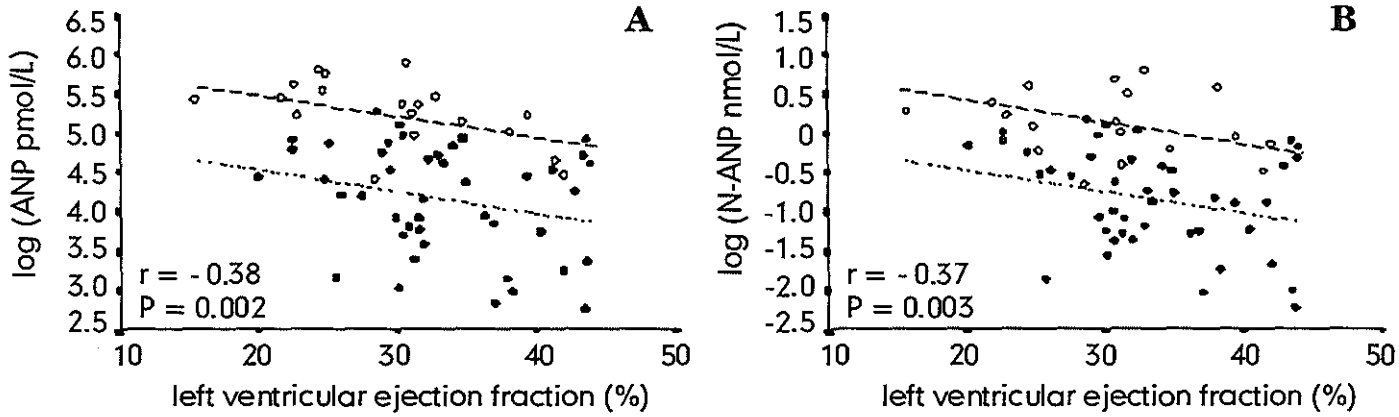

Figure 4
Linear regression model of the relation between plasma concentrations of (A) atrial natriuretic peptide (ANP) and (B) N-terminal proANP and left ventricular ejection fraction for patients with restrictive (o - - -) and non-restrictive (•···) left ventricular filling patterns.

Table 2
Relation between atrial natriuretic peptide concentrations and left ventricular filling pattern, left ventricular ejection fraction and age - multivariate analysis

	ANP		N-terminal proANP	
variables	β	P values	β	P values
restrictive filling pattern	2.31	<0.0001	2.00	0.0003
Age (years)	0.51	0.0002	0.58	<0.0001
Age * LV filling pattern	-1.69	0.002	-1.38	0.008
LVEF (%)	-0.20	0.03	-0.22	0.02

β = standardized regression coefficient. ANP = atrial natriuretic peptide; N-terminal proANP = N-terminal pro-atrial natriuretic peptide; LV = left ventricular; Age * LV filling pattern = interaction term between age and left ventricular filling pattern; LVEF = left ventricular ejection fraction.

The standardised regression coefficients (β) and corresponding P values are presented in Table 2. New York Heart Association functional class, use of diuretics and heart rate were included in the analyses, but appeared not to be related to ANP and N-terminal proANP concentrations. In addition to (restrictive) left ventricular filling pattern and left ventricular ejection fraction, age and the interaction term between age and filling pattern explained 57% ($R^2 = 0.57$) of the variation in ANP and 58% of the variation in N-terminal proANP. The presence of a restrictive left ventricular filling pattern by itself accounted for 39% of the variation in ANP and 36% of the variation in N-terminal proANP. The linear regression models of the relation between left ventricular ejection fraction and plasma ANP and plasma N-terminal proANP for patients with and without a restrictive left ventricular filling pattern graphically represent the contribution of the presence of a restrictive pattern to the plasma concentrations of atrial natriuretic peptides in patients with comparable left ventricular ejection fractions (Figure 4).

Discussion

The present study shows that, in patients with chronic heart failure, elevated plasma concentrations of atrial natriuretic peptides are related to impaired left ventricular systolic function as well as abnormal left ventricular filling. Severity of systolic dysfunction and left ventricular filling abnormalities are important clinical and prognostic parameters in patients with heart failure due to coronary artery disease or dilated cardiomyopathy.[7-9,19-21] In both cardiac disorders, impaired left ventricular systolic function leads to progressive left ventricular dila-

tation and increased filling pressures. The accompanying reduction in left ventricular compliance, which results in a restrictive pattern of left ventricular filling, is associated with elevated filling pressures as well.[8,22] Thus, the present finding that both left ventricular systolic impairment and abnormal left ventricular filling are related to plasma atrial natriuretic peptide concentrations can be explained by the fact that systolic as well as diastolic dysfunction lead to increased filling pressures, and, as atrial natriuretic peptides are known to be released in response to atrial stretch or pressure,[1,2] to elevated plasma concentrations of atrial natriuretic peptides.

Prior studies

In contrast with the present results, plasma ANP was shown to be related to systolic but not to diastolic function in patients 24 hours after myocardial infarction.[23] Furthermore, in patients with untreated essential hypertension a relation between a *decreased* E/A ratio and elevated concentrations of ANP has been described,[24] while in the present study higher ANP concentrations were found in patients with an *increased* E/A ratio. As Doppler assessment of diastolic function is known to be dependent on systolic function,[25] the results in hypertensives can not be compared with those in patients with heart failure due to left ventricular systolic dysfunction, nor can the results from our study be applied to patients with heart failure and normal systolic function.

Study limitations

Transmitral flow velocities are known to be affected by multiple factors, including age,[18] heart rate[6] and mitral regurgitation.[26] Since both patient groups were comparable for age, heart rate and presence of more than mild mitral regurgitation, these variables are not considered to have influenced our results. In conformance with other reports,[7,8] patients with a restrictive filling pattern were more symptomatic and were using diuretics more frequently compared to patients with a non-restrictive pattern. However, these differences did not contribute to the outcome of multivariate analysis. The definitions for restrictive and non-restrictive filling patterns could be considered as arbitrary. Nevertheless, atrial natriuretic peptide concentrations did not only differ between patients with different filling patterns, but correlated with transmitral E/A ratio and deceleration time as well. Finally, the time of the day that plasma samples were taken in relation to the time of drug administration might have been a source of variation in ANP and N-terminal proANP concentrations. Since all subjects were investi-

gated in the late morning, two to three hours after administration of heart failure medication, it was assumed that this contribution can be considered negligible.

Conclusion

In patients with chronic heart failure, elevated plasma concentrations of atrial natriuretic peptides are related to left ventricular systolic dysfunction as well as left ventricular filling abnormalities. This indicates that atrial natriuretic peptides can provide information on left ventricular systolic as well as diastolic function and points towards the potential value of determination of plasma atrial natriuretic peptides as simple test for overall cardiac function in the assessment of patients with heart failure.

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5

Cardiac peptides differ in their response to exercise: implications for patients with heart failure in clinical practice

Abstract

Background Cardiac peptides have diagnostic and prognostic value in heart failure. Their plasma concentrations, however, are sensitive to rapid changes in hemodynamics. As blood sampling under standard conditions is not feasible in clinical practice, it is important to know which peptides are most resistant to change. Therefore, this study investigated the differences in response to exercise between atrial natriuretic peptide, N-terminal pro-atrial natriuretic peptide, brain natriuretic peptide and N-terminal pro-brain natriuretic peptide.

Methods and results Fifty-two patients with chronic heart failure performed symptom-limited graded bicycle exercise. Blood samples for determination of plasma concentrations of cardiac peptides were drawn at rest and at peak exercise. There was a significant difference in percentage increase in response to exercise between the four peptides ($P < 0.0001$). N-terminal pro-atrial natriuretic peptide increased less than atrial natriuretic peptide ($5 \pm 18\%$ vs. $59 \pm 58\%$; $P < 0.0001$). The difference in increase between N-terminal pro-brain natriuretic peptide and brain natriuretic peptide was less distinct but still significant ($24 \pm 24\%$ vs. $38 \pm 52\%$, $P < 0.05$).

Conclusion Both N-terminal pro-atrial natriuretic peptide and N-terminal pro-brain natriuretic peptide increase less in response to exercise than their C-terminal counterparts. This implies that the circumstances under which blood sampling for measurements of N-terminal pro-atrial natriuretic peptide and N-terminal pro-brain natriuretic peptide should be performed are more favourable than the blood sampling conditions for atrial natriuretic peptide and brain natriuretic peptide.

Introduction

Atrial natriuretic peptide (ANP) is stored in atrial myocytes in the form of a prohormone that is secreted in response to increased atrial stretch.[1] On secretion, proANP is cleaved into a C-terminal peptide, ANP(99-126), and an N-terminal peptide, N-terminal proANP(1-98).[2] Because N-terminal proANP has a longer half-life than ANP, its plasma concentrations are higher and less sensitive to rapid changes in hemodynamics.[3,4]
Brain natriuretic peptide (BNP) is not only secreted from the atria, but also from the ventricles, especially in patients with chronic heart failure.[5,6] Although BNP shares many structural and functional similarities with ANP, there are still uncertainties about its circulating forms. Available evidence indicates that three forms of BNP circulate in human plasma: the C-terminal peptide, BNP(77-108), a large molecular weight peptide, presumably proBNP(1-108), and its N-terminal fragment, N-terminal proBNP(1-76).[7,8] Whether N-terminal proBNP, like N-terminal proANP, has more stable plasma concentrations than BNP is not known.

Several studies have shown that elevated plasma concentrations of ANP, N-terminal proANP and BNP have diagnostic and prognostic value in heart failure.[9-15] Likewise, N-terminal proBNP has been shown to be a marker of left ventricular dysfunction and an independent predictor of prognosis after myocardial infarction.[16,17] In previous research, blood sampling for cardiac peptide measurements has been performed under standard conditions. These requirements, however, are hard to meet in daily practice. Thus, the variability in plasma concentrations due to non-cardiac influences, such as body position or exercise, should be considered when deciding which peptide is most suitable for use in clinical practice. For that reason, the present study evaluated the differences in response to exercise between ANP, N-terminal proANP, BNP and N-terminal proBNP.

Methods

Patients

Within the framework of an outpatient heart failure research project, 52 patients with chronic heart failure and left ventricular systolic dysfunction (left ventricular ejection fraction < 45%) underwent echocardiography, cardiopulmonary exercise testing and blood sampling for measurement of plasma concentrations of cardiac peptides. Patients were eligible when they were able to perform exercise

without being limited by angina pectoris, pulmonary disorders or peripheral vascular disease.

Exercise protocol

Symptom-limited exercise was performed on a bicycle ergometer (Lode, Groningen, the Netherlands) at a constant pedalling speed of 60 rpm with workload increments of 10 Watts/min. Heart rate, blood pressure and a 12-lead electrocardiogram were monitored during the test. Gas volume and gas concentrations were measured continuously using a breath-by-breath system and a facemask with a digital volume sensor (Oxycon Champion, Mijnhardt Oxycon Systems, Bunnik, The Netherlands). Oxygen consumption and carbon dioxide production were recorded every 30 seconds. Peak oxygen consumption (defined as the maximal value measured at the end of the test) was expressed as absolute value divided by actual weight (ml/kg/min).

Cardiac peptide measurements

Venous blood samples were drawn from a catheter inserted in the left cubital vein after 30 minutes of supine rest and at peak exercise. The samples were collected in pre-chilled polystyrene tubes containing EDTA and aprotinin, placed immediately on ice and centrifuged within 10 minutes from sampling in a refrigerated centrifuge at 3000 g. Plasma was separated and stored at - 80 °C. Atrial natriuretic peptide measurements were performed in the Cardiovascular Research Laboratory, University Hospital Rotterdam, The Netherlands. Commercially available kits were used for measurement of plasma concentrations of ANP (Nichols Institute, Wijchen, The Netherlands) and N-terminal proANP (Biotop, Oulu, Finland), as described previously.[18] Brain natriuretic peptide measurements were performed in the Institute for Surgical Research, University of Oslo, Norway. For this purpose, the plasma neurohormone samples had been shipped on dry ice to Norway. Plasma BNP concentrations were measured using a immunoradiometric assay for human BNP (Shionoria BNP kit, Shionogi & Co. Ltd. Japan).[6] Plasma N-terminal proBNP concentrations were measured by radioimmunoassay directly in plasma utilising polyclonal antiserum raised in a rabbit immunised with proBNP(1-21) (Peninsula Laboratories Inc., CA, USA) as antigen. The assay has a limit of detection of 9.7 pmol/L, an intra-assay coefficient of variation of 7.3% (sample of 430.7 pmol/L) and a recovery of 81.5% of added peptide.

Echocardiography

Two-dimensional echocardiographic examinations were performed in all patients. Left ventricular ejection fractions were derived from the two-dimensional apical four-chamber and long-axis views using a biplane disk-method. Mean values were obtained by averaging three consecutive beats.

Statistical analysis

Cardiac peptide concentrations are expressed as median (range). Other values are presented as mean ± SD. Cardiac peptide concentrations at rest and at peak exercise were compared using a non-parametric test for paired samples (Wilcoxon). The differences in percentage change between cardiac peptides were tested using a non-parametric test for several related samples (Friedman). All analyses were performed using SPSS for Windows (version 6.1). Statistical significance was defined as $P < 0.05$.

Results

Study population

The study population consisted of 52 patients, 44 men and 8 women, aged 61 ± 10 years. At the time of the study, 10 patients were in New York Heart Association class I, 35 patients were in class II and 7 patients were in class III. The mean left ventricular ejection fraction was 32 ± 6%, and the cause of left ventricular systolic dysfunction was ischemic heart disease in 37 patients and idiopathic dilated cardiomyopathy in 15 patients. All patients were in sinus rhythm and none of the patients had renal failure (serum creatinin ranged from 59 to 148 μmol/L). The majority of the patients (n = 48) used angiotensin converting enzyme inhibitors, 37 patients used diuretics and 25 patients used digoxin.

Cardiopulmonary exercise testing

All patients performed symptom-limited exercise; the reason for discontinuing exercise was either shortness of breath or fatigue. In all cases, the ratio between carbon dioxide production and oxygen consumption exceeded 1.0, indicating that each patient had made a valid effort. Mean exercise duration was 10 ± 3 minutes. Heart rate increased from 74 ± 10 beats/min at rest to 143 ± 18

Table 1
Cardiac peptides at rest and at peak exercise

	Rest	Exercise	P
ANP (pmol/L)	83 (14 - 288)	117 (23 - 539)	< 0.0001
N-terminal proANP (pmol/L)	592 (99 - 2417)	628 (116 - 2507)	0.11
BNP (pmol/L)	30 (2 - 383)	38 (2-480)	< 0.0001
N-terminal proBNP (pmol/L)	67 (10 - 550)	83 (13 - 699)	< 0.0001

Data are presented as median (range). ANP = atrial natriuretic peptide; BNP = brain natriuretic peptide.

beats/min at peak exercise. Systolic blood pressure increased from 128 ± 18 mmHg to 176 ± 28 mmHg. Mean oxygen consumption at peak exercise was 17 ± 4 ml/kg/min.

Cardiac peptides

Plasma concentrations of ANP, N-terminal proANP, BNP and N-terminal proBNP at rest and at peak exercise are presented in Table 1. Exercise induced an in-

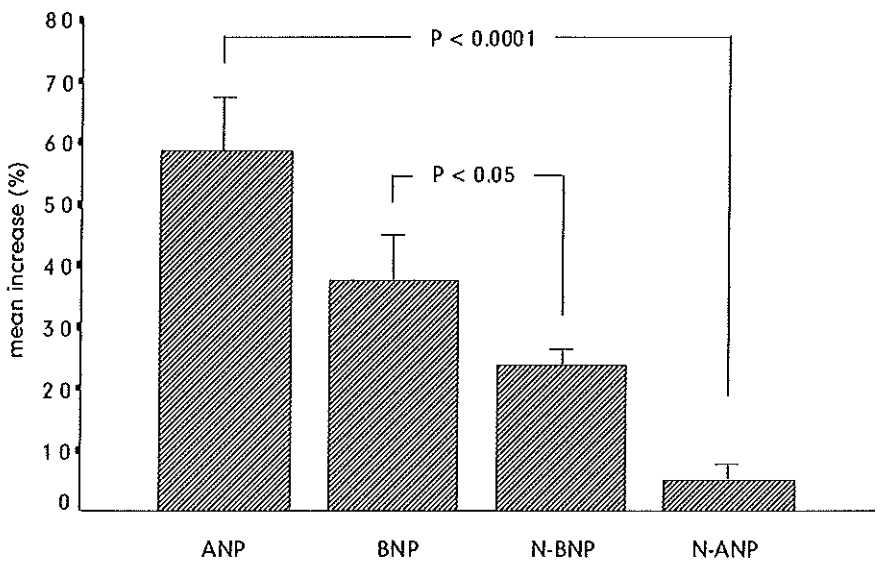

Figure 1
Percentage increase in atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), N-terminal proBNP (N-BNP) and N-terminal proANP (N-ANP) in response to exercise. Mean values + 1 standard error.

crease in ANP, BNP and N-terminal proBNP concentrations. The rise in N-terminal proANP, however, was not significant. There was a difference in percentage increase in response to exercise between the four peptides ($P < 0.0001$, Figure 1). N-terminal proANP increased less than ANP (5 ± 18% vs. 59 ± 58%; $P < 0.0001$). The difference in increase between N-terminal proBNP and BNP was less distinct but still significant (24 ± 24% vs. 38 ± 52%, $P < 0.05$). Finally, ANP increased more than BNP (59 ± 58% vs. 38 ± 52%, $P < 0.05$) and N-terminal proANP increased less than N-terminal proBNP (5 ± 18% vs. 24 ± 24%, $P < 0.0001$).

Discussion

The present study demonstrated that both N-terminal proANP and N-terminal proBNP increased less in response to exercise than their C-terminal counterparts. The rise in plasma concentrations of cardiac peptides in response to exercise can be attributed to augmented secretion due to an increase in filling pressures and heart rate on the one hand, and reduced clearance due to redistribution of blood flow on the other hand.[19] Previous research showed that both ANP and N-terminal proANP increase with exercise in patients with heart failure.[20] Like in the present study, the rise in ANP was larger than the rise in N-terminal proANP. Similar discrepancies between the responses of N-terminal proANP and ANP were found in healthy subjects.[21] Thus, despite the fact that N-terminal proANP and ANP are secreted on an equimolar basis, plasma concentrations of N-terminal proANP and ANP do not seem to show an equal response to exercise. Because of its short half-life of 2.5 minutes, ANP is rapidly cleared from plasma and its concentrations are low.[3] N-terminal proANP, with its longer half-life, has higher and more stable plasma concentrations.[4] Consequently, the percentage increase in plasma concentrations of N-terminal proANP will be smaller compared to ANP. In addition, when the performance of the applied assays is taken into account as well, relatively small changes in N-terminal proANP concentrations will be more difficult to measure than comparable changes in ANP concentrations. Half-life differences are therefore likely to be responsible for the differences in response to exercise between the two peptides.

The same can be said for N-terminal proBNP and BNP, although their plasma concentrations do not differ that much. In addition to BNP and N-terminal proBNP, a high molecular weight peptide which is presumed to be the intact proBNP circulates in human plasma.[7] Intact proBNP contributes to the immunoreactivity of BNP and thus attenuates the differences between immunoreactive BNP and N-terminal proBNP concentrations. Strong correlations between N-ter-

minal proBNP and BNP concentrations suggest that N-terminal proBNP is secreted from the heart along with BNP, in a similar manner to N-terminal proANP.[7,8] The clearance rate of N-terminal proBNP is not known, but higher plasma N-terminal proBNP concentrations imply that its half-life is longer than that of BNP.[7,8] The present finding that plasma concentrations of N-terminal proBNP show less increase in response to exercise than BNP fits well into this hypothesis.

In conformance with previous reports, BNP was found to be less responsive to exercise than ANP.[22,23] Because BNP has a longer half-life than ANP, its plasma concentrations may be less responsive to exercise.[24] Besides, differences in mode of secretion may play a role: ANP is prestored in granules and secreted rapidly in response to extracellular stimuli, whereas the secretory pattern of BNP, although not fully understood, is believed to lack a quantitatively important storage mechanism.[5]

Study limitations

Plasma cardiac peptide concentrations have been shown to be affected by multiple factors, including age, medication and heart rate.[25,26] For that reason, analyses of differences between patients were avoided, and analyses of differences between peptides were performed with paired tests only. Furthermore, the present study concentrated on patients with heart failure and impaired left ventricular systolic function. Previous research has indicated that changes in BNP concentrations in response to exercise in these patients differ from the response to exercise in patients with normal left ventricular systolic function.[22] Whether this is also the case for N-terminal proBNP requires further investigations.

Practical implications

Elevated plasma concentrations of cardiac peptides have been shown to be of practical use in the diagnostic and prognostic assessment of heart failure.[9-17] However, it is not clear which peptide should be used in clinical practice. In several studies it has been shown that BNP is a more accurate indicator of left ventricular systolic dysfunction and heart failure than N-terminal proANP and ANP,[10,11,14,15] but in other studies N-terminal proANP appeared to be a better marker for left ventricular dysfunction and early heart failure.[12,13] The clinical value of N-terminal proBNP has not been clarified yet. Nevertheless, its prognostic value after myocardial infarction and its elevated plasma concentrations and high correlations with BNP concentrations in patients with heart failure suggest that N-terminal proBNP might have the same predictive qualities as

BNP.[16,17] Not only the diagnostic or prognostic accuracy of each peptide, but also the stability of the samples and the blood sampling conditions are important prerequisites for the use of cardiac peptides in clinical routine. Previous studies have demonstrated that, in contrast to what has been found for ANP, the *in vitro* stability of both N-terminal proANP and BNP is sufficiently high.[27-29] In the present study the *in vivo* differences between ANP, N-terminal proANP, BNP and N-terminal proBNP were investigated by comparing their responses to exercise. It was shown that both N-terminal peptides increased less in response to exercise than their C-terminal counterparts. This implies that the circumstances under which blood sampling for measurements of N-terminal proANP and N-terminal proBNP should be performed are more favourable than the blood sampling conditions for ANP and BNP. Thus, these results confirm the practical superiority of N-terminal proANP and suggest that N-terminal proBNP might be a promising new tool for the assessment of heart failure.

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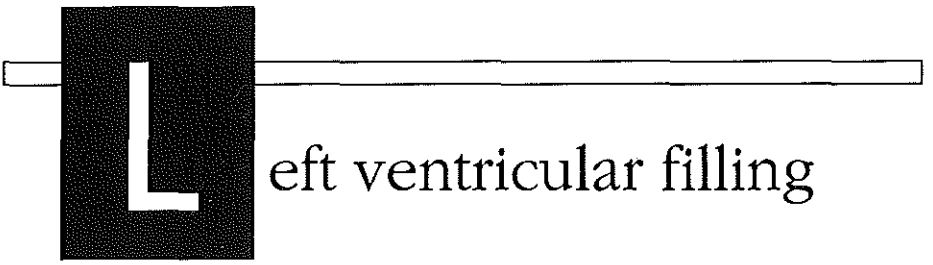

Left ventricular filling

6 Exercise capacity and left ventricular filling abnormalities in heart failure

Abstract

Background Both reduced exercise capacity and a restrictive left ventricular filling pattern are major predictors of prognosis in heart failure. This study examined the importance of left ventricular filling abnormalities measured at rest as a determinant of exercise capacity in patients with chronic heart failure.

Methods and results Fifty-two patients with chronic heart failure underwent cardiopulmonary exercise testing and Doppler echocardiography. Peak oxygen consumption was expressed as absolute value and as percentage of predicted maximum oxygen consumption according to age, body size and gender. Left ventricular filling patterns were classified as being restrictive or non-restrictive on the basis of transmitral E/A ratio and deceleration time. It was shown that absolute peak oxygen consumption was not related to left ventricular filling indices, whereas adjusted peak oxygen consumption was lower in patients with a restrictive filling pattern than in patients with a non-restrictive filling pattern (58% versus 71%, $p = 0.002$), and correlated with E/A ratio ($r = -0.44$, $p = 0.001$) and deceleration time ($r = 0.31$, $p = 0.03$).

Conclusion There is a significant difference in exercise capacity between patients with and without a restrictive left ventricular pattern at rest, provided that peak oxygen consumption is adjusted for differences in age, body size and gender. Because the correlations between left ventricular filling indices and peak oxygen consumption are rather weak, the contribution of left ventricular filling abnormalities to the variation in exercise capacity in patients with heart failure is only small.

Introduction

Assessment of exercise capacity is important in the management of patients with chronic heart failure. Oxygen consumption at peak exercise is an objective measure of exercise capacity and is related to the severity of heart failure.[1] Several studies have demonstrated that peak oxygen consumption provides prognostic information in patients with chronic heart failure.[2,3] Adjustment for differences in age, body size and gender by expressing peak oxygen consumption as percentage of predicted maximum oxygen consumption has been shown to increase its prognostic value even further.[4,5]

Abnormal left ventricular filling is an additional feature of heart failure that has been shown to influence prognosis as well.[6,7] Doppler recordings of mitral flow velocities are useful in the evaluation of left ventricular filling properties. Impaired relaxation results in a prolonged deceleration time and a reduced E/A ratio, whereas a restrictive left ventricular filling pattern is characterised by a shortened deceleration time and an increased E/A ratio.[8,9] Although the presence of a restrictive left ventricular filling pattern at rest has been shown to be related to more severe heart failure,[6,10] its relationship to maximal exercise capacity is less clear. As both reduced exercise capacity and a restrictive left ventricular filling pattern are major predictors of prognosis in heart failure, it is relevant to know how they are interrelated. Therefore, the present study examined the importance of left ventricular filling abnormalities measured at rest as a determinant of exercise capacity in patients with chronic heart failure.

Methods

Study population

Within the framework of an outpatient heart failure research project, 52 patients with chronic heart failure, left ventricular systolic dysfunction (left ventricular ejection fraction < 45%) and sinus rhythm underwent echocardiography and cardiopulmonary exercise testing. The aetiology of heart failure was established after careful review of clinical history and results of echocardiographic and angiographic examinations. Patients were eligible for the study when had been stable for at least three months and when they were able to perform exercise without being limited by angina pectoris, pulmonary disorders or peripheral vascular disease. In all cases, the echocardiographic examinations and exercise tests were performed within one week, and the investigators were blinded to the

results. The study was approved by the Medical Ethical Committee of the University Hospital Rotterdam, The Netherlands, and all study subjects gave informed consent.

Exercise testing

Symptom-limited exercise was performed on a bicycle ergometer (Lode, Groningen, The Netherlands) at a constant pedalling speed of 60 rpm with workload increments of 10 Watts/min. All patients had undergone a previous exercise test one week before the final examination to allow them to become familiar with the protocol and the equipment. Heart rate, blood pressure and a 12-lead electrocardiogram were monitored during the test. Gas volume and gas concentrations were measured continuously using a breath-by-breath system and a face mask with a digital volume sensor (Oxycon Champion, Mijnhardt Oxycon Systems, Bunnik, The Netherlands). Gas analyses were made by a paramagnetic oxygen and infrared carbon dioxide analyser. Calibration was performed before each test. Oxygen consumption and carbon dioxide production were recorded every 30 seconds. The predicted maximum oxygen consumption according to age, body size and gender was calculated for each patient.[11] Peak oxygen consumption (defined as the maximal value measured at the end of the test) was expressed as absolute value (ml/min), as absolute value divided by actual weight (ml/kg/min) and as percentage of the predicted maximum oxygen consumption (%).

Echocardiography

All patients were examined in partial left lateral decubitus position. Left ventricular ejection fractions were derived from the two-dimensional apical four-chamber and long-axis views using a biplane disk-method.[12] Mitral flow velocities were recorded from the apical four-chamber view using pulsed Doppler echocardiography with the sampling volume placed between the mitral leaflet tips. Mitral regurgitation was identified using continuous wave Doppler echocardiography and graded on a scale of one to four.[13] Mitral flow measurements were made by manual tracing of the outermost portion of the velocity contour using an off-line computer, a digitising tablet and a dedicated software program.[14] These measurements included heart rate, peak mitral flow velocity in early diastole (E), peak mitral flow velocity at atrial contraction (A) and deceleration time of E (obtained by extrapolating the initial slope to baseline). Mean values were obtained by averaging 10 consecutive beats. Heart rate was averaged from the same beats. Left ventricular filling patterns were classified as be-

ing restrictive or non-restrictive according to E/A ratio and deceleration time: an E/A ratio $\geq$ 2 or an E/A ratio between 1 and 2 and a deceleration time $\leq$ 150 msec was considered to be restrictive, whereas an E/A ratio $\leq$ 1 or an E/A ratio between 1 and 2 and a deceleration time > 150 msec was considered to be non-restrictive.[15]

Statistics

Comparisons between groups were made by χ^2 tests for categorical variables and unpaired t tests for continuous variables. Univariate linear regression analysis was used to study the relation of peak oxygen consumption to clinical and echocardiographic variables. The overall contribution of age, height, weight and gender to the variation in absolute peak oxygen consumption was calculated using multivariate linear regression analysis. The influence of heart rate, left ventricular ejection fraction, mitral regurgitation and use of diuretics on the relationship between adjusted peak oxygen consumption and left ventricular filling pattern was investigated by multivariate linear regression analysis. Because of its skewed distribution, the natural logarithmic transformed value of E/A ratio was used. Data are presented as mean $\pm$ SD unless otherwise specified. All analyses were performed using SPSS for Windows (version 6.1). Statistical significance was defined as $p < 0.05$.

Results

Study population

The study population consisted of 52 patients, 44 men and 8 women, aged 61 $\pm$ 10 (range 33 - 76) years. The mean height and weight were 173 $\pm$ 8 (range 156 - 194) cm and 78 $\pm$ 11 (range 57 - 117) kg, respectively. The cause of left ventricular systolic dysfunction was coronary artery disease in 37 patients and idiopathic dilated cardiomyopathy in 15 patients. The left ventricular ejection fraction was less than 45% in all patients, and the mean left ventricular ejection fraction was 32 $\pm$ 6%. Five patients were identified as having more than mild mitral regurgitation ($\geq$ grade 2). At the time of the study, 10 patients were in New York Heart Association class I, 35 patients were in class II and 7 patients were in class III. The majority of the patients (n = 48) used angiotensin converting enzyme inhibitors, 37 patients used diuretics, 25 patients used digitalis and 7 patients used betablockers.

Exercise data

All patients performed symptom-limited exercise; the reason for discontinuing exercise was either shortness of breath or fatigue. In all cases, the ratio between carbon dioxide production and oxygen consumption exceeded 1.0, indicating

Table 1
Clinical characteristics for patients with restrictive and non-restrictive left ventricular filling patterns.

	restrictive pattern	non-restrictive pattern
n	*15*	*37*
Age (years)	57 ± 11	62 ± 8
NYHA class *		
I	0 (0%)	10 (27%)
II	10 (68%)	25 (68%)
III	5 (33%)	2 (5%)
LVEF (%)	30 ± 5	32 ± 5
MR (≥ grade 2)	2 (14%)	3 (8%)
Etiology		
CAD	11 (73%)	26 (70%)
DCM	4 (27%)	11 (30%)
Heart rate (beats/min)	77 ± 12	72 ± 9
Medication		
ACE inhibitors	14 (93%)	34 (92%)
Diuretics **	15 (100%)	22 (59%)
Digitalis	9 (60%)	16 (43%)
Betablockers	2 (13%)	5 (13%)

Data are expressed as mean ± SD or number (%). * $p = 0.006$ ** $p = 0.004$. NYHA = New York Heart Association; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; CAD = coronary artery disease; DCM = idiopathic dilated cardiomyopathy; ACE = angiotensin converting enzyme.

Table 2
Exercise data for patients with restrictive and non-restrictive left ventricular filling patterns.

	restrictive pattern	non-restrictive pattern
n	*15*	*37*
Exercise duration (min)	9 ± 3	10.5 ± 3
Peak VO_2 (ml/min)	1245 ± 399	1414 ± 348
Peak VO_2 (ml/kg/min)	16 ± 5	18 ± 3
Peak VO_2 (%) *	58 ± 12	71 ± 12

Data are expressed as mean ± SD. * $p = 0.002$. VO_2 = oxygen consumption.

that each patient had made a valid effort. Mean exercise duration was 10 ± 3 minutes. Mean heart rate increased from 74 ± 10 beats/min at rest to 143 ± 18 beats/min at peak exercise. Systolic blood pressure increased from 128 ± 18 mm Hg to 176 ± 28 mm Hg. Mean oxygen consumption at peak exercise was 1367 ± 367 ml/min or 17.5 ± 4 ml/kg/min, corresponding with 66 ± 16% of predicted maximum oxygen consumption.

Exercise data in relation to left ventricular filling patterns

According to Doppler transmitral flow parameters, 15 patients had a restrictive and 37 patients had a non-restrictive left ventricular filling pattern. Both groups were comparable as regards age, left ventricular ejection fraction, presence of more than mild mitral regurgitation (≥ grade 2) on echocardiography, aetiology of heart failure, heart rate and use of angiotensin converting enzyme inhibitors, digitalis and betablockers. However, patients with a restrictive left ventricular filling pattern were more symptomatic and were using diuretics more frequently than patients with a non-restrictive filling pattern (Table 1). Patients with a restrictive filling pattern had lower adjusted values of peak oxygen consumption compared to patients with a non-restrictive filling pattern. Absolute values of peak oxygen consumption and exercise duration, however, did not differ between the two groups (Table 2).

Exercise data in relation to clinical and echocardiographic variables

Absolute peak oxygen consumption was higher in men ($r = 0.33$, $p = 0.02$), decreased with advancing age ($r = -0.42$, $p = 0.002$) and increased with higher height ($r = 0.51$, $p = 0.0002$) and weight ($r = 0.61$, $p < 0.0001$). Together, age, height, weight and gender accounted for 49% ($R^2 = 0.49$) of the variation in absolute values of peak oxygen consumption. There was no relationship between absolute peak oxygen consumption and left ventricular filling indices. In contrast, adjusted peak oxygen consumption correlated with E/A ratio ($r = -0.44$, $p = 0.001$) (Figure 1) and deceleration time ($r = 0.31$, $p = 0.03$) (Figure 2). There was no significant relationship between either absolute or adjusted peak oxygen consumption and left ventricular ejection fraction. In univariate analysis, adjusted peak oxygen consumption differed between patients with and without more than mild mitral regurgitation (57 ± 18 vs. 68 ± 12%, $p = 0.03$) and between patients with and without diuretics (64 ±14 vs. 74 ± 11%, $p = 0.02$). Multivariate analysis, however, demonstrated an independent relationship between adjusted peak oxygen consumption and left ventricular filling pattern ($p = 0.04$), whilst

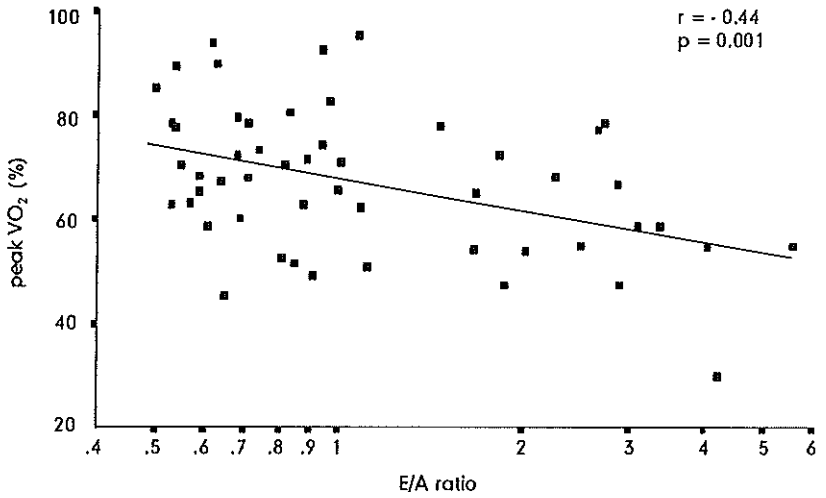

Figure 1
Relation between adjusted peak oxygen consumption (VO_2) expressed as percentage of predicted maximum oxygen consumption and transmitral E/A ratio.

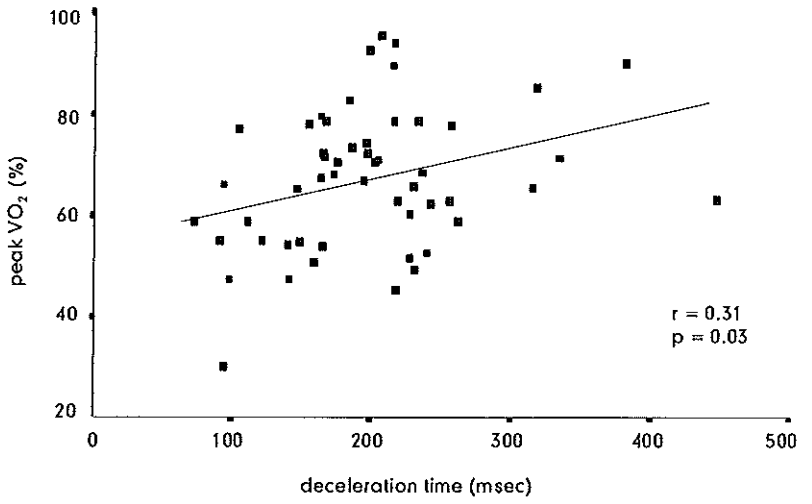

Figure 2
Relation between peak oxygen consumption (VO_2) expressed as percentage of predicted maximum oxygen consumption and transmitral deceleration time.

heart rate, left ventricular ejection fraction, mitral regurgitation and use of diuretics were found to be non-contributory.

Discussion

In patients with chronic heart failure multiple factors are of prognostic importance. Not only symptomatic status and exercise capacity, but also resting indices of left ventricular function are used to assess the severity and prognosis of heart failure.[2-7] Although impaired left ventricular systolic function is related to a poor prognosis, it does not seem to be correlated with severity of symptoms or exercise impairment in patients with chronic heart failure.[16] The present finding that peak oxygen consumption in patients with chronic heart failure is not related to left ventricular ejection fraction is thus in accordance with previous reports on exercise capacity and left ventricular performance. Diastolic function, on the other hand, seems to be a more likely determinant of exercise capacity in patients with chronic heart failure.[17,18] Invasive left ventricular filling indices measured at rest, such as wedge pressure, have been shown to be related to exercise capacity.[19,20] Several previous studies have demonstrated that non-invasive left ventricular filling indices, such as Doppler mitral flow velocities, are also related to functional class in patients with heart failure.[6,7,10] Like in the present study, all patients had a reduced left ventricular ejection fraction. Patients who had a restrictive left ventricular filling pattern had more symptoms,[10] had higher left ventricular filling pressures,[6] and a markedly increased cardiac death rate compared to patients with a non-restrictive filling pattern.[6,7] In patients with diseases that are known to affect left ventricular diastolic function, such as coronary artery disease or idiopathic dilated cardiomyopathy, a non-restrictive filling pattern suggests a reduced rate of left ventricular relaxation with relatively normal filling pressures. A restrictive filling pattern, on the other hand, is characterised by a fast, but abruptly ending increase in early filling which reflects a marked decrease in left ventricular compliance and an increase in left ventricular filling pressures.[8,9] The present finding that, despite a comparable reduction in left ventricular systolic function, patients with and without a restrictive left ventricular pattern had different levels of peak exercise oxygen consumption, supports the notion that left ventricular filling abnormalities play a role in reducing exercise capacity in patients with heart failure.

Study limitations

Doppler transmitral flow patterns are known to be influenced by multiple factors, including age, degree of mitral regurgitation, heart rate and loading conditions.[8,21,22] Besides, exercise capacity in chronic heart failure has been shown to be related to the aetiology of heart disease.[23] Because age, presence of more than mild mitral regurgitation, heart rate and aetiology of heart failure did not

differ significantly between patients with restrictive and non-restrictive left ventricular filling patterns, these variables were not considered to have influenced our results. Moreover, multivariate analysis showed that adjusted peak oxygen consumption was related to the left ventricular filling pattern independent of heart rate and degree of mitral regurgitation. Loading conditions were not defined in this study, but all patients were stable and the use of angiotensin converting enzyme inhibitors, digitalis and betablockers did not differ between patients with and without a restrictive left ventricular filling pattern. Furthermore, the difference in use of diuretics between the two groups was not statistically important in multivariate analysis and therefore unlikely to have affected our results. Finally, the definitions for restrictive and non-restrictive left ventricular filling patterns could be considered as arbitrary. Nevertheless, adjusted peak oxygen consumption did not only differ between patients with and without a restrictive filling pattern, but correlated with transmitral E/A ratio and deceleration time as well.

Conclusion

The present study shows that there is a difference in exercise capacity between heart failure patients with and without a restrictive left ventricular filling pattern at rest, provided that peak oxygen consumption is adjusted for differences in age, body size and gender. However, the determinants of both mitral flow and exercise capacity are complex and the observed correlations between left ventricular filling parameters and peak oxygen consumption were rather weak. For this reason we have to conclude that the contribution of left ventricular filling abnormalities to the variation in exercise capacity in patients with heart failure is only small.

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7

Potentials and limitations of the Valsalva manoeuvre as a method of differentiating between normal and pseudonormal left ventricular filling patterns

Abstract

Background Pseudonormalisation of the left ventricular filling pattern complicates the Doppler echocardiographic assessment of diastolic function in patients with heart failure. The inversion of E/A ratio in response to the Valsalva manoeuvre is recommended as a criterion for diagnosing pseudonormal filling patterns. However, neither a standardised Valsalva manoeuvre nor a healthy control population has been studied so far. For that reason, we studied changes in mitral flow velocities in response to a standardised Valsalva manoeuvre in heart failure patients and healthy individuals.

Methods and results The study group consisted of 55 heart failure patients with left ventricular systolic dysfunction and 35 healthy control subjects. The study subjects were instructed to elevate their intra-thoracic airway pressure to 40 mm Hg for 10 seconds. Doppler mitral flow velocities were recorded at rest and during the Valsalva manoeuvre. All study subjects had comparable decreases in early mitral flow velocity. However, mitral flow velocity at atrial contraction increased rather than decreased in patients with a restrictive pattern. In all but two of the patients and all control subjects with an E/A ratio between 1 and 2 inversion of the E/A ratio occurred.

Conclusion Patients with a restrictive left ventricular filling pattern show a markedly abnormal change in mitral flow velocity at atrial contraction in response to the Valsalva manoeuvre. This may be useful in detecting elevated filling pressures and pseudonormalised filling patterns. Contrary to previous beliefs, the inversion of E/A ratio does not differentiate normal from pseudonormal left ventricular filling patterns.

Introduction

Abnormalities of left ventricular filling are common in patients with heart failure. Doppler recordings of mitral flow velocities have been shown to be useful in the detection of abnormal left ventricular filling patterns: impaired relaxation results in a prolonged deceleration time and a reduced E/A ratio, whereas a restrictive left ventricular filling pattern is characterised by a shortened deceleration time and an increased E/A ratio.[1,2] A restrictive left ventricular filling pattern has been shown to be associated with increased filling pressures and more severe disease in patients with heart failure.[3,4] Pseudonormalisation occurs when an impaired relaxation pattern evolves towards restriction, reflecting the increase in filling pressures as heart failure progresses.[1] As a pseudonormal filling pattern at rest can not be distinguished from a normal pattern, Pseudonormalisation makes the assessment of left ventricular diastolic function by Doppler echocardiography difficult.

Left ventricular filling patterns are known to be preload dependent, and alterations in preload have been shown to be useful in detecting increased filling pressures.[5-9] The Valsalva manoeuvre is a simple and non-invasive method of reducing preload. Based on a previous study suggesting that the inversion of E/A ratio caused by the Valsalva manoeuvre is indicative of pseudonormalisation,[10] the Valsalva manoeuvre is recommended as a method of differentiating between normal and pseudonormal left ventricular filling patterns. Recently, it has been shown that the degree of decrease in E/A ratio during the Valsalva manoeuvre correlates with elevated left ventricular filling pressures.[8,9] However, as neither a standardised Valsalva manoeuvre was used nor a control population was studied, it could not be inferred from those studies whether the response to Valsalva is capable of distinguishing between normal and pseudonormal filling patterns. For that reason, we studied changes in mitral flow velocities in response to a standardised Valsalva manoeuvre in heart failure patients as well as healthy individuals, and reassessed whether the inversion of the E/A ratio in response to the Valsalva manoeuvre can differentiate between normal and pseudonormal left ventricular filling patterns.

Methods

Study population

Sixty-two consecutive patients with chronic heart failure, left ventricular systolic dysfunction (left ventricular ejection fractions < 45%) and sinus rhythm were

recruited from the cardiological outpatient clinic of the University Hospital Rotterdam, The Netherlands. The aetiology of heart failure was established after careful review of clinical history and results of echocardiographic and angiographic examinations. Forty randomly selected participants of the Rotterdam Study, a prospective study of determinants of chronic diseases in 7,983 inhabitants of the Rotterdam suburb of Ommoord, served as control population.[11] Only subjects with normal left ventricular systolic function and sinus rhythm were considered eligible for the study. Standardised interviews and physical examinations were performed in all control subjects to obtain information on medical history and current use of medication and to exclude the presence of signs or symptoms of heart failure.

Echocardiography

The study subjects were examined in partial left lateral decubitus position. In patients, left ventricular ejection fractions were derived from the two-dimensional apical four-chamber and long-axis views using a biplane disk-method.[12] In control subjects, M-mode echocardiography was used to measure left ventricular end-diastolic and end-systolic internal dimensions. The percentage fractional shortening was calculated from these measurements and the left ventricular ejection fraction was estimated using Quinones' prediction formula.[13] In both study groups, mitral flow velocities were recorded from the apical four-chamber view using pulsed Doppler echocardiography with the sampling volume placed between the mitral leaflet tips. Mitral regurgitation was identified using continuous wave Doppler echocardiography and graded on a scale of one to four.[14]

Valsalva manoeuvre

A dedicated system was used to ensure correct and standardised performance of the Valsalva manoeuvre. A disposable mouthpiece (Marquest Medical products, Inc. Englewood, USA) and a disposable pressure transducer (type TNF-R, Viggo-Spectramed, Bilthoven, The Netherlands) were connected by a homemade stainless steel tube. A tiny hole in the tube ensured elevation of the airway pressure in the thorax and not in the oral-pharynx alone. The calibrated output of the pressure transducer was displayed on a monitor to enable continuous observation of the actual intra-thoracic airway pressure. The study subjects were instructed to elevate their intra-thoracic airway pressure within half a second to 40 mm Hg, indicated by a solid line on the screen, and to maintain this strain for 10 seconds. Mitral flow velocities were recorded at rest and during the manoeuvre

(Figure 1). Care was taken to keep the sample volume placed between the tips of the mitral leaflets.

Mitral flow velocity measurements

Mitral flow velocity measurements were made by manual tracing of the outermost portion of the velocity contour using an off-line computer, a digitising tablet and a home-made software program.[15] Only recordings made at a tape speed of at least 50 mm/sec were used. The measurements included heart rate, peak mitral flow velocity in early diastole (E), peak mitral flow velocity at atrial contraction (A) and deceleration time of E (obtained by extrapolating the initial slope to baseline). Mean values at rest and during the Valsalva manoeuvre were obtained by averaging at least three consecutive beats before and three consecutive beats at the end of the manoeuvre at the point where the decrease in E was the largest. Left ventricular filling patterns were classified as being restrictive or non-restrictive according to E/A ratio and deceleration time: an E/A ratio ≤ 2 or an E/A ratio between 1 and 2 and a deceleration time ≤ 150 msec was considered to be restrictive, whereas an E/A ratio ≤ 1 or an E/A ratio between 1 and 2 and a deceleration time > 150 msec was considered to be non-restrictive.[16,17]

Statistics

Comparisons between patients with and without a restrictive left ventricular filling pattern and control subjects with an E/A ratio below or above 1 were made by unpaired t tests for continuous variables and χ^2 tests for categorical variables. Mitral flow velocity measurements at rest and during the Valsalva manoeuvre were compared using paired t tests. One way analysis of variance was used to compare changes in mitral flow velocity measurements in response to the Valsalva manoeuvre between control subjects and patients with different left ventricular filling patterns. The influence of heart rate was evaluated by both univariate and multivariate linear regression analysis. Comparisons between patients and control subjects with an E/A ratio between 1 and 2 were made by unpaired t tests. Because of its skewed distribution, the natural logarithmic transformed value of E/A ratio was used. Data are presented as mean $\pm$ SD. All analyses were performed using SPSS for Windows (version 6.1). Statistical significance was defined as $P < 0.05$.

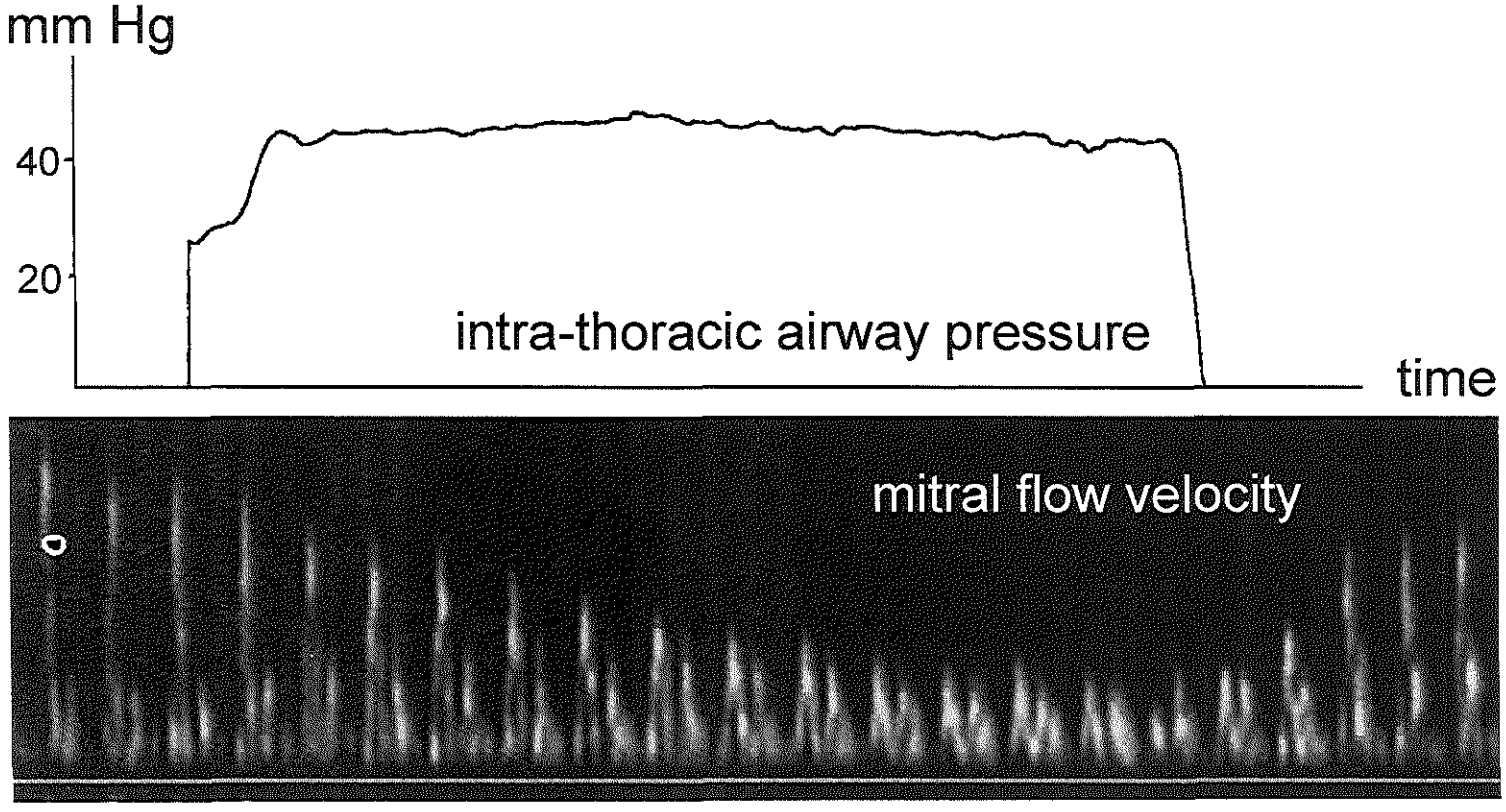

Figure 1
Intra-thoracic airway pressure and mitral flow velocities during a standardized Valsalva manoeuvre.

Results

Study population

All study subjects were able to elevate their intra-thoracic airway pressure to 40 mm Hg for 10 seconds. However, in 7 out of the 62 patients (8%) and 5 out of the 40 control subjects (12%) adequate mitral flow velocity measurements could not be obtained because of the poor quality of mitral flow recordings during the Valsalva manoeuvre. Thus, the study population was formed by the remaining 55 patients, 47 men and 8 women, aged 61 ± 10 years, and 35 control subjects, 19 men and 16 women, aged 62 ± 4 years.

According to mitral flow velocity measurements at rest, 20 patients had a restrictive and 35 patients had a non-restrictive left ventricular filling pattern. There were no significant differences between patients with and without a restrictive pattern (Table 1). All 35 control subjects had a non-restrictive left ventricular filling pattern at rest (Table 2).

Table 1
Clinical characteristics of patients

	total	non-restrictive pattern	restrictive pattern
n	*55*	*35*	*20*
Age (years)	61 ± 10	62 ± 8	58 ± 12
LVEF (%)	32 ± 7	33 ± 6	30 ± 7
MR (≥ grade 2)	5 (9%)	3 (8%)	2 (10%)
Aetiology			
Ischemic heart disease	37 (67%)	21 (60%)	16 (80%)
Dilated cardiomyopathy	18 (33%)	14 (40%)	4 (20%)
NYHA classification			
I/II	45 (82%)	30 (86%)	15 (75%)
III	10 (18%)	5 (14%)	5 (25%)
Medication			
ACE inhibitors	51 (93%)	33 (94%)	18 (90%)
Diuretics	42 (76%)	25 (71%)	17 (85%)
Digitalis	31 (56%)	19 (54%)	12 (60%)

Data are expressed as mean ± SD or number (%). LVEF = left ventricular ejection fraction; MR = mitral regurgitation; NYHA = New York Heart Association; ACE = angiotensin converting enzyme.

Comparison between mitral flow velocity measurements at rest and during the Valsalva manoeuvre

Heart rate, E, A and E/A ratio all changed in response to the Valsalva manoeuvre. Deceleration time, however, did not change significantly (Table 3).

Comparison between control subjects and patients with different left ventricular filling patterns

All study subjects showed a comparable decrease in E velocity in response to the Valsalva manoeuvre (Table 4). However, in patients with a restrictive left ventricular filling pattern, A velocity increased rather than decreased (Figure 2). Consequently, the decrease in E/A ratio in response to the Valsalva manoeuvre was larger in patients with a restrictive pattern compared to control subjects as well as patients with a non-restrictive pattern. The increase in heart rate was different in all three groups (Table 4). In univariate analysis, the amount of change in heart rate appeared to be significantly related to changes in E velocity ($r = -0.32$, $P = 0.002$) and E/A ratio ($r = -0.21$, $P = 0.04$), but not to changes in A velocity. Multivariate analysis showed that changes in E/A ratio differed between the various groups independent of the increase in heart rate ($P = 0.0004$). Out of all study subjects, five patients were identified as having more than mild mitral regurgitation (≥ grade 2). Exclusion of these subjects from the analysis did not lead to different results.

Table 2
Clinical characteristics of control subjects

	total	E/A ≤ 1	1 < E/A < 2
n	*35*	*20*	*15*
Age (years)	62 ± 4	63 ± 4	62 ± 4
LVEF (%)	73 ± 10	72 ± 11	74 ± 7
Hypertension *	9 (26%)	6 (30%)	3 (20%)
Ischemic heart disease †	3 (9%)	3 (15%)	-
Medication			
Betablockers	5 (14%)	3 (15%)	2 (13%)
Nitrates	2 (6%)	2 (10%)	-
Diuretics	1 (3%)	1 (5%)	-
Calcium antagonists	1 (3%)	1 (5%)	-

Data are expressed as mean ± SD or number (%). LVEF = left ventricular ejection fraction.
* Systolic blood pressure ≥ 160 or diastolic blood pressure ≥ 100 mm Hg or use of antihypertensive medication.
† Angina pectoris by Rose questionnaire, previous myocardial infarction, PTCA or CABG or use of anti-anginal medication.

Table 3
Mitral flow velocity measurements at rest and during the Valsalva manoeuvre

	controls			patients					
				non-restrictive pattern			restrictive pattern		
	Rest	Valsalva	P	Rest	Valsalva	P	Rest	Valsalva	P
E (cm/s)	68 ± 14	36 ± 11	< 0.0001	59 ± 19	30 ± 13	0.002	97 ±.29	52 ± 26	0.003
A (cm/s)	68 ± 14	58 ± 13	0.003	76 ± 24	59 ± 16	< 0.0001	40 ± 18	51 ± 19	< 0.0001
E/A (-)	1.02 ± 0.25	0.64 ± 0.21	0.03	0.86 ± 0.43	0.55 ± 0.29	< 0.0001	2.80 ± 1.33	1.39 ± 1.33	< 0.0001
DET (ms)	205 ± 48	322 ± 118	ns	239 ± 50	285 ± 64	ns	129 ± 40	195 ± 81	ns
HR (bpm)	64 ± 8	76 ± 14	< 0.0001	69 ± 10	75 ± 12	< 0.0001	77 ± 12	79 ± 14	< 0.0001

Data are expressed as mean ± SD. E = mitral flow velocity in early diastole; A = mitral flow velocity at atrial contraction; DET = deceleration time; HR = heart rate.

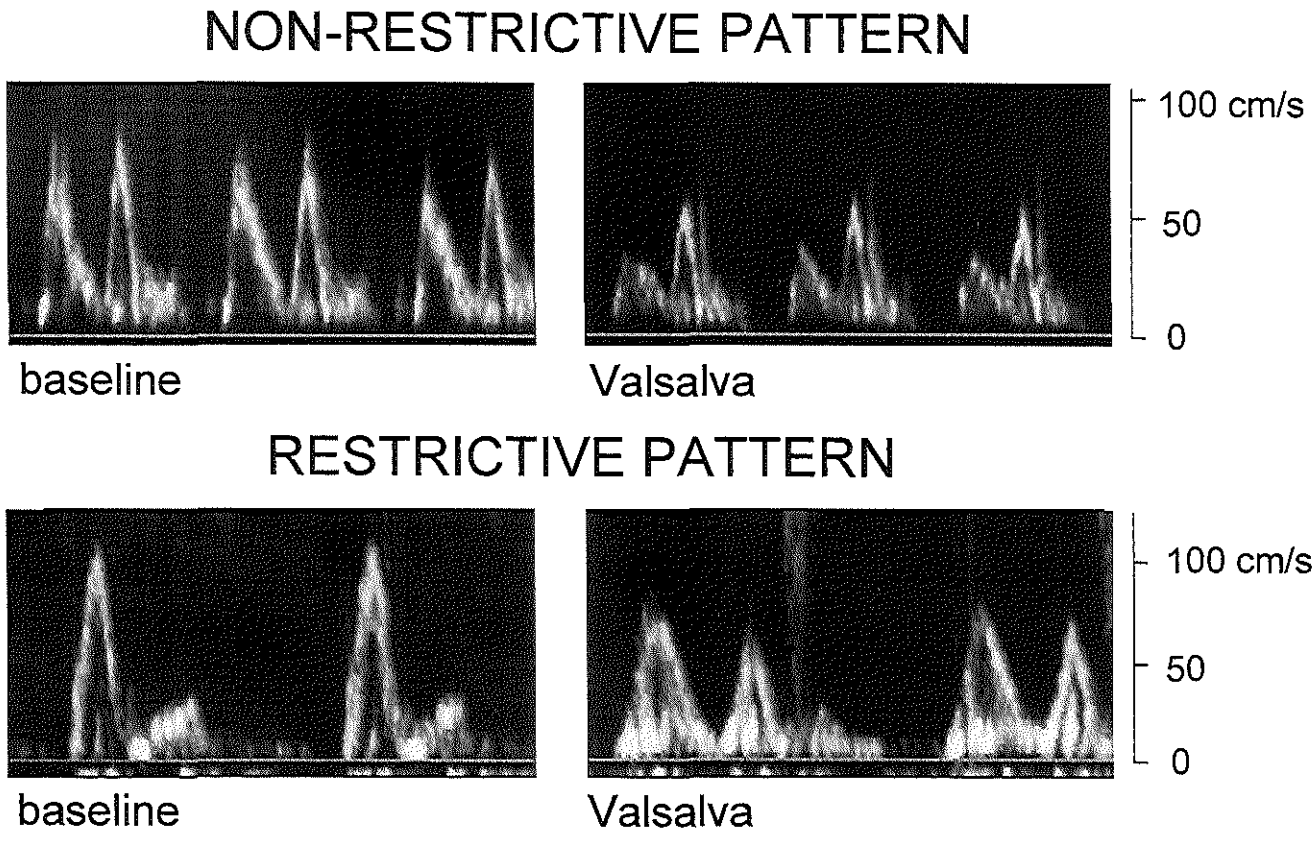

Figure 2
Mitral flow velocities at rest and during the Valsalva manoeuvre in a patient with a non-restrictive and a patient with a restrictive left ventricular filling pattern.

Table 4
Changes in mitral flow velocity measurements in response to the Valsalva manoeuvre

	controls	patients		p
		non-restrictive pattern	restrictive pattern	
Δ E (%)	- 46 ± 15	- 42 ± 18	- 41 ± 24	ns
Δ A (%)	- 20 ± 13	- 21 ± 19	+31 ± 36	< 0.0001
Δ E/A (%)	- 35 ± 22	- 25 ± 23	- 53 ± 21	0.003
Δ DET (%)	61 ± 54	23 ± 36	52 ± 51	0.01
Δ HR (%)	19 ± 17	7 ± 8	2 ± 12	< 0.0001

Data are expressed as mean ± SD. Δ = percentage change; E = mitral flow velocity in early diastole; A = mitral flow velocity at atrial contraction; DET = deceleration time; HR = heart rate.

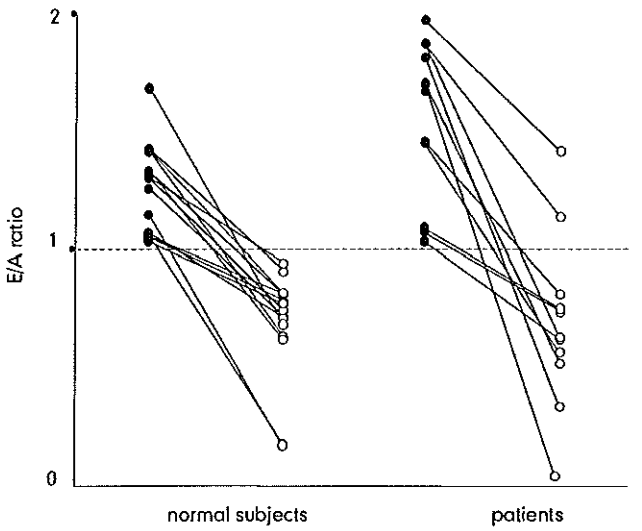

Figure 3
The E/A ratio at rest (solid circles) and during the Valsalva manoeuvre (open circles) in heart failure patients and control subjects with an E/A ratio between 1 and 2.

Comparison between control subjects and patients with an E/A ratio between 1 and 2

Eleven patients and 15 control subjects had a resting E/A ratio between 1 and 2. Out of these 15 control subjects, only three subjects had a medical history of hypertension of whom two were using betablockers (Table 2). Inversion of the E/A ratio in response to the Valsalva manoeuvre did not only take place in 9 out

of 11 patients with an E/A ratio between 1 and 2, but also in all 15 control subjects (Figure 3). The patients tended to have higher resting E/A ratios (1.54 ± 0.35 versus 1.26 ± 0.19; P = 0.03) and lower resting A velocities (51 ± 13 versus 62 ± 14 cm/s; P = 0.06) compared to the control subjects. The Valsalva manoeuvre induced a comparable decrease in E velocity (- 53 ± 20 versus - 49 ± 15%), but a significantly different change in A velocity (+ 16 ± 36 versus - 17 ± 15%, P = 0.004) and E/A ratio (- 54 ± 23 versus - 37 ± 11%, P = 0.04) between the two groups. An increase in A velocity was observed in 6 out of the 11 patients and 3 out of the 15 controls. Further analysis of the data of these 6 patients who showed an increase in A velocity did not reveal any significant differences compared to the patients who did not show this increase.

Discussion

The present study showed that, compared to patients and control subjects with a non-restrictive left ventricular filling pattern, patients with a restrictive left ventricular filling pattern have a similar reduction in mitral flow velocity in early diastole, but an increase rather than a decrease in mitral flow velocity at atrial contraction in response to a standardised Valsalva manoeuvre. Furthermore, it was demonstrated that the inversion of E/A ratio in response to the Valsalva manoeuvre occurred not only in patients but also in all healthy individuals with an E/A ratio between 1 and 2.

The Valsalva manoeuvre causes an abrupt reduction of preload. In normal subjects, preload reduction is known to affect the pattern of left ventricular filling by lowering mitral flow velocity in early diastole and, to a lesser extent, at atrial contraction.[5,6,18,19] In patients with elevated filling pressures, however, preload reduction has been shown to cause less or no decrease in mitral flow velocity at atrial contraction.[8,9] This is in conformance with the increase in mitral flow velocity at atrial contraction in patients with a restrictive left ventricular filling pattern that was observed in the present study. In these patients, high left atrial pressures increase mitral flow velocities in early diastole and cause rapid augmentation of left ventricular filling pressures, which results in minimal mitral flow velocity at atrial contraction.[1,16] Reduction in preload will lead to lower left ventricular pressure at the time of atrial contraction and, provided that atrial systolic function is preserved, cause an increase in the atrial contribution to left ventricular filling. The present findings thus confirm that elevated filling pressures can be detected by looking carefully at directional changes in mitral flow velocities in response to the Valsalva manoeuvre.

Since Pseudonormalisation of the left ventricular filling pattern occurs when elevated filling pressures are present, the Valsalva manoeuvre might be a suitable method of differentiating between normal and pseudonormal left ventricular filling patterns. In a previous study the normal response to the Valsalva manoeuvre was characterised by a similar decrease in mitral flow velocities in early diastole and at atrial contraction, whereas the inversion of E/A ratio was assumed to be indicative of a pseudonormalised left ventricular filling pattern.[10] In the present study, however, the inversion of E/A ratio did not only occur in patients with left ventricular systolic dysfunction and an E/A ratio between 1 and 2, but also in all control subjects with normal systolic function and, according to previously reported age-adjusted reference values,[20] normal E/A ratios. This proves that the inversion of E/A ratio alone does not allow differentiating normal from pseudonormal left ventricular filling patterns. The discrepancy between our and previous results is probably due to the fact that in the present study attention was paid to correct and standardised performance of the Valsalva manoeuvre. In other studies, the success of the manoeuvre has been based at a minimal reduction of 10% in mitral flow velocity in early diastole.[8-10] However, this does not take into account interindividual variations in ability to perform an adequate Valsalva manoeuvre and prevents objective comparison of its effects.

Study limitations

The attenuated heart rate response to the Valsalva manoeuvre in patients with heart failure, reflecting the impairment of baroreflex control,[21] may have influenced our results.[1] However, in multivariate analysis it was demonstrated that the changes in E/A ratio differed between the various groups independent of the heart rate response. Besides, in case the heart rates had increased equally in all groups, differences in changes in E/A ratio between the groups would have been even more pronounced. Age and mitral regurgitation may influence transmitral flow velocities as well.[22,23] Since patients and normal subjects were comparable for age and exclusion of subjects with more than mild mitral regurgitation did not lead to different outcomes, these variables were not considered to have influenced our results.

As filling pressures were not directly measured, we are not able to confirm which subjects with an E/A ratio between 1 and 2 were normal and which were pseudonormal. However, we assume that, like in patients with a restrictive left ventricular filling pattern, an increase in mitral flow velocity at atrial contraction in response to the Valsalva manoeuvre is indicative of elevated filling pressures and may thus detect pseudonormalised filling patterns. With the selection of age-matched subjects from a population-based cohort we have tried to come close to a truly normal control population. However, as with age the occurrence

of hypertension and ischemic heart disease increases, abnormalities of left ventricular filling could be present in this population. Nevertheless, out of the 15 control subjects with an E/A ratio between 1 and 2, only three subjects had a medical history of hypertension. None of the 12 remaining control subjects was suspected of having cardiac or non-cardiac diseases that influence left ventricular filling dynamics. The fact that inversion of the E/A ratio in response to the Valsalva manoeuvre occurred in all 15 subjects (also in those suspected of having hypertension) strengthens our conclusion that looking solely at the inversion of the E/A ratio can not differentiate between subjects with and without left ventricular filling abnormalities.

Finally, several other echocardiographic methods of detecting elevated filling pressures and pseudonormalised filling patterns have been described.[24-26] Nevertheless, as long as the inversion of E/A ratio in response to the Valsalva manoeuvre is still recommended as a criterion for diagnosing pseudonormal left ventricular filling patterns, we felt that it was important to report the limitations of this method.

Conclusions

The effects of the Valsalva manoeuvre on mitral flow are complex and should therefore be assessed by observing more than the E/A ratio alone. The distinct changes in mitral flow velocity at atrial contraction in patients with heart failure and a restrictive left ventricular filling pattern may be useful in detecting elevated filling pressures and pseudonormalised filling patterns. The inversion of E/A ratio, however, occurs not only in patients but also in healthy individuals, and is therefore incapable of differentiating between normal and pseudonormal left ventricular filling patterns.

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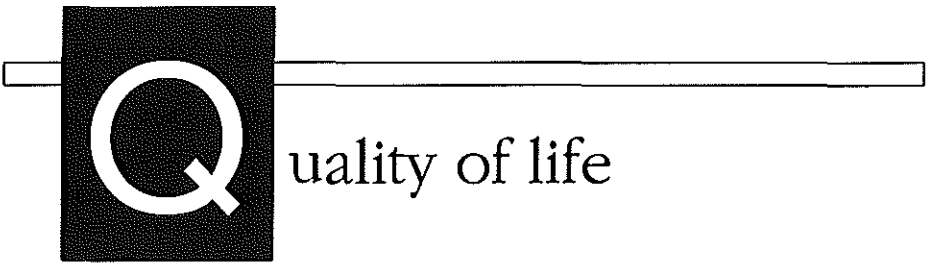
Quality of life

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Quality of life in chronic heart failure; validation of the Dutch version of the Minnesota Living with Heart Failure Questionnaire

Abstract

Background The Minnesota Living with Heart Failure Questionnaire was designed specifically to assess quality of life in patients with heart failure. This questionnaire has been shown to be reliable and valid for use in the United States. The aim of the present study was to validate the questionnaire for the Netherlands.

Methods and results The questionnaire was translated into Dutch and subsequently tested in a field testing procedure. The final version was administered to 224 patients with chronic heart failure. Factor analysis identified a physical and an emotional dimension. Both dimensions exhibited satisfactory levels of internal consistency and their test-retest reliability was high. The validity of the questionnaire was investigated by testing its relation to corresponding clinical and psychological measures of health status. The pattern of correlations between the Minnesota Living with Heart Failure Questionnaire and two other questionnaires was in agreement with the hypothesis that dimensions that are conceptually related correlate better than conceptually unrelated dimensions. Furthermore, measures of exercise capacity correlated better with the physical than with the emotional dimension, and the questionnaire scores were related to increasing severity of heart failure.

Conclusion The Dutch version of the Minnesota Living with Heart Failure Questionnaire is a reliable and valid instrument when administered to patients with chronic heart failure.

Introduction

Assessment of health-related quality of life is considered to be an important factor in the care of patients with heart failure.[1,2] In addition, there is a growing interest in using quality of life measurements in heart failure research.[3-6] A number of questionnaires are available to assess quality of life in general populations. The Minnesota Living with Heart Failure Questionnaire (LHFQ), however, was designed specifically for use in patients with chronic heart failure.[7] This questionnaire has been shown to be reliable and valid for a US population.[8,9] To use a questionnaire like the LHFQ in respondents with a native language other than English requires comprehensive testing of the reliability and validity of the translated version within the new context.[10] To our knowledge this has not been done for The Netherlands so far. In the present study, therefore, we investigated the internal structure and assessed the reliability and validity of the Dutch version of the Minnesota LHFQ in patients with chronic heart failure. Because there is no gold standard for quality of life in patients with heart failure, the validity of the Dutch LHFQ was investigated by testing its relationship to corresponding clinical and psychological measures of health status.

Methods

Questionnaires

The original LHFQ was developed to measure patients' perceptions of the effects of chronic heart failure on their lives. This self-administered questionnaire consists of 21 questions with response possibilities which range from a score of 0 (no impairment) to 5 (very much impaired). The total score is the sum of the responses for all 21 questions. In addition, subgroups of questions representing physical and emotional dimensions of the questionnaire have been identified.[8] The LHFQ was translated into Dutch and discussed in a multidisciplinary expert committee of which all participants were bilingual. The resulting first version was tested for comprehensibility by six patients with chronic heart failure. All patients were asked to read sentence after sentence aloud in the presence of the interviewer. Problems related to the administration of the questions were recorded, and afterwards the patients were encouraged to indicate what they found difficult to understand. After a few changes, this procedure led to the final version of the Dutch LHFQ.

Health-related quality of life was also assessed by two other questionnaires: patients enrolled during the first half of the study completed the Nottingham

Health Profile (NHP), whereas patients enrolled during the second half of the study completed the Heart Patients Psychological Questionnaire (HPPQ). Some patients completed both questionnaires (n = 24). The NHP is a generic instrument for measuring health status that consists of 38 items which cover six health-related dimensions of quality of life, namely Physical Mobility, Energy, Pain, Sleep, Social Isolation and Emotional Reaction, and seven questions concerning the influence of health status on specific domains of daily life.[11] No total score is derived, but the number of positively answered questions within each dimension is counted up. High scores indicate a poor quality of life. The reliability and validity of the Dutch version of the NHP has been described previously.[12]

The HPPQ was developed and validated in the Netherlands as a specific measure of health status for patients with heart disease.[13] The questionnaire consists of 52 items which are related to four dimensions of quality of life: Well-being, Feelings of being disabled, Displeasure and Social Inhibition. Higher scores in the Well-being dimension indicate a greater degree of well-being, whereas higher scores in Feelings of being disabled, Displeasure and Social Inhibition indicate a worse psychological condition.[14]

Study population

The study subjects were recruited from the cardiological outpatient clinic of the University Hospital Rotterdam, The Netherlands. From January 1996 to April 1997 all patients who had symptoms of heart failure for at least 3 months *and* impaired left ventricular function documented on echocardiography were considered eligible for the study. Patients were excluded when they had significant angina pectoris, acute myocardial infarction within the preceding 3 months, symptomatic arrhythmias or when they were not literate in Dutch. From the 239 patients who met the study criteria, 224 (94%) agreed to participate. Clinical characteristics are presented in Table 1. Twenty-four patients were asked to fill in the LHFQ again after two weeks to establish the test-retest reliability. None of these patients had significant changes in clinical status within this period.

Clinical data

Data regarding the cardiac history, duration and nature of the symptoms were derived from the patient record. All patients underwent echocardiography to confirm the presence of left ventricular dysfunction. A subgroup of 52 patients with mild to moderate heart failure who were participating in an outpatient heart

failure research project and 63 patients with severe heart failure who were evaluated for cardiac transplantation underwent cardiopulmonary exercise testing. Data collected included peak oxygen consumption, defined as the maximal value measured at the end of the test, and oxygen consumption at anaerobic threshold, defined as the intersection of the slope of carbon dioxide production and oxygen consumption (V-slope). In order to correct for differences in age, body size and gender, both variables were expressed as percentage of the predicted maximum oxygen consumption.[15]

Analysis

In order to confirm the *internal structure* of the LHFQ, factor analysis was performed. The *internal consistency* of the dimensions was measured by Cronbach's α. *Test-retest reliability* was assessed using Pearson's correlation coefficient. *Construct validity* was established by testing several predefined hypotheses. In the first place, it was hypothesised that those dimensions of the NHP and HPPQ that are conceptually related to the LHFQ dimensions should correlate better than unrelated dimensions. Furthermore, oxygen consumption at peak exercise and at anaerobic threshold should correlate better with the physical than with the emotional dimension. Finally, higher LHFQ scores were expected to be related

Table 1
Clinical characteristics (n = 224)

	mean ± SD	n (%)
Age (years)	60 ± 12	
Male gender		172 (77%)
Duration of heart failure (months)	40 ± 36	
Aetiology of heart failure		
Coronary artery disease		122 (55%)
Hypertension		16 (7%)
Idiopathic cardiomyopathy		72 (32%)
Valvular heart disease		14 (6%)
NYHA class		
I		25 (11%)
II		104 (46%)
III		80 (36%)
IV		15 (7%)
Heart failure medication		
ACE inhibitors		215 (86%)
Diuretics		192 (86%)
Digoxin		147 (66%)

NYHA = New York Heart Association; ACE = angiotensin converting enzyme.

to increasing severity of heart failure as assessed by the New York Heart Association class. Correlations between continuous variables were tested with Pearson's correlation coefficient. The difference between those correlation coefficients were tested using a test for the significance of the difference between dependent correlation coefficients.[16] The relation between LHFQ scores and New York Heart Association class was tested using analysis of variance. The variation due to regression divided by the total variation is given as measure of the strength of the linear relation between these variables. This measure is equal to the square of Pearson's correlation coefficient and can be considered as that part of the total variation that can be explained by differences in New York Heart Association class. Data are presented as mean ± SD unless otherwise specified. All analyses were performed using SPSS for Windows (version 6.1). Statistical significance was defined as $P < 0.05$.

Results

Internal structure

Two major dimensions were identified on the Dutch version of the LHFQ. Responses to questions 2 (having to rest during the day), 3 (difficulty with walking or climbing stairs), 4 (difficulty with working around the house), 5 (difficulty with going away from home), 6 (difficulty with sleeping), 12 (dyspnoea) and 13 (fatigue) were highly interrelated. As these items were related to physical functioning they were assumed to reflect a physical dimension. Questions 7 (difficulty with relating to or doing things with other people), 17 (feeling burdensome to other people), 18 (feeling a loss of self-control), 19 (worry), 20 (difficulty with concentrating or remembering things) and 21 (feeling depressed) were highly interrelated as well and were identified as the emotional dimension. In the original study on the validity of the LHFQ, question 7 was assigned to the physical dimension.[7] However, in the present study this question appeared to be more strongly related to questions addressing emotional functioning and was therefore included in the emotional dimension.

Reliability and validity

Internal consistency measured by Cronbach's α coefficient was 0.91 for the physical dimension and 0.87 for the emotional dimension. The test-retest reliability was 0.86 for the total score, 0.87 for the physical dimension and 0.85 for the emotional dimension. The scores for the various LHFQ, NHP and HPPQ di-

mensions are summarized in Table 2. As expected, the observed correlations between the LHFQ physical dimension and the NHP Physical Mobility and Energy and the HPPQ Well-being and Feelings of being disabled dimensions were higher than the correlations with less physically-oriented dimensions (Table 3). Similarly, the LHFQ emotional dimension correlated stronger with the NHP Social Isolation and Emotional Reaction and the HPPQ Well-being and Displeasure dimensions than with other dimensional scores (Table 3). Oxygen consumption at peak exercise and at anaerobic threshold correlated moderately with the LHFQ physical dimension ($r = -0.46$ and $r = -0.34$, $P < 0.0001$) and weakly with the LHFQ emotional dimension ($r = -0.22$ and $r = -0.20$, $P = 0.03$). In accordance with our hypothesis, both peak oxygen consumption and oxygen consumption at anaerobic threshold correlated better with the physical than with the emotional dimension ($P < 0.01$ and $P < 0.05$, respectively).

Finally, it was demonstrated that the physical and the emotional dimensional scores were associated with New York Heart Association class ($P < 0.0001$ for both) (Figure 1). In fact, differences in New York Heart Association class

Table 2
Clinical and psychological measures of health status

	mean ± SD	range
NYHA class (n = 224)	2.4 ± 0.8	1 - 4
Exercise testing (n = 115)		
VO_2 at peak exercise (%)	62 ± 17	25 - 97
VO_2 at V-slope (%)	39 ± 11	21 - 69
LHFQ (n = 224)		
Total score	32 ± 22	0 - 90
Emotional	7 ± 7	0 - 29
Physical	14 ± 10	0 - 35
NHP (n = 141)		
Physical Mobility	1.5 ± 1.8	0 - 8
Energy	0.9 ± 1.1	0 - 3
Pain	0.7 ± 1.4	0 - 8
Sleep	1.3 ± 1.5	0 - 5
Social Isolation	0.2 ± 0.5	0 - 2
Emotional reaction	1.3 ± 1.8	0 - 8
HPPQ (n = 107)		
Well-being	26 ± 9	13 - 39
Feelings of being disabled	12 ± 4	9 - 27
Displeasure	18 ± 5	8 - 24
Social Inhibition	12 ± 3.	6 - 18

LHFQ = Living with Heart Failure Questionnaire; NHP = Nottingham Health Profile; HPPQ = Heart Patients Psychological Questionnaire; NYHA = New York Heart Association; VO_2 = oxygen consumption.

Table 3
Correlation of the LHFQ dimensions with the NHP and HPPQ dimensions

LHFQ	NHP						HPPQ			
	PM	E	P	S	SI	ER	W	F	D	I
Emotional	0.64*	0.56*	0.23**	0.40*	0.66*	0.62*	0.65*	- 0.31***	- 0.63*	- 0.04
Physical	0.75*	0.76*	0.45*	0.60*	0.44*	0.60*	0.60*	- 0.59*	- 0.36*	- 0.11

* $P < 0.001$, ** $P = 0.006$, *** $P = 0.001$. LHFQ = Living with Heart Failure Questionnaire; NHP = Nottingham Health Profile; HPPQ = Heart Patients Psychological Questionnaire; PM = Physical Mobility; E = Energy; P = Pain, S = Sleep, SI = Social Isolation; ER = Emotional Reaction; W = Well-being; F = Feelings of being Disabled; D = Displeasure; I = Social Inhibition.

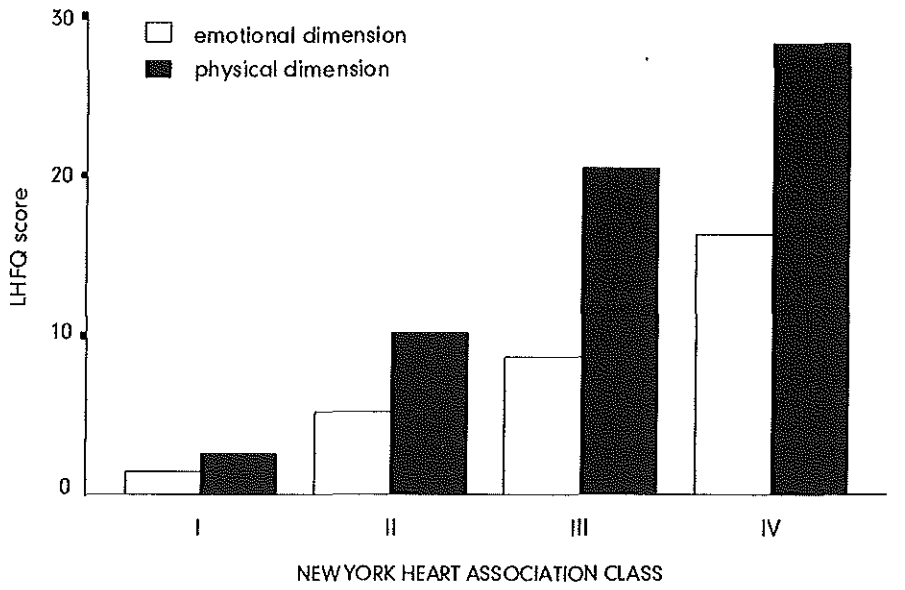

Figure 1
Mean physical and emotional dimension scores in relation to the New York Heart Association class. Both the emotional and the physical dimension scores differed significantly between the classes ($P < 0.0001$). LHFQ = Living with Heart Failure Questionnaire.

explained 52% ($R^2 = 0.52$) of the variation in physical and 24% of the variation in emotional dimensional score.

Discussion

In the present study, we investigated the internal structure and assessed the reliability and validity of the Dutch version of the LHFQ in a sample of 224 patients with chronic heart failure. Like in the original questionnaire, a physical as well as an emotional dimension could be identified.[8] However, one question addressing difficulties with relating to or doing things with other people was assigned to the emotional rather than the physical dimension. A possible explanation could be that the translation of the concept "relating to or doing things with" into the Dutch "omgang met" slightly changed the meaning of the question. Nevertheless, this difference may also have been caused by cultural or other factors as well.

Both the physical and the emotional dimensions of the Dutch LHFQ exhibited satisfactory levels of internal consistency. In addition, the test-retest reliability of the questionnaire was clearly demonstrated by the high correlation coefficients

among stable patients who completed the questionnaire twice within two weeks. In general, the pattern of correlations between the LHFQ dimensions and the NHP and HPPQ dimensions was in agreement with our hypothesis that dimensions that are conceptually related should correlate better than unrelated dimensions. Particularly striking were the high correlations between the LHFQ physical dimension and the NHP Physical Mobility and Energy dimensions ($r \geq 0.75$) and between the LHFQ emotional dimension and the NHP Social Isolation and HPPQ Well-being dimensions ($r \geq 0.65$).

As expected, the physical dimension, and not the emotional dimension, was inversely related to oxygen consumption at peak exercise and at anaerobic threshold. Both measures of exercise capacity can be used as objective and reliable parameters for evaluation of the severity of heart failure in terms of functional capacity.[17] Like in previous studies, the association between quality of life and exercise capacity was rather weak.[3,4,18,19] This may be due to the fact that oxygen consumption at peak exercise and at anaerobic threshold reflect near maximal exercise performance while most activities of daily living involve work below anaerobic threshold.[20] In addition, exertional symptoms in patients with heart failure are not exclusively related to circulatory dysfunction, but may also be caused by noncardiac factors.[21] Finally, the finding that both the physical and the emotional LHFQ scores were related to increasing severity of heart failure as assessed by the less comprehensive New York Heart Association class is consistent with other reports and supports the validity of the Dutch LHFQ.[7,18,22]

In conclusion, the present study showed that the Dutch version of the Minnesota Living with Heart Failure Questionnaire is a reliable and valid instrument when administered to patients with chronic heart failure. Nevertheless, future studies are needed to investigate its responsiveness to change in health status over time.

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Appendix

Dutch version of the Minnesota Living with Heart Failure Questionnaire

MINNESOTA VRAGENLIJST *

Instructie

Onderstaande vragen hebben betrekking op de mate waarin uw hartklachten ertoe geleid hebben dat u de afgelopen maand anders leefde dan u wilde. Deze vragen beschrijven verschillende manieren waarop sommige mensen daar last van kunnen hebben. Als u zeker weet dat een bepaalde vraag niet op u van toepassing is of niets met uw hartklachten te maken heeft, omcirkel dan de "0" (Nee) en ga verder met de volgende vraag. Is de vraag wel op u van toepassing, omcirkel dan het cijfer dat aangeeft in welke mate uw hartklachten ertoe geleid hebben dat u anders leefde dan u wilde. Het is de bedoeling dat u alleen aan de afgelopen maand denkt.

Hebben uw hartklachten ertoe geleid dat u de AFGELOPEN MAAND anders leefde dan u wilde, doordat:

		Nee	Nauwe-lijks				In hoge mate
1.	U last had van gezwollen enkels, benen, enz.?	0	1	2	3	4	5
2.	U overdag moest gaan zitten of liggen om te rusten?	0	1	2	3	4	5
3.	U moeite had met wandelen of trappen lopen?	0	1	2	3	4	5
4.	U moeilijk in huis of in de tuin kon werken?	0	1	2	3	4	5
5.	U moeilijk van huis kon?	0	1	2	3	4	5
6.	U 's nachts niet goed kon slapen?	0	1	2	3	4	5
7.	Uw omgang met vrienden of familie bemoeilijkt werd?	0	1	2	3	4	5

8.	U niet volledig meer in staat was de kost te verdienen?	0	1	2	3	4	5
9.	Het moeilijk voor u was om aan sport te doen of om zich aan uw hobbies of andere vrijetijdsbesteding te wijden?	0	1	2	3	4	5
10.	Uw seksuele activiteiten bemoeilijkt werden?	0	1	2	3	4	5
11.	U minder at van het voedsel dat u lekker vindt?	0	1	2	3	4	5
12.	U last had van kortademigheid?	0	1	2	3	4	5
13.	U moe of uitgeput was of weinig energie had?	0	1	2	3	4	5
14.	U in een ziekenhuis moest worden opgenomen?	0	1	2	3	4	5
15.	U kosten hebt moeten maken in verband met medische verzorging?	0	1	2	3	4	5
16.	U last had van bijwerkingen van medicijnen?	0	1	2	3	4	5
17.	U het gevoel had dat u uw familie of vrienden tot last was?	0	1	2	3	4	5
18.	U het gevoel had minder vat op uw leven te hebben?	0	1	2	3	4	5
19.	U zich ongerust maakte?	0	1	2	3	4	5
20.	U zich moeilijk kon concentreren of dingen kon onthouden?	0	1	2	3	4	5
21.	U zich depressief voelde?	0	1	2	3	4	5

9 Summary and discussion

Over the past decade our knowledge of the pathophysiology of heart failure has improved substantially due to intensive research. Traditionally, heart failure has been regarded as a mechanical disorder, but nowadays the development and progression of the syndrome is thought to result from a complex interplay of hemodynamic and neurohormonal factors. These enhanced insights into the pathophysiology of heart failure have led to the development of new methods that can be used for the assessment of specific aspects of heart failure. The aim of this thesis was to evaluate several of those recently developed methods from a clinical point of view. Amongst these are analysis of heart rate variability, measurement of cardiac peptides and Doppler echocardiographic assessment of left ventricular filling. In addition to these rather technical methods, attention is paid to assessment of quality of life in patients with chronic heart failure.

Heart rate variability

Analysis of heart rate variability is a non-invasive method to study the autonomic control of the heart. There are several methods to analyse heart rate variability: statistical and geometrical methods can be used to quantify the amount of overall variability in the time domain, whereas frequency domain analysis provides information on the amount of variability that can be attributed to sympathetic, parasympathetic or other physiological influences on the heart.[1,2] Previous studies have demonstrated a reduced heart rate variability in patients with heart failure.[3-6] Analysis of heart rate variability has also been used to assess the effect of medical therapy on autonomic abnormalities in heart failure patients.[7,8] In addition, several time-domain measures obtained from 24-hour electrocardiographic recordings have been shown to be related to the severity and the prognosis of heart failure.[6,9-14] Thus, analysis of heart rate variability could supply useful information in patients with heart failure. However, most methods used for the analysis of heart rate variability have the disadvantage that they require extensive editing of the electrocardiographic recordings to correct for ectopic beats, noise and signal loss.[1,15] This is not only difficult and time-consuming, but also often not feasible because of the frequent occurrence of ectopic beats in patients with heart failure. The heart rate variability index is a simple geometrical measure of heart rate variability that can be derived from only casually edited 24-hour electrocardiographic recordings.[16] Because of its robustness, this index overcomes the disadvantage of other heart rate variability measures. In **Chapter 2** the clinical and prognostic value of the heart rate variability index was evaluated in patients with chronic heart failure. This index was shown to be related to clinical parameters of severity of heart failure and to provide prognostic infor-

mation independent of and additive to conventional predictors of prognosis. Thus, it was concluded that the heart rate variability index, as simple and robust measure of heart rate variability, may be a useful tool in the clinical and prognostic assessment of chronic heart failure. Nevertheless, further studies in larger groups of patients are needed for a reliable assessment of its predictive value in clinical practice.

The role of heart rate variability in the early detection of heart failure has not been studied so far. Neurohormonal activation plays an important role in the development of heart failure, and both increased plasma concentrations of norepinephrine and cardiac peptides have been shown to be early markers of heart failure.[17-21] In **Chapter 3** the relationship between the heart rate variability index and neurohormonal activation in patients with asymptomatic or only mildly symptomatic left ventricular systolic dysfunction was studied. It was shown that the heart rate variability index was inversely related to plasma concentrations of norepinephrine and cardiac peptides. This suggests that analysis of heart rate variability, as a non-invasive measure of cardiac autonomic control, might be a useful tool in the early detection of heart failure and merits further investigations as such.

Cardiac peptides

Cardiac peptides are released from the myocardium in response to the wall stretch that occurs with increased filling pressures. Atrial natriuretic peptide and the N-terminal fragment of its prohormone (N-terminal pro-atrial natriuretic peptide) are mainly released from the atria, whereas brain natriuretic peptide (named after the place of first identification) and N-terminal pro-brain natriuretic peptide are also secreted by the ventricles.[22] Prior studies have shown that plasma concentrations of atrial natriuretic peptide and N-terminal pro-atrial natriuretic peptide reflect the severity of left ventricular systolic dysfunction and have prognostic value independent of measures of left ventricular systolic function.[19,23-25] In **Chapter 4** the relationship between atrial natriuretic peptide concentrations and echocardiographic measures of left ventricular systolic and diastolic function in patients with chronic heart failure was studied. As a reduced left ventricular ejection fraction as well as a restrictive left ventricular filling pattern are associated with increased atrial pressures, it was hypothesised that both measures of left ventricular function would be related to increased atrial natriuretic peptide concentrations. Indeed it was shown that both a reduced left ventricular ejection fraction and a restrictive left ventricular filling pattern were independently related to elevated plasma concentrations of atrial natriuretic pep-

tide and N-terminal pro-atrial natriuretic peptide. This proves that atrial natriuretic peptide concentrations provide information on left ventricular systolic as well as diastolic function and explains the additive value of measurement of atrial natriuretic peptides in the assessment of heart failure.

Atrial natriuretic peptide, N-terminal pro-atrial natriuretic peptide and brain natriuretic peptide have been demonstrated to reflect the presence of left ventricular dysfunction in an unselected population,[21] in patients referred for coronary angiography,[26,27] and in primary care patients suspected of heart failure.[20] In addition, high cardiac peptide concentrations in the subacute phase of myocardial infarction have been shown to identify patients with left ventricular systolic dysfunction and to predict morbidity and mortality.[25,28-34] The results of these studies imply that cardiac peptides may be of practical use in the detection of left ventricular dysfunction, especially after myocardial infarction, and in the diagnostic evaluation of suspected heart failure in primary care. However, it is not clear which peptide should be used in clinical practice. In several studies it has been shown that brain natriuretic peptide is a more accurate indicator of left ventricular systolic dysfunction and heart failure than N-terminal pro-atrial natriuretic peptide and atrial natriuretic peptide,[20,21,26,29] but in other studies N-terminal pro-atrial natriuretic peptide appeared to be a better marker for left ventricular dysfunction and early heart failure.[27,35] N-terminal pro-brain natriuretic peptide has only recently been identified.[36] Its clinical value has not been clarified yet, but its prognostic value after myocardial infarction and its high correlations with brain natriuretic peptide concentrations in patients with heart failure suggest that N-terminal pro-brain natriuretic peptide might have the same predictive qualities as brain natriuretic peptide.[34,37] Not only the diagnostic or prognostic accuracy of each peptide, but also the stability of the samples and the blood sampling conditions are important prerequisites for the use of cardiac peptides in clinical routine. Previous studies have demonstrated that, in contrast to what has been found for atrial natriuretic peptide, the *in vitro* stability of both N-terminal pro-atrial natriuretic peptide and brain natriuretic peptide is sufficiently high.[38-40] The stability of N-terminal pro-brain natriuretic peptide has not been studied so far. In **Chapter 5** the *in vivo* differences between atrial natriuretic peptide, N-terminal pro-atrial natriuretic peptide, brain natriuretic peptide and N-terminal pro-brain natriuretic peptide were investigated by comparing their responses to exercise. It was shown that both N-terminal peptides increased less in response to exercise than their C-terminal counterparts. This implies that the circumstances under which blood sampling for measurements of N-terminal pro-atrial natriuretic peptide and N-terminal pro-brain natriuretic peptide must take place are more favourable than the blood sampling conditions for atrial natriuretic peptide and brain natriuretic peptide. Thus, these re-

sults confirm the superiority of N-terminal pro-atrial natriuretic peptide for use in clinical practice and suggest that N-terminal pro-brain natriuretic peptide is a promising new tool in the assessment of heart failure.

Until now research interest has focused on the use of cardiac peptide measurements in the screening and diagnosis of patients at risk or suspected of heart failure. Knowledge of the potential value of cardiac peptides in the clinical and prognostic assessment of patients with chronic heart failure is hampered by the lack of data in unselected study populations. Cardiac peptide concentrations increase with renal impairment and higher age and will be decreased by treatments that lower cardiac filling pressures.[41,42] The potential influences of these confounding factors need to be investigated in unselected groups of patients with chronic heart failure. Furthermore, cardiac peptide measurements could be used to monitor the clinical course of heart failure and to optimise heart failure therapy in the individual patient. However, although cardiac peptides are markers of cardiac function, their reduction does not necessarily imply an improvement in cardiac function. New studies are needed to assess the clinical relevance of changes in cardiac peptide concentrations. Finally, more natriuretic peptides have been and will be identified.[43,44] Their potential role in the management of patients with heart failure remains to be investigated.

Assessment of left ventricular filling

Doppler recordings of mitral flow velocities can be used to assess left ventricular filling and diastolic function. Left ventricular filling abnormalities are common in patients with heart failure. In particular the presence of a restrictive filling pattern in patients with impaired left ventricular systolic function has been associated with more severe heart failure and a poor prognosis.[45-47] This is, directly and indirectly, confirmed by findings in this thesis: in **Chapter 2** patients with a restrictive left ventricular filling pattern had reduced heart rate variability and a worse prognosis, **Chapter 4** showed that these patients had higher plasma concentrations of atrial natriuretic peptide and N-terminal pro-atrial natriuretic peptide, and in **Chapter 6** there was a significant difference in exercise capacity between patients with a restrictive as opposed to a non-restrictive left ventricular filling pattern. In addition, others have demonstrated that the presence of a restrictive left ventricular filling pattern after an acute myocardial infarction is an independent predictor of heart failure and cardiac death.[48,49] Furthermore, left ventricular filling indices can be used to estimate left ventricular filling pressures.[45,50-54] Finally, recent studies have shown that the changes in left ventricular

filling patterns or related variables in response to varying loading conditions are related to changes in hemodynamics and can be used to improve the prognostic value of Doppler assessment of left ventricular filling in patients with heart failure.[55-58]

Despite these promising results, several pitfalls and limitations must be taken into account when interpreting left ventricular filling patterns. First, technically adequate recordings in patients with sinus rhythm are required. Second, left ventricular filling indices are sensitive to variations in heart rate, mitral regurgitation and loading conditions, and change with increasing age.[50,59-62] These confounding factors can partly be controlled for by using age-adjusted reference values, by reducing heart rate and by inducing loading manipulations.[57,59,63] Finally, pseudonormalisation of the left ventricular filling pattern complicates the Doppler echocardiographic assessment of left ventricular filling.[50] Pseudonormalisation occurs when an impaired relaxation pattern evolves towards restriction, reflecting the increase in filling pressures as heart failure progresses.[50] The Valsalva manoeuvre is one of the methods that is recommended to differentiate between normal and pseudonormal patterns.[64] However, since neither a standardised Valsalva manoeuvre nor a healthy control population has been studied, its clinical value is not clear. Therefore, we studied the changes in left ventricular filling indices in response to a standardised Valsalva manoeuvre in patients with heart failure and healthy control subjects. The results of this study are described in **Chapter 7**. All study subjects had comparable decreases in early mitral flow velocity, but mitral flow velocity at atrial contraction increased rather than decreased in patients with a restrictive left ventricular filling pattern. This markedly abnormal response might be useful in detecting elevated filling pressures and pseudonormal filling patterns. Furthermore, it was shown that in all but two of the patients and all healthy control subjects with an E/A ratio between 1 and 2 inversion of the E/A ratio occurred. This proves that, in contrast to previous beliefs, inversion of the E/A ratio does not differentiate between normal and pseudonormal left ventricular filling patterns. Nevertheless, other echocardiographic measurements, such as evaluation of pulmonary venous flow, can be used to identify patients with pseudonormalised filling patterns.[65]

Though care must be taken in the interpretation of Doppler left ventricular filling patterns, they add significantly to the clinical and prognostic assessment of patients with heart failure and left ventricular systolic dysfunction, and thus help to provide optimal therapy. Because Doppler assessment of left ventricular filling is highly dependent on systolic function,[66] the results from studies in patients with impaired left ventricular systolic function cannot be applied to patients with heart failure and normal systolic function (i.e. to patients with diastolic heart

failure). In fact, the significance of Doppler echocardiographic indices of left ventricular filling in the diagnosis of diastolic dysfunction in these patients is not clear at all.[67-69] Refinement of the currently used methods and clarification of the role of newer methods for the non-invasive assessment of left ventricular filling status is therefore needed.[65,70,71]

Assessment of quality of life

Chronic heart failure has a major impact on quality of life.[72,73] Symptoms, such as dyspnoea and fatigue, result in a significant reduction of functional capacity which in its turn often leads to reduced physical and emotional well-being and social problems. Assessment of the New York Heart Association class and objective measurements of exercise capacity are frequently used to monitor the clinical course of heart failure and the effect of its treatment. These methods, however, have certain shortcomings. It is the doctor who assesses the New York Heart Association class and not the patient. Furthermore, reliable assessment of the functional class is difficult because patients tend to alter their level of activity to minimise the occurrence of symptoms, and exercise tests reflect maximal or near maximal capacity rather than functional capacity.[74,75] It is likely that a method that gives a reliable and valid assessment of the effect of heart failure on quality of life would be of additive value in the assessment of heart failure and its treatment. The Minnesota Living with Heart Failure Questionnaire was designed specifically to meet this need.[76] This questionnaire does not provide a complete assessment of quality of life, but focuses on the patients' perceptions of how their heart failure prevented them from living as they wanted. The questionnaire has been shown to be useful in the USA.[77,78] However, before it can be used in respondents with a native language other than English its translation needs to be tested in the new context. In **Chapter 8** is described how the reliability and validity of the Dutch version of the Minnesota Living with Heart Failure Questionnaire has been evaluated. The questionnaire was translated and administered to 224 patients with chronic heart failure. Like in the original questionnaire, an emotional and a physical dimension could be identified. Both dimensions exhibited satisfactory levels of internal consistency and the test-retest reliability in stable patients who filled in the questionnaire twice within two weeks was high. Because there is no gold standard for quality of life in patients with heart failure, the validity of the questionnaire was investigated by testing its relationship to corresponding clinical and psychological measures of health status. The pattern of correlations between the emotional and physical dimensions of the questionnaire and these variables was in agreement with the hypothesis that dimensions that are conceptually related correlate better than un-

related dimensions. Therefore, it was concluded that the Dutch version of the Living with Heart Failure Questionnaire is a reliable and valid instrument when administered to patients with chronic heart failure. These results justify further research into the responsiveness of the questionnaire. Once its sensitivity to changes in health status has been determined, the Dutch version of the Living with Heart Failure Questionnaire can be used to monitor patients over time for clinical or research purposes.

Conclusions

Chronic heart failure is a complex syndrome: as such it is too simplistic to expect any single measure to provide an accurate assessment of heart failure. At present, measures of systolic function and functional capacity are used to assess the severity of heart failure due to left ventricular systolic dysfunction. The studies described in this thesis and other studies suggest that methods for the assessment of other aspects of heart failure, such as analysis of heart rate variability, measurement of cardiac peptides, Doppler echocardiographic assessment of left ventricular filling and assessment of quality of life may be of additive value in the clinical evaluation of these patients. Future studies will be needed to define the ultimate role of these new methods in clinical practice.

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10 Samenvatting

Gedurende de afgelopen tien jaar is de kennis van de pathofysiologie van hartfalen aanzienlijk toegenomen. Het inzicht dat zowel hemodynamische als neurohormonale factoren een belangrijke rol spelen bij de ontwikkeling en progressie van hartfalen heeft geleid tot de ontwikkeling van nieuwe methoden om specifieke aspecten van hartfalen te beoordelen. Dit proefschrift beschrijft de klinische evaluatie van verschillende van deze recent ontwikkelde methoden, waaronder de analyse van hartritmevariabiliteit, het meten van plasma concentraties van cardiale peptiden en de beoordeling van het linker ventrikel vullingspatroon met behulp van Doppler echocardiografie. Daarnaast wordt aandacht besteed aan het meten van kwaliteit van leven.

Hartritmevariabiliteit

Analyse van de variaties in tijdsduur tussen opeenvolgende hartslagen, oftewel analyse van de hartritmevariabiliteit, is een niet-invasieve methode om de autonome beïnvloeding van het hart te bestuderen. Er zijn verschillende manieren waarop de hartritmevariabiliteit geanalyseerd kan worden: voor de tijdsdomeinanalyse worden statistische en geometrische maten gebruikt om de totale hoeveelheid variabiliteit te kwantificeren, terwijl de frequentie-domeinanalyse inzicht verschaft in de hoeveelheid variabiliteit die kan worden toegeschreven aan sympathische, parasympathische of andere fysiologische invloeden op het hart. Eerdere onderzoeken hebben uitgewezen dat de hartritmevariabiliteit in patiënten met hartfalen verminderd is. Daarnaast zouden verschillende tijdsdomeinmaten klinisch bruikbare informatie verschaffen in patiënten met hartfalen. De meeste van deze maten hebben echter het nadeel dat de 24-uurs electrocardiografische opnamen waaruit zij berekend worden uitgebreid nagekeken en bewerkt moeten worden om te corrigeren voor ectopische slagen, ruis en signaalstoringen. Dit is niet alleen tijdrovend en moeilijk, maar ook praktisch gezien vaak niet haalbaar vanwege de vele ectopische slagen die patiënten met hartfalen hebben. De hartritmevariabiliteit index is een eenvoudige geometrische maat die kan worden berekend uit slechts oppervlakkig bewerkte 24-uurs opnamen. Deze robuuste maat zou daarom van praktisch nut kunnen zijn bij de beoordeling van patiënten met hartfalen. In **Hoofdstuk 2** werd de klinische en prognostische waarde van de hartritmevariabiliteit index in patiënten met chronisch hartfalen geëvalueerd. Aangetoond werd dat de hartritmevariabiliteit index is gerelateerd aan de ernst van het hartfalen en dat deze robuuste maat voor de hartritmevariabiliteit onafhankelijk van de mate van de pompfunctiestoornis een voorspellende waarde heeft bij patiënten met chronisch hartfalen.

De rol die de analyse van hartritmevariabiliteit bij de detectie van vroege vormen van hartfalen speelt is nog niet onderzocht. Neurohormonale activatie is een belangrijk aspect van de ontwikkeling van hartfalen, en zowel verhoogde plasma concentraties van noradrenaline als cardiale peptiden zijn aanwezig in een vroeg stadium van hartfalen. In **Hoofdstuk 3** werd het verband tussen de hartritmevariabiliteit index en neurohormonale activatie in patiënten met een asymptomatische of slechts licht symptomatische verminderde pompfunctie bestudeerd. Aangetoond werd dat de hartritmevariabiliteit index negatief was gecorreleerd aan de plasma concentraties van noradrenaline en verschillende cardiale peptiden. Dit suggereert dat de analyse van hartritmevariabiliteit, als niet-invasieve maat voor de autonome beïnvloeding van het hart, van nut zou kunnen zijn bij de vroege detectie van hartfalen.

Cardiale peptiden

Cardiale peptiden worden uitgescheiden door het hartspierweefsel wanneer bij toename van de vullingsdrukken de wandspanning stijgt. Atriaal natriuretisch peptide en het N-terminale fragment van het pro-atriaal natriuretisch peptide (N-terminaal pro-atriaal natriuretisch peptide) worden hoofdzakelijk uitgescheiden door de atria, terwijl het brein natriuretisch peptide (vernoemd naar de plaats waar het peptide voor het eerst geïdentificeerd werd) en het N-terminaal pro-brein natriuretisch peptide ook worden uitgescheiden door de ventrikels. Eerdere studies hebben aangetoond dat plasma concentraties van atriaal natriuretisch peptide en N-terminaal pro-atriaal natriuretisch peptide gerelateerd zijn aan de ernst van het hartfalen en onafhankelijk van de mate van pompfunctiestoornis van voorspellende waarde zijn bij patiënten met chronisch hartfalen. In **Hoofdstuk 4** werd het verband tussen plasma concentraties van atriaal natriuretische peptiden en de pomp- en vullingsfunctie van het hart bij patiënten met chronisch hartfalen bestudeerd. Omdat zowel een verminderde pompfunctie als een restrictief vullingspatroon geassocieerd zijn met verhoogde vullingsdrukken, werd verwacht dat beide aspecten van de hartfunctie gerelateerd zouden zijn aan verhoogde plasma concentraties van atriaal natriuretische peptiden. Aangetoond werd dat een verminderde linker ventrikel ejectie fractie en een restrictief vullingspatroon inderdaad onafhankelijk van elkaar verband hielden met verhoogde plasma concentraties van deze peptiden. Dit bewijst dat plasma concentraties van atriaal natriuretische peptiden informatie verschaffen over zowel de pomp- als de vullingsfunctie van het hart en verklaart de toegevoegde waarde van het meten van atriaal natriuretisch peptiden in patiënten met hartfalen.

Verschillende studies hebben het nut van het meten van cardiale peptiden voor de detectie en diagnose van hartfalen aangetoond. Het is echter niet duidelijk welk peptide gebruikt zou moeten worden in de praktijk. In meerdere studies is beschreven dat brein natriuretisch peptide een accuratere voorspeller van cardiale dysfunctie en hartfalen is dan atriaal natriuretisch peptide en het N-terminaal pro-atriaal natriuretisch peptide, maar uit sommige andere studies blijkt dat N-terminaal pro-atriaal natriuretisch peptide een betere marker voor de aanwezigheid van cardiale dysfunctie en hartfalen zou zijn. Daarnaast suggereren recente studies dat N-terminaal pro-brein natriuretisch peptide dezelfde goede diagnostische en prognostische eigenschappen zou kunnen hebben als brein natriuretisch peptide. Naast de verschillen in diagnostische en prognostische eigenschappen zijn de verschillen in stabiliteit tussen de peptiden van belang bij het vaststellen welk peptide het meest geschikt is voor gebruik in de praktijk. In **Hoofdstuk 5** werden de verschillen in *in vivo* stabiliteit tussen atriaal natriuretisch peptide, brein natriuretisch peptide en hun N-terminale tegenhangers onderzocht door hun veranderingen in respons op inspanning te vergelijken. Er werd aangetoond dat beide N-terminale peptiden stabieler waren dan de C-terminale peptide. Dit betekent dat de bloedafname voor meting van N-terminaal pro-atriaal natriuretisch peptide en N-terminaal pro-brein natriuretisch peptide minder gebonden is aan vaste condities dan bloedafname voor meting van atriaal natriuretisch peptide en brein natriuretisch peptide en suggereert dat de N-terminale peptiden beter geschikt zijn voor de praktijk.

Beoordeling van het linker ventrikel vullingspatroon

Doppler echocardiografische opnamen van de bloedstroomsnelheid over de mitralis klep kunnen worden gebruikt om de vullingsfunctie van het hart te beoordelen. In patiënten met hartfalen komen afwijkingen in de vullingsfunctie van het hart veelvuldig voor. Met name de aanwezigheid van een restrictief vullingspatroon in patiënten met een verminderde pompfunctie is gerelateerd aan verhoogde vullingsdrukken, ernstiger hartfalen en een slechtere prognose. Dit wordt direct en indirect bevestigd in dit proefschrift: in **Hoofdstuk 2** hadden patiënten met een restrictief vullingspatroon een lagere hartritmevariabiliteit index en een slechtere prognose, in **Hoofdstuk 4** hadden zij hogere plasmaconcentraties van atriaal natriuretisch peptide en N-terminaal pro-atriaal natriuretisch peptide, en in **Hoofdstuk 6** werd aangetoond dat deze patiënten een lagere inspanningstolerantie hebben in vergelijking met patiënten met een niet-restrictief vullingspatroon.

Er zijn diverse nadelen verbonden aan de Doppler echocardiografische beoordeling van het linker ventrikel vullingspatroon. Allereerst zijn adequate opnamen in patiënten met sinusritme vereist. Vervolgens dient rekening te worden gehouden met het feit dat Doppler parameters beïnvloed worden door leeftijd, hartfrequentie, mitralis klep insufficiëntie en voor- en nabelasting van het hart. Tenslotte kan de beoordeling van het vullingspatroon bemoeilijkt worden door pseudonormalisatie. Pseudonormalisatie treedt op wanneer het patroon dat past bij verminderde relaxatie van de linker ventrikel zich ontwikkelt in de richting van een restrictief patroon. De Valsalva manoeuvre wordt beschouwd als één van de methoden waarmee onderscheid gemaakt kan worden tussen normale en pseudonormale patronen. Omdat echter nooit gebruik is gemaakt van een gestandaardiseerde Valsalva manoeuvre en geen controle populatie is onderzocht, is de klinische toepasbaarheid van deze methode nog niet duidelijk. In **Hoofdstuk 7** werden de veranderingen in Doppler parameters in respons op een gestandaardiseerde Valsalva manoeuvre in patiënten met hartfalen en in een gezonde controlegroep bestudeerd. Alle deelnemers aan het onderzoek vertoonden een vergelijkbare afname van de bloedstroomsnelheid in het vroege deel van de vulling van de linker ventrikel, maar de bloedstroomsnelheid in het late deel van de vulling steeg in plaats van daalde in patiënten met een restrictief vullingspatroon. Deze abnormale respons op de Valsalva manoeuvre zou van nut kunnen zijn bij de detectie van verhoogde vullingsdrukken en pseudonormale vullingspatronen. Daarnaast werd gevonden dat in alle behalve twee patiënten en alle controle deelnemers met een E/A ratio tussen de 1 en 2 omkering van de E/A ratio optrad. Dit toont aan dat, in tegenstelling tot wat tot nu gedacht werd, omkering van de E/A ratio geen onderscheid kan maken tussen normale en pseudonormale vullingspatronen.

Kwaliteit van leven

Chronisch hartfalen heeft een grote impact op de kwaliteit van leven van de patiënt. Een betrouwbare en valide methode om de invloed van hartfalen op de kwaliteit van leven te meten zou van nut kunnen zijn bij de beoordeling van hartfalen en het effect van de behandeling ervan. De Minnesota Living with Heart Failure Questionnaire is speciaal hiervoor ontwikkeld en wordt sinds enige jaren in de Verenigde Staten toegepast. Om hier ook in Nederland gebruik van te kunnen maken is niet alleen vertaling van de vragen noodzakelijk, maar dient de vragenlijst tevens uitgebreid getest te worden in de nieuwe context. **Hoofdstuk 8** beschrijft hoe de betrouwbaarheid en validiteit van de Nederlandse versie van de Minnesota Living with Heart Failure Questionnaire werd

geëvalueerd. De vragenlijst werd vertaald, aangepast en voorgelegd aan 224 patiënten met chronisch hartfalen. Net als in de oorspronkelijke vragenlijst konden een emotionele en fysieke dimensie worden onderscheiden. De interne consistentie en test-hertest betrouwbaarheid van beide dimensies waren hoog. Omdat er geen gouden standaard voor de kwaliteit van leven bestaat werd de validiteit van de vragenlijst getest door de twee dimensies te relateren aan corresponderende klinische en psychologische variabelen. Het patroon van correlaties tussen de Minnesota vragenlijst en deze variabelen was in overeenstemming met de hypothese dat conceptueel gerelateerde dimensies beter met elkaar correleren dan niet gerelateerde dimensies. Daarom werd geconcludeerd dat de Nederlandse versie van de Minnesota Living with Heart Failure Questionnaire een betrouwbaar en valide instrument is om kwaliteit van leven te meten in patiënten met chronisch hartfalen.

Conclusies

Chronisch hartfalen is een dusdanig complexe aandoening dat niet verwacht kan worden dat één enkele maat volstaat bij de beoordeling ervan. Tot op heden wordt hartfalen ten gevolge van een pompfunctiestoornis van de linker ventrikel voornamelijk beoordeeld op grond van de mate van de pompfunctiestoornis en de functionele capaciteit van de patiënt. Uit verschillende studies, waaronder die beschreven in dit proefschrift, blijkt dat methoden die zich richten op andere aspecten van hartfalen, zoals analyse van de hartritmevariabiliteit, het meten van plasmaconcentraties van cardiale peptiden, het beoordelen van de vullingsfunctie van de linker ventrikel en het meten van kwaliteit van leven, van toegevoegde waarde kunnen zijn bij de klinische evaluatie van deze patiënten. Meer onderzoek is nodig om te kunnen bepalen wat de uiteindelijke plaats van deze nieuwe methoden in de praktijk zal zijn.

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Curriculum vitae

Anke Wijbenga werd op 29 april 1967 geboren te Papendrecht. Na het behalen van het VWO diploma aan de Rijksscholengemeenschap Oud Beijerland in 1985 startte zij met de studie Scheikunde aan de Rijksuniversiteit Leiden. In 1986 werd de overstap gemaakt naar de studie Geneeskunde aan de Erasmus Universiteit in Rotterdam. Tijdens deze studie werkte zij in het studententeam van de afdeling Medium Care van het Hartcentrum Rotterdam en deed zij, onder begeleiding van dr. A.H.M.M. Balk, onderzoek naar de resultaten van reconstructieve chirurgische ingrepen bij patiënten die verwezen werden voor harttransplantatie. Na het behalen van het artsexamen in juli 1994 werkte zij als onderzoeker in opleiding bij het Hartcentrum Rotterdam en de vakgroep Medische Informatica van de Erasmus Universiteit Rotterdam (promotoren Prof. dr. M.L. Simoons en Prof. dr. ir. J.H. van Bemmel). Van september tot en met december 1997 bracht zij een werkbezoek aan de St. George's Hospital Medical School te Londen om ervaring op te doen met de analyse van heart rate variability (Prof. M. Malik). In januari 1999 is zij begonnen als assistent geneeskundige op de afdeling Interne Geneeskunde van het St. Clara Ziekenhuis te Rotterdam (opleider dr. A.F. Grootendorst), als onderdeel van de opleiding tot cardioloog welke vanaf juli 2001 zal worden voorgezet in het Hartcentrum Rotterdam (opleider Prof. dr. J.R.T.C. Roelandt).

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