Autonomic dysfunction in patients with mild heart failure and coronary artery disease and the effects of add-on β-blockade

ARTICLE *in* EUROPEAN JOURNAL OF HEART FAILURE · JANUARY 2001

Impact Factor: 6.53 · DOI: 10.1016/S1388-9842(00)00119-7 · Source: PubMed

ELSEVIER

European Journal of Heart Failure 3 (2001) 33–39

The European Journal of Heart Failure

www.elsevier.com/locate/heafai

Autonomic dysfunction in patients with mild heart failure and coronary artery disease and the effects of add-on β-blockade

Geert Tjeerdsma[a], Balázs M. Szabó[a], Leen M. van Wijk[b], Jan Brouwer[a], René A. Tio[a], Harry J.G.M. Crijns[a], Dirk J. van Veldhuisen[a,*,1]

[a]*Department of Cardiology / Thoraxcenter, University Hospital Groningen, P.O. Box 30 001, 9700 RB Groningen, The Netherlands*
[b]*Department of Cardiology, Refaja Hospital, Stadskanaal, The Netherlands*

Received 7 April 2000; received in revised form 11 July 2000; accepted 16 August 2000

Abstract

Aim: Autonomic impairment is related to the incidence of sudden death in chronic heart failure (CHF). Our objective was to study autonomic profiles in patients with mild CHF due to coronary artery disease, and to investigate the value of add-on β-blockade. *Methods and results:* Measures of autonomic function (plasma norepinephrine, heart rate [HR] variability, autonomic function testing), and exercise capacity, were compared between 24 patients with mild CHF, and 24 healthy controls. In this mechanistic study, we assessed the effect of 26 weeks metoprolol treatment in a double-blind, randomized, placebo-controlled design. All patients received metoprolol sustained release (200 mg; $n = 12$) or placebo ($n = 12$). Assessments were made at baseline and after 10 and 26 weeks' treatment. At baseline, norepinephrine levels were elevated, while HR variability parameters were decreased in patients vs. controls (both $P < 0.05$). Autonomic function testing showed only small differences, although significant alterations were observed with deep breathing and head up tilting (both $P < 0.05$). After 26 weeks', metoprolol did not affect exercise capacity or norepinephrine concentrations. In contrast, HR variability was markedly improved in metoprolol-treated patients vs. placebo-treated patients ($P < 0.05$). In particular, a shift toward normal in the sympathovagal balance was observed ($P < 0.05$). Autonomic function testing showed only small, and generally non-significant trends after metoprolol. *Conclusions:* Marked autonomic abnormalities are already present in mild CHF, which may be (partially) reversed by metoprolol. These observations support the reported reduction of sudden death by β-blockade in patients with CHF.

Keywords: Beta-Adrenergic receptor blockers; Autonomic failure; Heart rate variability

1. Introduction

Neurohormonal activation and autonomic dysfunction are hallmarks of chronic heart failure (CHF) and the severity of these changes is correlated with the severity and prognosis of this syndrome [1,2]. Experimental [3] and clinical studies [4] suggest that autonomic abnormalities occur already in the early stages of CHF, but only few data are available on this issue. These autonomic abnormalities are clinically relevant, as they have been associated with the occurrence of sudden cardiac death [5,6]. Angiotensin converting enzyme (ACE) inhibitors have become a cornerstone in the treatment of CHF, but despite their success, total mortality and the incidence of sudden

* Corresponding author. Tel.: +31-50-361-2355; fax: +31-50-361-4391.
E-mail address: d.j.van.veldhuisen@thorax.azg.nl (D.J. van Veldhuisen).
[1] Dr. Van Veldhuisen is a Clinical Established Investigator of the Netherlands Heart Foundation.

1388-9842/01/$20.00
PII: S1388-9842(00)00119-7

cardiac death remain high. In the last few years, several large-scale trials with β-blockers have shown that these drugs may reduce sudden cardiac death and total mortality in CHF [7–9]. It has been suggested that this beneficial effect may be due to an improvement in autonomic tone [10]. The purpose of the present mechanistic study was, therefore, to examine autonomic function in patients with mild CHF and coronary artery disease, and to compare them with healthy controls. In addition, we examined the effects of add-on β-blockade with metoprolol during prolonged (26 weeks) treatment.

2. Methods

2.1. Study design

The present study consisted of two parts: in the first we compared autonomic function in patients with mild (New York Heart Association functional class II) CHF, with their age- and sex-matched controls. In the second part, we conducted a randomized, double-blind, parallel group comparison of metoprolol and placebo. The drug intervention study consisted of a single-blind placebo run-in period of 1 week, and a double-blind treatment period of 26 weeks. The study was approved by the local ethics committee and conforms with the principles outlined in the Declaration of Helsinki (*British Medical Journal* 1964;ii:177).

Prior to the start of the double-blind treatment protocol, severity of CHF and clinical stability were confirmed by evaluation of CHF symptoms, and by a screening treadmill exercise test, including peak VO_2 measurement. At baseline, peak VO_2 testing was repeated, and this test was taken as baseline value. At baseline, blood samples for plasma norepinephrine concentrations were taken for patients and healthy controls. In addition, a 24-h ambulatory electrocardiogram was recorded for analysis of HR variability, and non-invasive autonomic function testing (Ewing battery) [11] was performed in both groups. Subsequent visits were planned at 2, 4, 6, 10, 18 and 26 weeks. Patients were started on 25 mg metoprolol sustained release (SR); the first dose was given in the out-patient clinic, and HR and blood pressure were monitored for 2 h. After 2 weeks, the dose was doubled to 50 mg SR, followed by an increase to 100 mg at 4 weeks, and to 200 mg metoprolol after 6 weeks. The dose was not increased if systolic blood pressure was < 90 mmHg, heart rate was < 50 bpm, or clinical signs and symptoms did not allow further uptitration.

After 10 weeks of treatment and at the end of the study (26 weeks) all measurements of the baseline visit were repeated. Progression of CHF requiring hospitalization, symptomatic hypotension requiring discontinuation, or intolerable side effects were predefined withdrawal criteria during the study period.

2.2. Patients

Patients > 18 years, with clinically stable, mild CHF (New York Heart Association functional class II), due to old myocardial infarction (> 3 months ago) were eligible for the study. Patients had to be clinically stable on oral CHF medication, which had to include an ACE inhibitor, for at least 3 months. Concomitant use of digoxin or calcium antagonists was not allowed. Left ventricular ejection fraction had to be < 0.40, and peak $VO_2 < 80\%$ of the age predicted value [12] with a maximal upper limit of 25 ml/min per kg. Exercise tolerance had to be limited by fatigue or dyspnea, and patients had to be in sinus rhythm. Exercise limiting angina pectoris, and hemodynamically significant valvular dysfunction, or any other contraindication for β-blocker treatment (including chronic obstructive pulmonary disease, bradycardia (< 60 bpm), sick sinus syndrome, 2nd or 3rd grade AV-block, hypotension (systolic pressure < 110 mmHg) were exclusion criteria.

For comparison of autonomic function in the patients with CHF, healthy subjects were also studied. No abnormalities were allowed on routine physical examination, standard electrocardiography and exercise testing. Within 1 month before participation, use of drugs was not permitted.

2.3. Exercise testing

Peak VO_2 was determined during symptom limited treadmill exercise testing, using the modified Naughton protocol, as previously described in detail [13]. Oxygen consumption, carbon dioxide production and the respiratory exchange ratio were measured continuously during the test using an automated gas exchange measuring system (Sensormedics system 2900, Sensormedics Corp., Anaheim, California). Patients were familiar with treadmill exercise testing and were encouraged to continue exercise until symptoms forced them to stop, and the gas exchange anaerobic threshold and a respiratory exchange ratio > 1.0 were reached. Peak VO_2 was calculated as the mean of the oxygen consumption values obtained during the last minute of exercise.

2.4. Plasma norepinephrine

For the purpose of neurohormonal blood sampling, an intravenous, indwelling antecubital cannula was inserted. After 30 min of supine rest blood samples for resting plasma norepinephrine were drawn. Blood specimens were centrifuged immediately and the

plasma was separated. Plasma norepinephrine was measured using high-performance liquid chromatography with electrochemical detection [14].

2.5. Heart rate variability analysis

Ambulatory 24 h ECGs were recorded using Marquette 3 channel AM recorders (8500 series, Laser System, Marquette Electronics Inc., Milwaukee, Wisconsin). HR variability was analyzed with a Holter analysis system (Marquette Series 8000) by one single analyst. Recordings with more than 15% of noise or ectopic beats were excluded from the HR variability analysis. After classification of the QRS morphology, both time domain and frequency domain HR variability parameters were calculated, employing only normal to normal intervals. Time domain HR variability parameters included mean RR interval (mean NN), standard deviation of mean RR interval (SDNN) and the root mean square of successive difference (rMSSD). These parameters are considered to be mainly under vagal control [15]. The average value of the interval series was subtracted before spectral analysis was performed using a discrete Fourier transformation algorithm. Frequency domain parameters included total power (TP), low frequency power (LF) and high frequency power (HF). The low frequency component is influenced by sympathetic and parasympathetic control mechanisms, whereas the high frequency component is almost exclusively under vagal control. The power of LF and HF was computed in both absolute (ms^2) and normalized units (nu). Finally, LF/HF ratio, was calculated, which is considered a measure of sympathovagal balance [15].

2.6. Autonomic function testing

A series of autonomic function tests (sympathetic, parasympathetic or combined), based on cardio-vascular reflexes, the so-called Ewing battery [11] was performed as described earlier in detail [16]. Before the tests no caffeine-containing beverages/foods or tobacco was permitted.

2.6.1. Deep breathing (parasympathetic)

The maximum heart rate during each breath during deep inspiration and expiration six times in 1 min was recorded. The mean of six breaths was used to calculate the ratio between in- and expiratory heart rate.

2.6.2. Valsalva manoeuvre (parasympathetic)

The ratio between the highest heart rate during 15 s Valsalva manoeuvre, and the lowest heart rate afterwards during normal breathing. This manoeuvre was performed twice, and the mean of the two Valsalva ratios was calculated.

2.6.3. Cold pressor test (sympathetic)

The hand of the patient was put in iced water for 3 min. The increase of heart rate and mean arterial blood pressure during this period was calculated.

2.6.4. Mental stress test (sympathetic)

Increase of heart frequency and blood pressure during repeated difficult subtractions, keeping the patient under constant strain.

2.6.5. Isometric handgrip test (combined parasympathetic and sympathetic)

The increase of heart rate and diastolic blood pressure during a 3-min handgrip held at 30% of the previously established maximum force of the patient.

2.6.6. Head up tilting (combined parasympathetic and sympathetic)

Decrease of blood pressure after tilting of the bed to 80 grade upright position. The tilting was performed twice, first for 2 min, and the second time for 10 min.

2.6.7. Standing up (combined parasympathetic and sympathetic)

Patients were instructed to stand up from the bed. The 30/15 ratio was computed (ratio between the highest and lowest heart rate after standing up), and the difference in systolic blood pressure between standing up and the supine position immediately preceding standing was computed.

2.7. Statistical analysis

To achieve a study power of 80% power analysis was performed on primary endpoints (changes in peak VO_2, exercise time, plasma (nor)epinephrine, HR variability and Ewing battery score). Differences in the autonomic parameters between patients with mild CHF and the control group were compared by unpaired *t*-test. The distribution of all variables at baseline and at the endpoint evaluation was compared with analysis of variance and *t*-test. Statistical differences of $P < 0.05$ were considered statistically significant.

3. Results

3.1. Patient characteristics

Baseline characteristics of the two CHF groups (placebo and metoprolol) are presented in Table 1; the two groups were generally well-matched, although age was slightly higher in the metoprolol group ($P =$ NS). The age and gender of the overall CHF group

and the healthy controls was identical. Of the 24 CHF patients, who entered the treatment protocol, 18 finished the study (metoprolol: $n = 8$, placebo: $n = 10$). One patient in the metoprolol arm died suddenly 24 weeks after study inclusion (no autopsy). Of the other five patients, three dropped out due to progressive CHF (metoprolol $n = 2$, both after > 10 weeks treatment, placebo $n = 1$, after 8 weeks study treatment), and one patient developed skin allergy to the study drug (metoprolol). In addition, one patient in the placebo group used prohibited medication at baseline (haloperidol). All these exclusions were made prior to unblinding of the data. The maximum tolerated dose for all eight patients treated with metoprolol was 200 mg/day. After 26 weeks of treatment heart rate decreased in the metoprolol group [78 (11) vs. 67 (eight), $P < 0.05$] without any effect in the placebo group [74 (11) vs. 74 (nine)]. Finally, both systolic and diastolic blood pressure were not effected after 26 weeks of treatment, although a slight but not significant decrease was observed in the metoprolol group [133 (13) vs. 126 (13)].

3.2. Exercise parameters

Compared with the healthy control group, patients had lower exercise time [882 (221) vs. 1128 (186) seconds] and lower peak VO_2 [17.4 (3.5) vs. 37.5 (8.1)] at baseline (both $P < 0.05$). Metoprolol neither affected exercise time, nor peak VO_2 after 10 and 26 weeks of treatment, compared with placebo (Fig. 1). Peak heart rate during exercise was calculated before and after treatment. Before treatment no differences for peak heart rate during exercise were observed between the placebo and the metoprolol group [140 (18) and 148 (23) beats per minute (bpm), respectively]. In contrast, peak heart rate was decreased in the metoprolol group [125 (21) bpm] compared with the placebo group [146 (22) bpm] after starting treatment, ($P < 0.05$ between both groups).

3.3. Plasma norepinephrine

At baseline, resting plasma norepinephrine and epinephrine levels were elevated in CHF patients, as compared with the healthy control group [472 (230) pg/ml vs. 223 (97) and 189 (45) pg/ml vs. 38 (six), both $P < 0.05$]. After 10 and 26 weeks, metoprolol did not affect plasma neurohormone levels.

3.4. Heart rate variability analysis

Results are presented in Table 2 and Fig. 2. At baseline, HR variability parameters were generally depressed ($P < 0.05$), as compared with the healthy control group. Within the CHF group, baseline HRV variables were well-matched between the two treatment groups. After 26 weeks of metoprolol treatment, all HR variability parameters were affected, although this effect did not reach statistical significance for SDNN and TP. In general, a shift toward higher parasympathetic and lower sympathetic activity was observed.

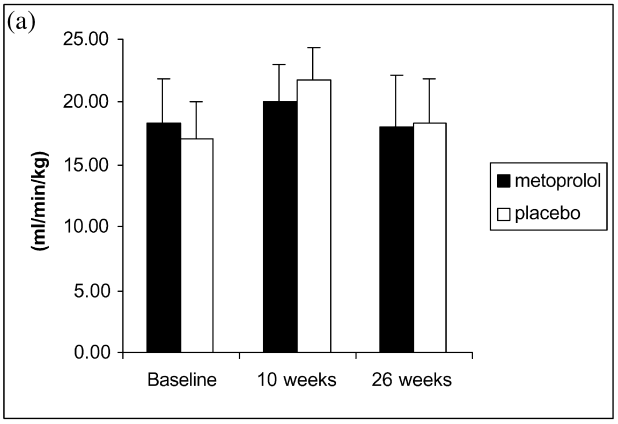
3.5. Ewing battery

At baseline, of the parasympathetically mediated autonomic tests, heart rate response to deep breath-

Table 1
Baseline characteristics of healthy controls and patients with mild heart failure (metoprolol vs. placebo)[a]

	Healthy controls	CHF group	
		Metoprolol	Placebo
Age (years)	57 (8)	61 (8)	54 (8)
Sex (male/female)	18/6	9/3	9/3
Localization prior myocardial infarction			
Anterior/inferior-posterior		9/3	6/6
Time since myocardial infarction [months]		41 (15)	49 (14)
Concomitant medication			
Angiotensin converting enzyme inhibitors		12	12
Diuretics		6	7
Vasodilators		4	2
Blood pressure (mmHg)			
Systolic		133 (13)	134 (13)
Diastolic		77(6)	84 (5)
Heart rate (bpm)		78 (11)	74 (11)
Left ventricular ejection fraction		0.28 (0.06)	0.27 (0.06)
Exercise time (seconds)	1128 (186)	887 (202)	857 (239)
Peak VO_2 absolute value(ml/min kg)	37.5 (8.1)	19.5 (3.6)	21.9 (2.9)
% of normal	103.3 (6)	73 (13)	73 (10)
Resting plasma norepinephrine (pg/ml)	223 (97)	452 (193)	492 (293)

[a] Values are presented as mean (S.D.), or number of subjects, as appropriate.



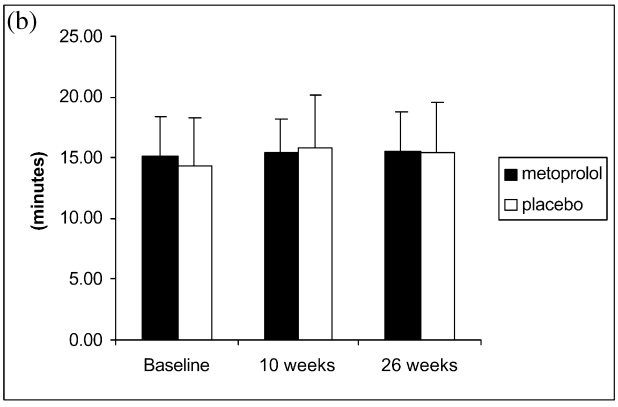


Fig. 1. (a) Changes of peak VO_2 (ml/min per kg) and (b) exercise time (min) after 26 weeks' study treatment (per protocol analysis). Data are presented as mean ± 95% CI.

ing was significantly depressed in the CHF group ($P < 0.05$ vs. controls), while of the combined sympathetically and parasympathetically affected parameters blood pressure response to head up tilt testing was strongly elevated ($P < 0.05$ vs. controls). In the treatment (CHF) study, there were no statistically significant baseline differences between the metoprolol and the placebo groups.

Deep breathing, Valsalva manoeuvre, mental arrhythmic test, head up tilting and standing up test were all unaffected by 26 weeks' metoprolol treatment.

3.5.1. Cold pressor test

In metoprolol-treated patients, the HR increase after 3 min was reduced, as compared with placebo (−12 vs. +1 bpm, $P < 0.05$), after 26 weeks' treatment.

3.5.2. Isometric handgrip test

After 26 weeks' treatment, metoprolol caused a stronger reduction of HR response than placebo (−12 vs. +1 bpm, $P < 0.05$), while blood pressure remained unaffected (−6 vs. −2 mmHg).

4. Discussion

There is increasing awareness, that drug treatment in patients with CHF must have a favorable, or at least a neutral, effect on autonomic function, since autonomic dysfunction is significantly related to the incidence of sudden death [5,6,17]. The main findings of the present study are that, even in patients with only mild CHF, autonomic function is already markedly disturbed, but that treatment with the β-blocker metoprolol improves this disturbance of autonomic tone. Given the fact, that recent large-scale trials with β-blockers in patients with CHF have shown

Table 2
HRV parameters for patients (at baseline and after 26 weeks treatment with metoprolol or placebo) and healthy controls[a]

Parameter	Healthy controls	CHF — all patients Baseline	6 months treatment (changes vs. baseline)	
			Placebo	Metoprolol
Time domain parameters				
Mean NN (ms)	856 (18)	786 (21)**	+24	+139#
SDNN (ms)	157 (8)	137 (6.5)*	+5	−2
rMSSD (ms)	31.3 (2.6)	8.0 (2.2)*	+0.6	+2.9##
Frequency domain parameters				
TP (ms^2)	4107 (494)	2726 (257)	+415	+991
LF (ms^2)	957 (101)	508 (76)**	−36	+112##
HF (ms^2)	365 (66)	173 (21)**	−25	+48##
LFnu (%)	75 (2)	69 (2)**	+1	−4##
HFnu (%)	25 (8)	30 (3)**	0	+4##
LF/HF ratio	4.6 (0.4)	3.6 (0.4)**	−0.1	−1.0##

[a]Values expressed as mean (S.D.). *$P < 0.005$, **$P < 0.05$, both CHF vs. healthy controls: #$P < 0.005$, ##$P < 0.05$, both metoprolol vs. placebo treatment in CHF patients. Mean NN, mean RR interval; SDNN, standard deviation of mean RR interval; rMSSD, root mean square of successive difference; TP, total power; LF, low frequency power; HF, high frequency power.

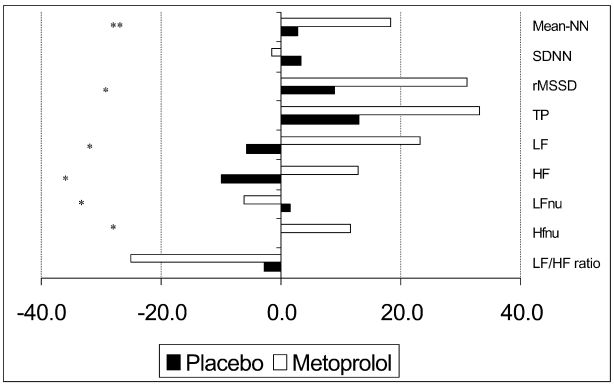


Fig. 2. Change in time domain and frequency domain parameters of heart rate variability after 26 weeks' of treatment, expressed as percent of baseline values. $^{*}P < 0.05$, $^{**}P < 0.005$, metoprolol vs. placebo group.

a marked reduction of all-cause mortality, but also of the incidence of sudden death [7–9], the present small mechanistic study may provide further insight into possible mechanisms involved. As such, these findings support recent other data, which have examined the mechanistic effects of β-blockers in CHF [10].

ACE inhibitors have been shown to markedly reduce morbidity and total mortality in patients with CHF [18], but the incidence of sudden death was unaffected. Still, sudden death accounts for a large proportion of deaths in patients with early CHF [8]. Since sudden death in these patients is particularly devastating, identification of such patients is important [19]. Left ventricular dysfunction, caused by coronary artery disease remains the most common underlying disorder in CHF. Therefore, in the present study the effects of metoprolol on exercise parameters and measures of autonomic function (serum norepinephrine, HR variability and autonomic function tests) were investigated in homogeneous population of post-myocardial patients with stable mild CHF. At baseline, plasma norepinephrine concentrations and HR variability parameters showed marked signs of disturbed autonomic balance, with signs of sympathetic activation and parasympathetic depression. Plasma norepinephrine was not helpful in this small population to evaluate drug effects. This may be related to the fact, that a single measurement is subject to considerable bias, particularly in patients with mild CHF, and for this reason may be less sensitive in these patients than the use of a more stable parameter like HR variability [6]. HR variability parameters were significantly affected by metoprolol in this study, and may thus be used to examine drug effects in these patients. Metoprolol caused a shift in autonomic balance, as it increased parasympathetic power, and reduced sympathetic power. Both components have been related to a vulnerable autonomic profile, and the changes induced by metoprolol in this study may thus be interpreted as a protective mechanism against the incidence of sudden death. Further, they are in line with earlier studies in CHF, in which similar autonomic effects of β-blockade in patients with ischemic heart disease were observed [20,21]. Autonomic function testing, using the Ewing battery did not provide additional information in this study. Given the fact, that this technique is rather time-consuming and expensive, the clinical value appears rather small to assess autonomic changes.

Exercise time and peak VO_2 were not improved after 10 and 26 weeks in the present study. This may be related to the fact that the number of patients in this study was rather small, and follow-up was only 26 weeks. Still, several other studies have also shown less pronounced results of exercise parameters by β-blockade in patients with mild CHF [22]. However, during long-term treatment, a favorable effect on the progression of disease, as shown in several studies, will most likely also translate into a beneficial effect on clinical parameters, such as exercise capacity. It may thus be speculated, that in the first period after treatment initiation, β-blockade is more effective in reducing the risk profile, than by affecting quality of life in patients with CHF.

Acknowledgements

We would like to thank Jaap Haaksma for technical assistance in the analysis of HR variability data and Pieter J. de Kam for statistical assistance and Andries Smit for supervising the autonomic function test. This study was supported by a grant from Astra Pharmaceutica BV, Zoetermeer, The Netherlands.

References

[1] Richards AM, Nicholls MG, Yandle et al. Neuroendocrine prediction of left ventricular function and heart failure after acute myocardial infarction. The Christchurch Cardioendocrine Research Group. Heart 1999;81:114–120.
[2] Nolan J, Batin PD, Andrews R et al. Prospective study of heart rate variability and mortality in chronic heart failure: results of the united kingdom heart failure evaluation and assessment of risk trial (UK-heart). Circulation 1998; 98:1510–1516.
[3] Eaton GM, Cody RJ, Nunziata E, Binkley PF. Early left ventricular dysfunction elicits activation of sympathetic drive and attenuation of parasympathetic tone in the paced canine model of congestive heart failure. Circulation 1995;92: 555–561.
[4] Grassi G, Seravalle G, Cattaneo BM et al. Sympathetic activation and loss of reflex sympathetic control in mild congestive heart failure. Circulation 1995;92:3206–3211.
[5] Barr CS, Naas A, Freeman M, Lang CC, Struthers AD. QT dispersion and sudden unexpected death in chronic heart failure. Lancet 1994;343:327–329.

[6] Brouwer J, Van Veldhuisen DJ, Man in't Veld AJ et al. Prognostic value of heart rate variability during long-term follow-up in patients with mild to moderate heart failure. The Dutch Ibopamine Multicenter Trial Study Group. J Am Coll Cardiol 1996;28:1183–1189.
[7] CIBIS Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet 1999;353:9–13.
[8] MERIT-HF study group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999;353:2001–2007.
[9] Spargias KS, Hall AS, Greenwood DC, Ball SG. Beta blocker treatment and other prognostic variables in patients with clinical evidence of heart failure after acute myocardial infarction: evidence from the AIRE study. Heart 1999;81:25–32.
[10] Sanderson JE, Yeung LY, Chan S et al. Effect of beta-blockade on baroreceptor and autonomic function in heart failure. Clin Sci 1999;96:137–146.
[11] Rodrigues EA, Ewing DJ. Immediate heart rate response to lying down: simple test for cardiac parasympathetic damage in diabetics. Br Med J 1983;287:800.
[12] Bruce RA, Kusumi F, Hosmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. Am Heart J 1973;85:546–562.
[13] Patterson JA, Naughton J, Pietras RJ, Gunnar RM. Treadmill exercise in assessment of the functional capacity of patients with cardiac disease. Am J Cardiol 1972;30:757–762.
[14] Smedes F, Kraak JC, Poppe H. Simple and fast solvent extraction system for selective and quantitative isolation of adrenaline, noradrenaline and dopamine from plasma and urine. J Chromatogr 1982;231:25–39.
[15] Tjeerdsma G, Meinardi MT, van den Berg MP, Mulder NH, Crijns HJGM, Van Veldhuisen DJ. Early detection of anthracycline-induced cardiotoxicity in asymptomatic patients with normal left ventricular systolic function; autonomic versus echocardiographic parameters. Heart 1999;81:419–423.
[16] Imai Y, Abe K, Munakata M et al. Circadian blood pressure variations under different pathophysiological conditions. J Hypertens Suppl 1990;8:S125–S132.
[17] Packer M. The neurohormonal hypothesis: a theory to explain the mechanism of disease progression in heart failure. J Am Coll Cardiol 1992;20:248–254.
[18] The SOLVD investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 1992;327:685–691.
[19] Goldman S, Johnson G, Cohn , Cintron G, Smith R, Francis GS. Mechanism of death in heart failure. The Vasodilator-Heart Failure Trials. The V-HeFT VA Cooperative Studies Group. Circulation 1993;87:VI24–VI31.
[20] Tuininga YS, Van Veldhuisen DJ, Brouwer J et al. Heart rate variability in left ventricular dysfunction and heart failure: effects and implications of drug treatment. Br Heart J 1994;72:509–513.
[21] Pousset F, Copie X, Lechat P et al. Effects of bisoprolol on heart rate variability in heart failure. Am J Cardiol 1996;77:612–617.
[22] MacMahon S, Sharpe N, Doughty R. Randomised, placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischaemic heart failure. Lancet 1997;349:375–380.