ORIGINAL ARTICLE

Comprehensive rehabilitation in chronic heart failure - Better psycho-emotional status related to quality of life, brain natriuretic peptide concentrations, and clinical severity of disease

Kurt Laederach-Hofmann¹, MD
Rebecca Rohrer-Gübeli¹, MD
Nadine Messerli^{1,3}, PhD
Katharina Meyer², PhD, MPH

¹Department of General Internal Medicine, Psychiatric Out-Patient Clinic, Autonomic Laboratory, Inselspital, University of Berne, Switzerland

²Swiss Health Observatory Neuchâtel, and Department of Medicine, University of Berne, Switzerland

³Institute of Psychology, Faculty of Human Sciences, University of Berne, Switzerland

Manuscript submitted 14th November, 2006

Manuscript accepted 28th December, 2006

Clin Invest Med 2007; 30 (2): E54-E62.

Abstract

Purpose: To evaluate the effects of a comprehensive out-patient rehabilitation program in chronic heart failure (CHF) on quality of life (QoL) in relation to emotional status and clinical severity of disease.

Patients and Methods: 25 patients with CHF were included in the 12-week comprehensive rehabilitation program. Initially, and at the end of the program, patients underwent graded cardio-pulmonary exercise testing, echocardiography, and determination of brain natriuretic peptide (BNP) concentration. In addition, they were assessed using: The Minnesota Living with Health Failure Questionnaire [MLHFQ]) for disease Specific QoL, the Hospital Anxiety and Depression Scale [HADS], and the State-Trait Anger Expression Inventory [STAXI]).

Results: After 12 weeks of rehabilitation improvements in NYHA class, left ventricular ejection fraction (LVEF), and peak oxygen consumption were found, while mean BNP concentrations did not change. Disease specific QoL demonstrated improvements in physical component and the

total score. Relative improvement of psycho-emotional scores correlated positively with relative improvement of disease specific QoL. In patients with LVEF $\geq 30\%$ at baseline, changes in BNP concentration were positively associated with both anxiety and state anger, and with the emotional component score of MLHFQ.

Conclusion: Improvements in disease-specific QoL were closely associated to improvements of psycho-emotional status and clinical severity of CHF.

Keywords: Chronic heart failure, comprehensive rehabilitation, disease specific quality of life, depression, anxiety, brain natriuretic peptide

Chronic heart failure (CHF) is associated with compromised quality of life.¹ In addition, in CHF anxiety and depression are strongly correlated with and often accompanied by impaired quality of life.² In turn, impaired quality of life affects compliance negatively³⁻⁵,

and depression has been shown to be an independent risk factor for morbidity and mortality CHF.⁶

Brain natriuretic peptide (BNP) is considered to represent a reliable marker for severity and treatment responsiveness of CHF.⁷ N-Terminal Pro-ANP has been shown to play a role in modifying emotions, especially anxiety.^{8,9} These peptides and their receptors represent an important neuro-modulatory system within the central nervous system which directly exerts its influence on emotional behaviour, such as anxiety and arousal.¹⁰ In CHF, patients who undergo a rehabilitation program may exhibit changes in anxiety, depression and quality of life, and in BNP as well.¹¹

The purpose of this study was to evaluate the changes in disease-specific quality of life, psycho-emotional status and clinical markers of severity of CHF after a multidisciplinary out-patient rehabilitation program. We postulated that patients with higher concentrations of BNP score higher on anxiety and depression and lower on quality of life measures compared to those who score lower on anxiety and depression and higher on disease specific quality of life. The analysis is part of a comprehensive evaluation of the rehabilitation program which was developed and implemented in the University Hospital setting for the first time.

Patients and Methods

In this case series twenty five patients (20 male/5 female) with clinically stable CHF underwent a 12-week comprehensive rehabilitation program. Patient characteristics are presented in Table 1. Etiology of CHF was coronary artery disease (n=8/1), dilated/idiopathic cardiomyopathy (n=9/3), and other factors such as RV dysplasia (1/0), and cytostatica induced cardiomyopathy (2/1). Inclusion criteria were stable heart failure for at least 3 months and optimized medication regimen unchanged for more than 1 month. Before and in the course of intervention, 13 patients received a triple therapy (including beta-blockers, diuretics, and ACE-inhibitors), 8 had a two-drug regimen (including beta-blockers or ACE-inhibitors, and diuretics), whereas 4 patients were exclusively treated with A-II blockers. Exclusion criteria

TABLE 1. Clinical status and aerobic exercise capacity at baseline and changes between baseline and after 12 weeks of rehabilitation

Clinical status and exercise capacity	Baseline (mean ± SD)	Baseline vs. week 12 of rehabilitation	P
Body mass index (kg/m ²)	27.2 ± 4.8	+0.1	0.942
New York Heart Association classification (mean ± SD)	1.7 ± 0.7		
NYHA I (n)	11	improved: 9	0.002
NYHA II (n)	10	stable: 16	
NYHA III (n)	4	worse: 0	
Left-ventricular ejection fraction (%) (echocardiography)	28.7 ± 7.2	+4.9	0.002
Brain Natriuretic Peptide (BNP; pg/ml)	314 ± 269	-46	0.181
Peak VO ₂ (ml/kg/min)	18.2 ± 4.1	+2.0	0.050

were resting- or exercise-induced angina pectoris, electrocardiographic evidence for myocardial ischemia in resting conditions, significant arrhythmia, orthopedic or neurological disorders, severe chronic obstructive pulmonary disease, and peripheral arterial occlusive disease. The study protocol was approved by the local Ethics Committee of the University of Bern. Before inclusion, all patients had given their written informed consent to the study.

Education Program

Once a week, patients and their partners attended 1.5-hour counseling session, which spouses or other family members could attend upon request. Counseling was offered by a team of multidisciplinary health professionals including dietitians, psychologists, physicians, and exercise therapists. It focused on the role of sodium restriction and fluid intake, pharmacological therapy and its side effects, warning symptoms of progressive heart failure and guidelines on how to act, adherence to dietary and medical therapy, physical activity in daily living, and sexuality. Additionally, psychological support in coping with heart failure-related problems was offered to patients and partners.

Testing Procedures

All tests were performed at baseline and after 12 weeks of rehabilitation at the same time of day, under identical conditions and with prescribed medication. Left ventricular ejection fraction (LVEF) was determined by 2-D echocardiography using Simpson's bi-plane method. Patients underwent cycle cardiopulmonary exercise testing using ramp-like protocol. After 3 minutes unloaded, work load started at 12.5 watts, and then work load was increased every minute by 12.5 watts each until leg fatigue or dyspnea forced them to stop (score ≥ 16 on the Borg Scale (range 6 to 20)¹⁴). Peak oxygen uptake (VO_2 ; ml/kg/min) was measured breath by breath with an Oxycon Sigma system (E. Jaeger AG, Würzburg, Germany); for detailed methods see¹²).

Determination of Brain Natriuretic Peptide

Five milliliters venous blood was taken to determine brain natriuretic peptide (BNP; pg/ml) by fluorescence immunoassay (Triage BNP-Test, Biosite Diagnostic).

Measurement of Quality of Life

Physical, psychological, and socio-economic impairment was assessed by means of the 21-item Minnesota Living with Heart Failure Questionnaire (MLHFQ) – a self-administered and disease-specific instrument.¹⁵ Using a Likert-scale, answers were given by choosing a score between 0 (no impairment) and 5 (very much impaired), resulting in a total score variation from 0 (no impairment) to 105 (severe impairment). The higher the score, the more severely impaired a patients feels.

Assessment of Psycho-Emotional Status

To measure anxiety and depression, the 14-item Hospital Anxiety and Depression Scale (HADS)^{16,17} was administered. This questionnaire is a screening test for clinically important anxiety (7 items) and depression (7 items) with high re-test reliability.¹⁸ Each item has 4 answer options. After calculation of the sum scores of each of the 2 scales, a sum score of > 10 confirms the presence of a disorder, whereas as score < 8 indi-

cates that there is none.

To assess anger components the 44 item State-Trait Anger Expression Inventory (STAXI)¹⁹ was used to assess situational anger (state anger, 10 items), trait anger (10 items), anger-in (8 items), anger-out (8 items), and anger control (8 items). All items are rated by means of a 4- step Likert Scale, and component values are calculated by adding the respective Likert values.

Statistics

Statistical analysis was performed using SPSS 13.0 (Statistical Package for Social Sciences, Windows Version, SPSS Inc. Los Angeles, USA). Descriptive statistics included arithmetic mean and standard deviation for numeric, continuous, and categorical variables. For dependent samples, the Student's *t*-test was applied to calculate changes in outcome parameters between baseline and week 12 of intervention. When ordinal variables had to be distinct, the Kendall or the Spearman Test was used. To determine evidence of strength of changes in quality of life scores, the effect sizes of normalized values were calculated by relating mean change (baseline versus week 12) divided by standard deviation of measures obtained at week 12. Otherwise, Z-transformed values were used to correct for possible skewness of the distribution of distinct variables. In order to assess differences of effects on quality of life parameters, a median half-split for baseline ejection fraction (LVEF < 30 versus $\geq 30\%$) was calculated. By using unpaired *t*-tests the subgroups were compared for changes in disease specific quality of life variables. Correlations were determined by Pearson's correlation coefficient (*r*). Two-sided *P*-values < 0.05 .

Results

Disease-Specific Quality of Life

The initial sum score of the MLHFQ indicated moderate impairment in quality of life (Table 2).

TABLE 2. Quality of life status as assessed by the disease-specific questionnaire "The Minnesota Living with Heart Failure Questionnaire" (MLHFQ). Baseline values and changes between baseline and week 12 of rehabilitation

MLHFQ	Baseline mean $\pm$ SD	Baseline vs. week 12 of rehabilitation*	Fisher's Z	P
Physical component score	14.8 $\pm$ 8.2	6.1	0.5	0.02
Emotional component score	7.1 $\pm$ 6.3	3.2	0.3	0.1
Sum score	31.9 $\pm$ 18.5	11.7	0.5	0.007

* a positive difference indicates a lower level of impairment and/or a better quality of life

After rehabilitation significant improvements in the physical component score and total score were discernible.

Anxiety, Depression and Anger

Initially, mean sum values of both Hospital Anxiety Depression Scale (HADS) for anxiety and depression were in the normal range of values (i.e. < 8 for both). Compared with the initial values, mean values of depression and anxiety scores did improve significantly (Table 3).

At baseline, mean values of all State and Trait Anger Expression Inventory (STAXI) scores on anger

were also within the range of age- and gender-adjusted normal values. However, at the end of rehabilitation all mean scores had significantly improved (Table 3).

Focusing on individual patients' scores at baseline, 2 of the 25 patients' (7%) qualified for a mildly depressed mood, and 4 patients (14%) indicated an abnormally elevated anxiety sum score (cut-off scores for both ≥ 10). At the end of the study, although all individual scores above the cut-off level had improved (i.e. were lower), one of the depressed and two of the anxious patients still scored abnormally high (i.e. ≥ 10).

TABLE 3. Baseline values and changes (baseline -week 12) of emotional status as assessed by Hospital Anxiety and Depression Scale (HADS) and the State-Trait Anger Expression Inventory (STAXI).

HADS	Baseline mean $\pm$ SD	Baseline vs. week 12 of rehabilitation*	Z-value	P
Anxiety	5.5 $\pm$ 4.1	-0.8	3.7	0.0002
Depression	5.1 $\pm$ 3.6	-1.1	3.2	0.002

* A negative value represents an alleviation of a component

STAXI	Baseline (T1) mean $\pm$ SD	Baseline vs. week 12 of rehabilitation*	Z-value	P
State anger	13.5 $\pm$ 4.6	-2.0	2.5	0.01
Trait anger	16.9 $\pm$ 5.0	-1.4	3.8	0.0001
Anger-in	15.0 $\pm$ 4.8	-1.2	2.0	0.04
Anger-out	11.0 $\pm$ 3.6	-0.4	2.7	0.008
Anger control	24.4 $\pm$ 6.2	+1.7	2.7	0.008

* A negative value represents an alleviation of a component

Correlations between Anxiety, Depression, Anger and Quality of Life

At baseline anxiety, depression, and anger control were significantly associated with emotional component score, mental health, and mental sum score of disease specific quality of life (Table 4a).

After rehabilitation, changes in anxiety and depression from HADS were significantly correlated with the physical and emotional component score and of the scores of disease specific quality of life measures (Table 4b).

TABLE 4a. Pearson's r for correlations of disease specific quality of life variables (MLHFQ) with anxiety, anger and depression (HADS, STAXI) at baseline.

		MLHFQ		
		Physical component score	Emotional component score	Total score
		r	r	R
HADS	Anxiety	0.09	**0.63	0.36
	Depression	0.36	*0.49	**0.58
STAXI	State anger	-0.2	0.13	-0.02
	Trait anger	-0.06	*0.44	0.12
	Anger-in	-0.06	0.29	0.12
	Anger-out	-0.1	0.38	0.08
	Anger-control	-0.26	*-0.41	-0.39

*P<0.05; **P<0.01

TABLE 4b. Pearson's r for correlations of changes in psycho-emotional variables (HADS, STAXI) and disease specific quality of life scale (MLHFQ). Differences from baseline to week 12 in brackets; negative values denote an amelioration of the respective scores.

		MLHFQ		
		Physical component score	Emotional component score	Total score
		r	r	R
HADS	Anxiety	*0.43	*0.44	*0.49
		(-0.21)	(-0.35)	-0.17
	Depression	0.38	**0.62	**0.53
		(-0.3)	(-0.08)	(-0.24)
STAXI	Trait anger	0.14	0.21	0.08
		(-0.37)	(-0.07)	(-0.03)
	State anger	-0.33	-0.2	-0.22
		(-0.04)	(*0.43)	(-0.21)
	Anger-in	-0.16	0.06	-0.16
		(-0.11)	(-0.31)	(-0.06)
	Anger-out	-0.22	-0.25	-0.26
		(-0.08)	(-0.2)	(-0.01)
	Anger-control	0.07	0.08	-0.03
		-0.16	-0.19	-0.09

*P<0.05; **P<0.01

TABLE 5. Pearson's r for correlations of absolute and/or percent differences of brain natriuretic peptide (BNP) with a) absolute and/or percent differences of psycho-emotional (HADS, STAXI), b) disease-specific quality of life variables (MLHFQ). Measures were obtained at the end of rehabilitation.

	Absolute or percent changes in	Percent change of BNP r.	Absolute change of BNP r.
HADS	Anxiety	*0.48	-0.19
	Depression	-0.04	0.08
STAXI	Total anger	-0.03	-0.31
	State anger	**0.53	0.14
	Anger in	0.12	-0.11
	Anger out	0.23	-0.38
	Anger control	-0.10	0.34
MLHFQ	Physical component score	*0.47	-0.01
	Emotional component score	**0.68	-0.07
	Total score	0.35	0.00

*P<0.05; **P<0.01

Correlations between Anger, Anxiety, Depression, and BNP

The LVEF of the total group (range: 15-43%), was used to split patients up into severely and moderately impaired left ventricular function, respectively. A median of 30% was used to determine possible differences in psycho-emotional scores (depression, anger, anxiety (Table 5).

In patients with LVEF $\geq 30\%$, percent changes in BNP observed during the course of rehabilitation correlated significantly with those in anxiety and anger. In addition, percent change in emotional distress was associated with percent changes in both, disease specific physical component score and emotional score of the MLHFQ (Table 6).

Discussion

This paper represents explorative findings based on evaluation of a pilot rehabilitation program. Multiple studies^{6,20,21} have yielded evidence for an interdependence between clinical and functional status and quality of life CHF. A limited number of studies have focused on anxiety and depression in CHF (for over-

view see 2). It remains unclear whether a multidisciplinary CHF rehabilitation program involving pharmacological treatment, exercise training, education, counseling and emotional support could modify anxiety and depression along with improving clinical status and quality of life. Since a multidisciplinary rehabilitation program should be near daily practice, our pilot study evaluated its gross effect but not the relative impact of a single intervention component.

Clinical Status and Quality of Life

Twelve weeks of rehabilitation resulted in an improvement of clinical parameters (NYHA class, LVEF) and peak VO₂ (Table 1). Besides, disease specific physical functioning and quality of life sum score improved (Table 2).

In the patients who exhibit NYHA class II, the initial mean quality of life sum score of 31.9 indicated a moderate impairment. Similar sum scores were reported for an American and a German heart failure reference population in NYHA class II and III patients.^{22,23} In 3 months of rehabilitation, improvements by 36% in sum score and by 41% in physical

TABLE 6. Pearson's r coefficient for correlations of percent changes in BNP with a) percent changes in psycho-emotional status (HADS and STAXI) and b) disease specific quality of life (MLHFQ). Measures were obtained at the end of rehabilitation.

	Percent change of values for	Percent changes of BNP	
		EF < 30% n=12	EF ≥ 30% n=9
		r.	r.
HADS	Anxiety	0.37	*0.76
	Depression	0.34	-0.33
STAXI	State anger	0.29	-0.18
	Total anger	0.33	**0.80
	Anger-in	-0.10	0.33
	Anger-out	0.11	0.56
	Anger-control	-0.39	0.61
MLHFQ	Physical component score	0.34	0.60
	Emotional component score	0.24	**0.75
	Total score	0.25	0.29

*P<0.05; **P<0.01

component score on average corresponded to improvements of 30%, 37% and 22% on average for sum score, physical and emotional component scores, which were reported after 2 and 14 months of exercise training, respectively.²⁴ Improved clinical status and exercise capacity might have enabled patients to cope better with their everyday lives, thereby becoming more self-reliant and emotionally more stable.²⁵ This could be the reason for an improvement in the disease-specific quality of life.

Anxiety and Depression

Although at baseline the mean scores of patients did not indicate anxiety or depression (i.e. ≥ 8), mean values of both scales did improve throughout the rehabilitation period as indicated by a decrease in values (Table 3). The two and four patients, respectively, who exhibited pathological depression and anxiety sum scores demonstrated lower values after the 12 week rehabilitation program, suggesting a positive effect on emotional functioning. Carels et al. found that the impact of depression on quality of life in CHF patients was more pronounced than the impact of severity of

heart failure as defined by LVEF.²⁶ Not only quality of life but also depression has been demonstrated to be directly associated to survival in CHF patients^{2,6}. Moreover, in the Montreal Heart Attack Readjustment Trial (M-Hart) results indicated that highly anxious men might significantly increase their chances of long-term survival by modifying their coping styles.²⁷ These experiences imply the importance of both recognizing and treating anxiety and depression in patients with CHF so as to improve their quality of life.

Neurohumoral Markers of Changes of Anxiety and Depression

We tested the association of BNP to psycho-emotional and quality of life measures. In patients with LVEF ≥30%, percent change in BNP in the course of rehabilitation correlated significantly with percent change in anxiety and anger, which was not the case in the group with LVEF <30% (Table 6). This might be an indication that BNP could attenuate central arousal effects by lowering sympathetic outflow.¹⁰ Moreover, the compensatory activity of high concentrations of

BNP has been reported to be attenuated.²⁸ These facts may partly explain why correlations of BNP concentrations to psycho-emotional factors were not found in patients who exhibited ejection fraction below 30%.

Study Limitations

The paper presents explorative findings based on an evaluation of a pilot multidisciplinary out-patient rehabilitation program. A control group was not included in the design due to the fact that a pilot program is under investigation. However, according to a consensus of the Association Francophone pour la Prévention et la Réadaptation Cardiovasculaire, lack of a control group is partly justified granted the unethical aspects of restraining CHF patients totally from rehabilitation. The small number of patients may not be representative for stable CHF patients who participate in such programs. When assessing parameters of quality of life, depression and anxiety, a reporting bias could affect the results. In our study, psycho-emotional factors such as depression, anger, and anxiety have been measured by means of questionnaires. Since self-reports are often less sensitive in diagnosing psycho-emotional disorders, the instruments used may have underestimated the effective prevalence of these emotional disturbances.²⁹

BNP concentrations are known to be reduced after beta blocker treatment³⁰, whereas plasma concentrations are reported to increase after treatment with angiotensin-converting inhibitors.³¹ Thus, an uncertain amount of variance of BNP has to be taken into account in a thorough interpretation of our data.

Need for Future Research

Randomized controlled trials are needed to verify the association of improvement in quality of life and improvement of anxiety and depression in relation to clinical severity of disease in CHF patients undergoing multidisciplinary rehabilitation. Focusing on the field of psychological and neurobiological adaptation, the mechanism underlying the improvement in anxiety and depression should be clarified. The question whether the natriuretic peptides, namely BNP, are reliable clinical markers for anxiety and depression in

CHF - as is true for severity and treatment responsiveness - should be examined.

Clinical Implications

This pilot study demonstrated that rehabilitation-induced improvements of disease-specific quality of life are closely associated with improvement in psycho-emotional status and clinical severity of CHF.

References

1. Falk K, Swedberg K, Gaston-Johansson F, et al. Fatigue and anaemia in patients with chronic heart failure. *Eur J Heart Fail* 2006; 8:744-9
2. Jiang W, Kuchibhatla M, Cuffe MS, et al. Prognostic value of anxiety and depression in patients with chronic heart failure. *Circulation* 2004; 110:3452-6
3. Brodie DA, Inoue A. Motivational interviewing to promote physical activity for people with chronic heart failure. *J Adv Nurs* 2005; 50:518-27
4. Weber MA. Angiotensin-II receptor blockers for hypertension and heart failure: quality of life and outcomes. *Manag Care Interface* 2005; 18:47-54
5. Jaarsma T, Halfens R, Abu-Saad HH, et al. Quality of life in older patients with systolic and diastolic heart failure. *Eur J Heart Fail* 1999; 1:151-60.
6. Junger J, Schellberg D, Muller-Tasch T, et al. Depression increasingly predicts mortality in the course of congestive heart failure. *Eur J Heart Fail* 2005; 7:261-7
7. Dao Q, Krishnaswamy P, Kazanegra R, et al. Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in an urgent-care setting. *J Am Coll Cardiol* 2001; 37:379-85
8. Hulsmann M, Berger R, Sturm B, et al. Prediction of outcome by neurohumoral activation, the six-minute walk test and the Minnesota Living with Heart Failure Questionnaire in an outpatient cohort with congestive heart failure. *Eur Heart J* 2002; 23:886-91
9. Krieger J, Grunstein R. Natriuretic peptides in sleep apnea. *Am J Cardiol* 2005; 95:708
10. Wiedemann K, Jahn H, Kellner M. Effects of natriuretic peptides upon hypothalamo-pituitary-adrenocortical system activity and anxiety behaviour. *Exp Clin Endocrinol Diabetes* 2000; 108:5-13
11. Ford CM, Pruitt R, Parker V, et al. CHF: effects of cardiac rehabilitation and brain natriuretic peptide. *Nurse Pract* 2004; 29:36-9

12. Meyer K, Samek L, Schwaibold M, et al. Interval training in patients with severe chronic heart failure: analysis and recommendations for exercise procedures. *Med Sci Sports Exerc* 1997; 29:306-12.
13. Noble B, Borg G, Jakobs I, et al. A category-ratio perceived exertion scale: relationship to blood and muscle lactates and heart rate. *Med Sci Sports Exerc* 1983; 15:523-528
14. Borg G. Perceived exertion as indicator of somatic stress. *Scand J Rehab Med* 1970; 2:92-96
15. Rector T, Kubo SH, Cohn JN. Patients' self-assessment of their congestive heart failure. Part 2: Content, reliability and validity of a new measure, The Minnesota living with heart failure questionnaire. *Heart Failure* 1987; October, November:198-208
16. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; 67:361-70
17. Herrmann C. International experiences with the Hospital Anxiety and Depression Scale--a review of validation data and clinical results. *J Psychosom Res* 1997; 42:17-41
18. Meyer T, Klemme H, Herrmann-Lingen C. Prevalence and effects of depressive and anxiety symptoms in internal medicine inpatients during the first year after hospital discharge. *Z Psychosom Med Psychother* 2002; 48:174-91
19. Schwenkmetzger P, Hodapp v. A questionnaire for assessing anger and expression of anger. *Z Klin Psychol Psychopathol Psychother* 1991; 39:63-8
20. Krumholz HM, Butler J, Miller J, et al. Prognostic importance of emotional support for elderly patients hospitalized with heart failure. *Circulation* 1998; 97:958-64.
21. Davidson P, Cockburn J, Daly J, et al. Patient-centered needs assessment: rationale for a psychometric measure for assessing needs in heart failure. *J Cardiovasc Nurs* 2004; 19:164-71
22. Rector TS, Francis GS, Cohn JN. Patients' self-assessment of their congestive heart failure; Part 1: Patient perceived dysfunction and its poor correlation with maximal exercise tests. *Heart Failure* 1987; October, November:192-196
23. Quittan M, Sturm B, Wiesinger GF. Quality of life in patients with chronic heart failure: A randomized controlled trial of changes induced by a regular exercise program. *Scand J Rehab Med* 1999; 31:223-228
24. Belardinelli R, Georgiou D, Cianci G, et al. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. *Circulation* 1999; 99:1173-82.
25. Luskin F, Reitz M, Newell K, et al. A controlled pilot study of stress management training of elderly patients with congestive heart failure. *Prev Cardiol* 2002; 5:168-72
26. Carels RA. The association between disease severity, functional status, depression and daily quality of life in congestive heart failure patients. *Qual Life Res* 2004; 13:63-72
27. Frasure-Smith N, Lesperance F, Gravel G, et al. Long-term survival differences among low-anxious, high-anxious and repressive copers enrolled in the Montreal heart attack readjustment trial. *Psychosom Med* 2002; 64:571-9
28. Tsutamoto T, Wada A, Maeda K, et al. Attenuation of compensation of endogenous cardiac natriuretic peptide system in chronic heart failure: prognostic role of plasma brain natriuretic peptide concentration in patients with chronic symptomatic left ventricular dysfunction. *Circulation* 1997; 96:509-16
29. Mihura JL, Nathan-Montano E. An interpersonal analysis of Rorschach aggression variables in a normal sample. *Psychol Rep* 2001; 89:617-23
30. Kawai K, Hata K, Takaoka H, et al. Plasma brain natriuretic peptide as a novel therapeutic indicator in idiopathic dilated cardiomyopathy during beta-blocker therapy: a potential of hormone-guided treatment. *Am Heart J* 2001; 141:925-32
31. Talwar S, Squire IB, Downie PF, et al. Profile of plasma N-terminal proBNP following acute myocardial infarction; correlation with left ventricular systolic dysfunction. *Eur Heart J* 2000; 21:1514-21

Correspondence to:

PD Kurt Laederach-Hofmann, MD, FMH, APPM
Department of General Internal Medicine
University of Berne, Inselspital
CH-3010 Berne
Email: laederach@insel.ch