BRIEF REPORT

Safety, Acceptance, and Physiologic Effects of Sauna Bathing in People With Chronic Heart Failure: A Pilot Report

Jeffrey R. Basford, MD, PhD, Jae K. Oh, MD, Thomas G. Allison, PhD, MPH, Charles G. Sheffield, PT, Barbara G. Manahan, RDCS, David O. Hodge, MSci, A. Jamil Tajik, MD, Richard J. Rodeheffer, MD, Chuwa Tei, MD

ABSTRACT. Basford JR, Oh JK, Allison TG, Sheffield CG, Manahan BG, Hodge DO, Tajik AJ, Rodeheffer RJ, Tei C. Safety, acceptance and physiologic effects of sauna bathing in people with chronic heart failure: a pilot report. Arch Phys Med Rehabil 2009;90:173-7.

Objectives: To perform a pilot study and make a preliminary assessment of the safety and acceptance of supervised sauna bathing at moderate temperatures in people with chronic heart failure (CHF). Secondary measures included its impact on exercise tolerance and neuroendocrine concentrations.

Design: Randomized, controlled, cross-over trial.

Setting: Physical medicine and rehabilitation clinic.

Participants: Six men and 3 women (age, 62–87y) with New York Heart Association Class III and IV CHF.

Interventions: Subjects were randomized into 2 groups and told to maintain their normal medication and activity regimens. One group then began a 3-times-a-week, 4-week sauna bathing program at 60±1°C while the other continued with their usual activities and medications. Assignments were then reversed. Sessions were 15 minutes in length but were prolonged an additional 5 minutes for oral temperature increases less than 1.0°C.

Main Outcome Measures: Patient acceptance, Minnesota Living With Heart Failure Questionnaire (MLWHFQ) scores; treadmill exercise duration and plasma adrenaline, noradrenalin, aldosterone, atrial naturectic factor, adrenomedulin, and endothelin.

Results: Sauna bathing was well tolerated and no adverse effects were reported. Improvements in MLWHFQ scores and treadmill endurance did not achieve statistical significance on a between-group basis but were more marked after the sauna than during the control phase. Neuroendocrine concentrations showed no clear effect of sauna treatment with a between-group statistically significant difference (P=.049) found only in the case of noradrenalin's 24% decrease.

Conclusions: Sauna bathing under the moderate and supervised conditions of this study appears to be well tolerated and may be safe for people with CHF. More research is needed to further evaluate the safety and potential benefits of this approach.

From the Department of Physical Medicine and Rehabilitation (Basford, Sheffield), Divisions of Cardiovascular Disease and Internal Medicine (Oh, Allison, Manahan, Tajik, Rodeheffer), and Biostatistics (Hodge), Mayo Clinic Rochester, Rochester, MN; and the First Department of Internal Medicine, Faculty of Medicine, Kagoshima University, Sakuragaoka, Kagoshima, Japan (Tei).

Supported by the Mayo Clinic, Rochester, MN (grant no. 300-95).

No commercial party having a direct financial interest in the results of the research supporting this article has or will confer a benefit on the authors or on any organization with which the authors are associated.

Correspondence to Jeffrey R. Basford, MD, PhD, 200 Second Street SW, Rochester, MN 55905, e-mail: *basford.jeffrey@mayo.edu.* Reprints are not available from the author.

0003-9993/09/9001-00357$36.00/0
doi:10.1016/j.apmr.2008.06.029

Key Words: Cardiac disease; Heart failure; Hyperthermia; Rehabilitation; Sauna.

CHRONIC HEART FAILURE affects about 5 million Americans and is a leading cause of hospitalization among the elderly.[1] Our understanding of the condition has improved markedly over the years and treatment now may take into account the influences of peripheral vascular activity, heart rate, and cardiac contractility as well as the potentially cardiotoxic effects of the neuroendocrine hormones.[2,3] Our views of the nature and treatment of this condition will undoubtedly continue to change; it may be that activities such as exercise that were once thought to be harmful[4] may also prove to be innocuous or even beneficial.

Sauna bathing may be a case in point, because systemic hyperthermia is often proscribed for people with heart disease and failure. This proscription at first glance appears reasonable in that hyperthermia increases heart rate and cardiac output, and, thereby potentially cardiac stress. However, the facts may not support this view. For example, although heat does increase cardiac rate and output, it also has potential benefits in the form of afterload reduction from vasodilation and salt loss. In addition, many people, including some with heart disease, have long found sauna bathing pleasurable and relaxing.[5,6] More recent research adds support to a benign view of sauna bathing in that it finds that hyperthermia appears to improve left ventricular function and vascular activity in people with cardiac and peripheral vascular disease.[7-9] This work, however, focuses on cardiac and vascular parameters. Far less is known about the effects of controlled hyperthermia exposure on the functional activities, exercise tolerance, and neuroendocrine profiles of people with heart failure and cardiac disease.

The question arises whether this prohibition on sauna bathing is overly restrictive. It may be that not only are safety concerns needlessly limiting the activities of people with CHF, but also that excessive caution is preventing the use of a potentially beneficial modality.

Problem Statement

This pilot study had 4 goals. The primary goal was to make a preliminary assessment of the safety and acceptance of sauna bathing at moderate temperatures on people with CHF. The

List of Abbreviations

BP	blood pressure
CHF	chronic heart failure
CID	clinically important difference
MLWHFQ	Minnesota Living With Heart Failure Questionnaire
NYHA	New York Heart Association

second was to assess the impact of sauna bathing on the subjects' quality of life and exercise tolerance. The third consisted of monitoring a number of cardiotoxic neuroendocrine hormones with the thought that changes in their concentrations might provide information about sauna bathing's physiologic effects. Our final goal was to estimate the sample sizes necessary to establish the benefits of sauna bathing in a definitive randomized controlled trial.

METHODS

Subjects

This study was approved by the Mayo Clinic Institutional Review Board. Inclusion criteria included age 18 years or older, stable NYHA Class III or IV CHF, left ventricular ejection fraction of less than 40% and maintenance of a stable activity and pharmacologic regimen for at least a month. Subjects were also required to agree to participate in treadmill exercise testing and a 3-times-a-week, 4-week sauna program. Exclusion criteria included significant (more than moderate) valvular stenotic disease, fever, diabetes mellitus, history of symptomatic lung disease, myocardial infarction within 3 months, the presence of an implantable cardioverter-defibrillator or pacing device, or a history of sustained ventricular dysrhythmia.

Methods

The goals and procedures of this randomized, crossover study were reviewed with potential participants by one of the investigators. Volunteers were assessed by one of 2 cardiologists (J.K.O. and A.J.T.) who were members of the team. Those meeting the inclusion and exclusion criteria then signed an informed consent form. The investigators assessed the subjects at an initial baseline visit as well as at the completion of each treatment assignment.

Baseline evaluation included an interview and physical examination during which demographic variables, medication use, and vital signs were collected. Subjects also filled out the well-validated 21-item MLWHFQ about the effect of CHF on their lives[10] and answered 2 global questions; "How much does heart failure affect your life?" (6-point scale ranging from "no effect" to "very large effect") and "How much has the treatment you received in the last 4 weeks changed your way of life?" (5-point scale ranging from "much worse" to "much better"). Subjects also underwent standard clinical treadmill exercise testing according to American College of Cardiology/American Heart Association standards with a modified Naughton Protocol.[11] Tests were symptom-limited (rating of perceived exertion$<$19 on standard Borg scale) and administered by test personnel who were blinded to patient assignment and provided no special coaching). Blood sampling to obtain resting adrenaline, noradrenaline, aldosterone, atrial naturectic factor, adrenomedulin, endothelin, and cyclic guanosine monophosphate plasma concentrations was done prior to participation in study activities. Subjects then underwent a 15-minute sauna bath trial (see below) with blood pressure, heart rate, oral temperatures, and weight obtained immediately before and after treatment as well as 30 minutes later.

We randomized the subjects into 2 groups. One group began a 3-times-a-week, 4-week sauna bathing program (ie, the "sauna phase" in our hospital's rehabilitation clinic) while the members of the other served as controls. Subjects were instructed to maintain their normal drug regimens and usual level of activities throughout the study period.

Subjects were reassessed at the end of the treatment period (within 48 hours of the last session for those in the sauna phase) in the manner outlined above. Assignments were then reversed with those in the previous phase's control group undergoing the sauna regimen, and those that had been enrolled in the sauna phase no longer undergoing saunas but otherwise maintaining their normal level of activities. A third and final assessment occurred 4 weeks later.

Table 1: Demographic Data

Subject Demographics	
Variable	Value
N	9
Men/women	6/3
Age (y)	71.6±9.8
Height (cm)	171.2±8.0
Mass (kg)	80.3±19.2
Body mass index (kg/m^2)	28.6±3.7
Previous myocardial infarction	3
NYHA functional class	
III	7
IV	2
Left ventricle ejection fraction (%)	20.0±6.9

NOTE. Values are mean ± SD.

Equipment and Procedures

Sauna treatments were performed individually in a previously described dry sauna bath.[6] Heart rate, BP, body weight, and oral temperatures were obtained immediately before each session. The subject then lay supine in the sauna at 60±1°C for 15 minutes (extended to 20 minutes if an oral temperature increase of 1.0°C had not been achieved). Subjects were then wrapped in dry blankets and lay quietly for an additional 30 minutes before being dried and reweighed. Subjects losing more than 454g (1lb) were given 300 to 400ml of water to drink; those losing lesser amounts were given half that amount. Adverse events were defined as any undesirable outcome ranging in severity from the serious (eg, dysrhythmias, palpitations, increasing dyspnea, and angina) to patient complaints of discomfort. All sessions were monitored by a trained physical therapist and occurred during normal business hours in close proximity to cardiologists in a nearby Cardiovascular Health Clinic.

Data and Statistics

Baseline measurements were compared with those obtained at the 4- and 8-week intervals marking the end of the treatment phases with rank-sum and 2-tailed paired *t* tests as appropriate. Changes were considered significant if *P* values were less than or equal to 0.05. All data are expressed as mean ± SD.

RESULTS

Demographics

Six men and 3 women with ages ranging from 62 to 87 years participated in the study. All were on stable pharmacologic regimens; 7 were categorized as NYHA Functional Class III and 2 as Class IV at the time of initial screening (table 1).

Clinical Outcomes

There were no adverse events. Subjects tolerated the sauna sessions well with 3 desiring to continue bathing after the study's close. One patient was reassigned from a screening assignment of NYHA Class III to Class II at their baseline session. NYHA scores showed a trend towards improvement in

Table 2: Subjective Measures

Assessments	Subjective Measures			
	Baseline	Control Phase	Sauna Phase	Comparison of Sauna and Control Phase Enrollment Outcomes *P* Values‡
MLWHFQ	33.1 (16.1)	23.3 (13.1)*	19.04 (14.5)†	0.13
NYHA score				
I	0 (0)	0 (0)	0 (0)	
II	1 (11.1)	4 (44.4)	5 (62.5)	0.25
III	6 (66.7)	4 (44.4)	3 (37.5)	
IV	2 (22.2)	1 (11.1)	0 (0)	
Does heart failure prevent you from living as you want?§	1.56 (1.51)	2.22 (1.56)	1.77 (1.76)	0.31
Effect of treatment on your way of life?§	2.67 (0.71)	2.78 (0.44)	2.22 (0.67)	0.14

NOTE. In the MLWHFQ, higher scores indicate worsened function.
*$P<.035$ relative to baseline.
†$P<.0023$ relative to baseline.
‡Paired *t* tests except for use of sign test for the NYHA scores.
§Higher scores indicate improved function.

both the control and sauna phases from their baselines that was not statistically significant on a between-group basis but that did obtain significance ($P=.020$) for the subjects during the sauna phase (table 2).

The MLWHFQ (see table 2) did not reveal statistically significant between-group changes but improvements relative to baseline were more marked during the sauna (14.1 points, $P<.0023$) than during the control (9.8 points, $P<.035$) phase. Similarly, responses to the 2 global questions about the effect of treatment on the subjects' quality of life did not reveal statistically significant differences on a between-group basis although the lower scores (indicating improvement) occurred after the sauna rather than after the control treatment assignments (see table 2).

Exercise Data

No statistically significant between-group changes in response to exercise testing were noted. Treadmill endurance time after sauna treatment (5.3±2.1min) was slightly higher but statistically unchanged, relative to its values at either baseline (4.8±1.8min) or at the end of the control phase (4.9±2.1min) (table 3). Statistically significant within-group changes during exercise testing were limited to systolic blood pressure and occurred in both the sauna and control phases. Electrocardiographic interpretations for ischemia did not change with treatment assignment (data not shown). Subject weight as well as resting heart rate and BP changed minimally over the study (table 4).

Neuroendocrine Findings

Six neuroendocrine factors (adrenaline, noradrenalin, aldosterone, atrial naturectic factor, adrenomedulin, and endothelin) were assessed (see table 4). Within-group changes in subject neuroendocrine levels reached statistical significance only during their sauna exposure and were limited to 2: noradrenalin ($P<.049$) and endothelin ($P<.0039$). Between-group statistical significance was obtained only for noradrenalin's 24% decrease ($P<0.049$).

DISCUSSION

This pilot study had modest goals and was designed primarily to be a preliminary assessment of the safety and acceptance of supervised moderate temperature sauna bathing in people with CHF. We believe that this trial, despite its small size and pilot nature, provides support for the hypothesis that sauna bathing, at least under the controlled conditions of the study (dry sauna at 60°C relative to the 70–80°C values often available in the community), is well tolerated and may be safe for people with CHF. More specifically, there were no adverse events, the subjects tolerated the sauna sessions well and 3 subjects volunteered that they would like to continue at the conclusion of the study. It is also intriguing that although the changes in quality of life measures did not reach statistical significance on an inter-group basis, 4 subjects (including the 3 who wished to continue the sauna baths) informally mentioned to the physical therapist that they believed their sauna bathing allowed them to be more active in their daily lives.

The objective findings are also interesting. Perhaps most importantly neither exercise testing nor the electrocardiographic studies revealed a detrimental effect of sauna treatment. Although one might have wished for an improvement in treadmill endurance after the subjects' sauna exposures, the lack of a deterioration is encouraging. Similarly, we chose to assess the impact of sauna bathing on a number of cardioactive neuroendocrine factors due to the latter's importance as markers of CHF and their known and potential roles in cardiotoxicity.[12-16] The overall lack of significant between-group change in their levels (with the exception of noradrenalin's 24% decrease) as a result of sauna bathing is encouraging from a safety point of view. It is, however, disappointing from the perspective of sauna bathing as a potential tool in the treatment of CHF.

It is also encouraging that there is some mechanistic support for the idea that sauna bathing may be beneficial. For example, CHF is characterized by progressive fluid retention,[17] and sauna bathing is marked by a loss of fluid and electrolytes. Improvements in afterload reduction as a result of sweating, peripheral vasodilatation, and improved vasoactivity[8] that occurs in a sauna's warm environment[18,19] may be beneficial.

Study Limitations

A major limitation of this study is its small sample size. Our original plan was to enroll 20 subjects, but difficulties in recruitment led to the ultimate entry of only 9 participants. We feel that our primary goal of making a preliminary assessment of the safety and acceptance of sauna bathing under the conditions of the study was met: all subjects tolerated the saunas well and there were no adverse effects. However, our power for the other variables was, as expected, inadequate.

As far as we know, the MLWHFQ has not been used to assess the potential benefits of sauna bathing. Nevertheless, it

Table 3: Naughton Treadmill Exercise Protocol

Parameter	Baseline Mean ± SD	Drug Mean ± SD	Drug and Sauna Mean ± SD	Between Group Comparison *P* Values[§]
Exercise protocol time (min)	4.8±1.8	4.9±2.1	5.3±2.1	0.40
Submaximal exercise				
SBP (mmHg)	132.0±24.9	147.4±31.8*	139.3±26.7	.062
DBP (mmHg)	76.0±11.1	77.0±8.7	74.6±11.1	0.52
$\dot{V}O_2$ (mL/kg/min)	918.7±424.2	960.7±500.2	916.7±415.2	0.57
$\dot{V}CO_2$ (mL/kg/min)	871.3±516.6	832.7±457.4	834.4±444.1	0.97
$\dot{V}E$ (L/min)	31.2±11.3	31.0±14.2	30.7±14.1	0.81
RPE	13.3±2.8	12.4±2.9	11.8±1.5	0.56
HR (beats/min)	108.7±23.2	107.2±22.5	107.9±21.6	0.78
RER	0.88±0.13	0.89±0.16	0.89±0.14	0.89
Maximal exercise				
SBP (mmHg)	138.0±36.3	145.8±41.4[†]	151.8±37.3[‡]	0.21
DBP (mmHg)	79.0±15.0	77.3±10.3	76.0±11.8	0.36
$\dot{V}O_2$ (mL/kg/min)	1101.4±451.4	1094.3±499.3	1162.4±437.8	0.18
$\dot{V}CO_2$ (mL/kg/min)	1203.2±570.4	1160.1±684.8	1288.8±557.1	.095
$\dot{V}E$ (L/min)	46.9±18.5	45.9±23.9	48.9±19.1	0.26
HR (beats/min)	118.8± 29.4	115.3±32.2	126.6±27.4	0.61
$\dot{V}E/\dot{V}CO_2$	41.4±11.4	41.6±9.2	38.8±6.5	.075
RER	1.08±0.13	1.09±0.20	1.10±0.13	0.12
O_2 Pulse (mL/beat)	9.2±3.2	9.7±4.1	9.8±3.5	0.72
RR	32.9±10.5	32.1±12.2	35.3±15.6	0.10
$\dot{V}T$ (mL/kg)	1516.4±659.3	1486.2±698.4	1493.9±589.7	0.91
30 seconds recovery				
$\dot{V}O_2$	1074.4±507.1	1014.1±539.8	1092.0±484.6	

Abbreviations: DBP, diastolic blood pressure; HR, heart rate; RER, Respiratory exchange ratio; RPE, rating of perceived exertion; RR, respiratory rate; SBP, systolic blood pressure; $\dot{V}CO_2$, maximal CO_2 elimination; $\dot{V}E$, minute ventilation during exercise; $\dot{V}O_2$, maximal oxygen uptake; $\dot{V}T$, tidal volume.
*$P<.013$ relative to baseline.
[†]$P<.033$ relative to baseline.
[‡]$P<.0002$ relative to baseline.
[§]Paired *t* tests.

might be the most useful measure to use as a power determining benchmark because it is widely used and accepted as a way to measure clinically significant effects in changes of quality of life in people with CHF. This questionnaire has a relatively well established CID of 5 to 7 points on its total 105-point score.[20] Our pilot study was designed to make an initial assessment of the safety and acceptance of sauna bathing. As such, it was woefully underpowered and was not designed to detect clinically meaningful changes in MLWHF scores. However, we can use it to determine the number needed to do so. Thus, using the SD in the MLWHFQ of about 14 found in our investigation and choosing a mid-range value for the CID of 6

Table 4: Clinical and Neuroendocrine Factors

Parameter	Baseline Mean ± SD	Control Phase Mean ± SD	Sauna Phase Mean ± SD	Sauna vs Control Phase Enrollment Outcome Comparisons *P* Values[§]
Clinical data				
Weight (kg)	80.3±19.2	80.2±20.1	80.6±19.1	0.56
HR (beats/min)	77.1±12.7	76.6±15.1	72.2±11.9*	0.02
Resting SBP (mmHg)	119.8±15.2	130.2±13.4	122.9±12.1	0.054
Resting DBP (mmHg)	77.8±8.8	77.3±7.1	74.7±7.4	0.36
Neurohormonal factors				
Adrenaline (pg/ml)	25.4±16.5	21.9±10.9	22.1±11.2	0.97
Noradrenaline (pg/ml)	514.8±215.1	539.1±212.6	391.9±156.6[†]	0.042
Atrial naturetic factor (pg/ml)	136.8±97.5	131.2±106.8	85.5±64.8	0.065
Endothelin (pg/ml)	17.5±8.5	12.9±6.0	10.7±5.6[‡]	0.35
Adrenomedullin (pg/ml)	18.1±6.7	24.2±20.1	19.9±15.51	0.11
Aldosterone (ng/ml)	11.7±10.4	8.9±5.4	10.5±12.8	0.72

NOTE. All differences relative to baseline.
Abbreviations: DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.
*$P<.046$ relative to baseline.
[†]$P<.049$ relative to baseline.
[‡]$P<.0029$ relative to baseline.
[§]Paired *t* tests.

would result in the requirement for a study with 2 independent groups and a power of 80% to have 84 subjects in each group.

The lack of patient blinding in our trial might be avoided in future studies with the use of a larger sample size (about 85 according to the calculations outlined above) and a randomized controlled trial design. It is impossible for a subject not to know if he or she is undergoing a sauna. However, a design that included a group either undergoing saunas at a different temperature or participating in supervised exercise programs might lessen concerns about blinding. Another issue is treatment frequency and dosage. Other choices (including single sauna sessions) are possible but we believe that our 3-times-a-week, 4-week schedule was optimal because we wanted to study the effects of a realistic schedule of serial sauna bathing in a manner that would not impose an undue burden on the volunteers. Clearly, generalization to people with less stable disease or differing sauna regimens cannot be made without further research.

The study has a number of other limitations. One of these is that its small size forced the use of a crossover design and the appropriate length for a washout period is unknown. We debated this issue and ultimately chose to proceed with a design that included no washout period and compared the outcomes during each assignment to the baseline values obtained at the beginning of the study prior to when treatment was initiated. These choices are arguable, but given concerns about patient retention, they seem the most reasonable now as well as at the time of the trial. The effect of this decision for our primary goal of assessing the safety and subject acceptance of sauna bathing seems minimal because there were no adverse effects and all subjects appeared to tolerate the sessions.

Implications

Although the results of this pilot study provide some encouragement about the safety of sauna bathing under the restricted conditions of this study, a larger randomized controlled trial is needed to address its safety more definitively as well as to explore the nature of its benefits. Recruitment for such a trial is obviously an issue because our power calculations suggested that a sample of 85 subjects would be necessary to detect clinically meaningful differences on the MLWHFQ.

We have a number of reasons to expect that such a trial is not only possible but that its design can benefit from what we have learned. First, recruitment for our study was hampered by the understandable hesitancy of our colleagues to refer patients; this reluctance should be lessened by the subjects' enjoyment of their sessions and the lack of adverse events. Second, our recruitment efforts were focused on a limited number of physicians in a single cardiovascular clinic; more aggressive community-wide recruitment now seems reasonable. Third, dropouts were not a problem; once recruited the subjects enjoyed the saunas and completed the course. Fourth, cost was an issue in the pilot and a definitive randomized controlled trial might focus on less expensive outcome measures such as the six-minute walk test, changes in body composition, edema, and the MLWHFQ rather than more expensive and intensive procedures such as treadmill testing.

CONCLUSIONS

This study suggests that systemic sauna bathing at moderate temperatures may be safe and well tolerated by people with CHF. Further research into the safety and potential benefits of this approach appears warranted.

References

1. Hall MJ, DeFrances CJ. National Hospital Discharge Survey: Advanced Data from Vital and Health Statistics. Hyattsville: National Center for Health Statistics; 2003. No. 332.
2. Goldsmith SR. Congestive heart failure: potential role of arginine vasopressin antagonists in the therapy of heart failure. Congest Heart Fail 2002;8:251-6.
3. Klein L, O'Connor CM, Gattis WA, et al. Pharmacologic therapy for patients with chronic heart failure and reduced systolic function: review of trials and practical considerations. Am J Cardiol 2003;91:18F-40F.
4. Larsen A, Dickstein K. Can sedentary patients with heart failure achieve the beneficial effect of exercise training without moving? Eur Heart J 2004;25:104-6.
5. Luurila OJ. Cardiac arrhythmias, sudden death and the Finnish sauna bath. Adv Cardiol 1978;25:73-81.
6. Tei C, Horikiri Y, Park JC, et al. Acute hemodynamic improvement by thermal vasodilation in congestive heart failure. Circulation 1995;91:2582-90.
7. Kihara T, Biro S, Ikeda Y, et al. Effects of repeated sauna treatment on ventricular arrhythmias in patients with chronic heart failure. Circ J 2004;68:1146-51.
8. Kihara T, Biro S, Imamura M, et al. Repeated sauna treatment improves vascular endothelial and cardiac function in patients with chronic heart failure. J Am Coll Cardiol 2002;39:754-9.
9. Kisanuki A, Daitoku S, Kihara T, Otsuji Y, Tei C. Thermal therapy improves left ventricular diastolic function in patients with congestive heart failure: a tissue doppler echocardiographic study. J Cardiol 2007;49:187-91.
10. Rector TS, Kubo SH, Cohn JN. Validity of the Minnesota Living With Heart Failure questionnaire as a measure of therapeutic response to enalapril or placebo. Am J Cardiol 1993;71:1106-7.
11. Naughton J, Haider R. Exercise testing and exercise training in coronary heart disease. In: Naughton J, Hallerstein HK, editors. Methods of exercise testing. New York: Academic Press; 1973. p 79-91.
12. Costa VM, Silva R, Ferreira LM, et al. Oxidation process of adrenaline in freshly isolated rat cardiomyocytes: formation of adrenochrome, quinoproteins, and GSH adduct. Chem Res Toxicol 2007;20:1183-91.
13. Pepper G, Lee RW. Sympathetic activation in heart failure and its treatment with beta-blockade. Arch Intern Med 1999;159:225-34.
14. Floras JS. Sympathetic activation in human heart failure: diverse mechanisms, therapeutic opportunities. Acta Physiol Scand 2003; 177:391-8.
15. Wieczorek SJ, Wu AH, Christenson R, et al. A rapid B-type natriuretic peptide assay accurately diagnoses left ventricular dysfunction and heart failure: a multicenter evaluation. Am Heart J 2002;144:834-9.
16. Hinson JP, Kapas S, Smith DM. Adrenomedullin, a multifunctional regulatory peptide. Endocr Rev 2000;21:138-67.
17. Gheorghiade M, Gattis WA, O'Connor CW, et al. Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: a randomized controlled trial. JAMA 2004;291:1963-71.
18. Allison TG, Miller TD, Squires RW, Gau GT. Cardiovascular responses to immersion in a hot tub in comparison with exercise in male subjects with coronary artery disease. Mayo Clin Proc 1993;68:19-25.
19. Kirsch KA, Röcker DL, von Ameln H, Hrynyschyn K. The cardiac filling pressure following exercise and thermal stress. Yale J Biol Med 1986;59:257-65.
20. Rector TS, Cohn JN. Minnesota Living With Heart Failure Questionnaire. Available at: http://www.mlhfq.org/default.htm. Accessed November 20, 2008.