

Effects of Repeated Sauna Treatment on Ventricular Arrhythmias in Patients With Chronic Heart Failure

Takashi Kihara, MD; Sadatoshi Biro, MD; Yoshiyuki Ikeda, MD; Tsuyoshi Fukudome, MD; Takuro Shinsato, MD; Akinori Masuda, MD; Masaaki Miyata, MD; Shuichi Hamasaki, MD; Yutaka Otsuji, MD; Shinichi Minagoe, MD; Suminori Akiba, MD*; Chuwa Tei, MD

Background The aim of the present study was to determine whether repeated 60°C sauna treatment improves cardiac arrhythmias in chronic heart failure (CHF) patients, because ventricular arrhythmias are an important therapeutic target in CHF.

Methods and Results Thirty patients (59±3 years) with New York Heart Association functional class II or III CHF and at least 200 premature ventricular contractions (PVCs)/24 h assessed by 24-h Holter recordings were studied. They were randomized into sauna-treated (n=20) or non-treated (n=10) groups. The sauna-treated group underwent a 2-week program of a daily 60°C far infrared-ray dry sauna for 15 min, followed by 30 min bed rest with blankets, for 5 days per week. Patients in the non-treated group had bed rest in a temperature-controlled room (24°C) for 45 min. The total numbers of PVCs/24 h in the sauna-treated group decreased compared with the non-treated group [848±415 vs 3,097±1,033/24 h, p<0.01]. Heart rate variability (SDNN, standard deviation of normal-to-normal beat interval) increased [142±10 (n=16) vs 112±11 ms (n=8), p<0.05] and plasma brain natriuretic peptide concentrations decreased [229±54 vs 419±110 pg/ml, p<0.05] in the sauna-treated group compared with the non-treated group.

Conclusion Repeated sauna treatment improves ventricular arrhythmias in patients with CHF. (*Circ J* 2004; 68: 1146–1151)

Key Words: Heart failure; Heart rate variability; Premature ventricular contractions; Sauna

Patients with chronic heart failure (CHF) have a high prevalence of potentially serious arrhythmias and consequently, a high incidence of sudden cardiac death^{1–4}. The presence of ventricular arrhythmias defines a higher-risk patient group with either ischemic or non-ischemic cardiomyopathy^{5–9}. Antiarrhythmic medications, such as class I drugs, have been tested in myocardial infarction survivors with depressed ventricular function and in atrial fibrillation patients with a history of congestive heart failure, and most were found not to be helpful and may even increase the occurrence of arrhythmias and cardiac mortality^{10–12}. Some studies have shown that amiodarone improves ventricular arrhythmias and sudden cardiac death mortality in patients with CHF, yet the improvement in total mortality remains controversial^{13–15}. Previous studies have demonstrated that vasodilators, such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, improve the prognosis and ventricular arrhythmias in patients with CHF^{16–18} therefore arrhythmia is an important target for therapy in patients with CHF.

We have used thermal therapy with a 60°C dry sauna in patients with CHF, and found that it improves hemodynamic parameters, endothelial function, and clinical symptoms

in many patients^{19–21}. Furthermore, we have demonstrated that repeated sauna treatment improves the prognosis in hamsters with CHF²². It is well recognized that alterations in the neural control of the heart, characterized by decreased vagal activity and relative sympathetic predominance, play a key role in the occurrence of cardiac arrhythmias in patients with CHF²³. Several studies have shown that reduced heart rate variability (HRV), determined from 24-h ambulatory electrocardiographic (ECG) recordings, is associated with a greater risk for ventricular fibrillation and poor prognosis in patients with CHF^{24–27}. Therefore, we prospectively investigated the effects of thermal therapy on cardiac arrhythmias and HRV in patients with CHF.

Methods

Study Population

We studied 30 patients with CHF, aged 28–80 years (mean age: 59±3 years): 24 patients (16 men, 8 women) had idiopathic dilated cardiomyopathy and 6 (5 men, 1 woman) had ischemic cardiomyopathy. Inclusion criteria included the presence of symptomatic CHF, left ventricular ejection fraction (LVEF) <50% by echocardiography, New York Heart Association (NYHA) functional class II–III, and >200 premature ventricular contractions (PVCs) per day on 24-h Holter monitoring. Seven patients were in NYHA functional class II, and the other 23 were in class III. They were randomized into a sauna-treated group (n=20) or a non-treated group (n=10). The mean number of PVCs/24 h was 3,123±819; the mean cardiothoracic ratio (CTR) on chest radiography was 58.5±1.0% (range: 49–75%); and the mean LVEF on echocardiography was 29±2% (range:

(Received April 5, 2004; revised manuscript received September 21, 2004; accepted September 28, 2004)

Departments of Cardiovascular, Respiratory and Metabolic Medicine, *Epidemiology and Preventive Medicine, Graduate School of Medicine, Kagoshima University, Kagoshima, Japan

Mailing address: Chuwa Tei, MD, Department of Cardiovascular, Respiratory and Metabolic Medicine, Graduate School of Medicine, Kagoshima University, 8-35-1 Sakuragaoka, Kagoshima 890-8520, Japan. E-mail: tei@med2.kufm.kagoshima-u.ac.jp

Table 1 Baseline Clinical Characteristics of the 2 Groups

| | Sauna-treated group (n=20) | Non-treated group (n=10) | p value |
|--------------------------|----------------------------|--------------------------|---------|
| Age | 59±3 | 59±4 | NS |
| M/F | 14/6 | 7/3 | NS |
| DCM/ICM | 16/4 | 8/2 | NS |
| Atrial fibrillation (n) | 5 | 2 | NS |
| NYHA (I/II/III) | 0/5/15 | 0/2/8 | NS |
| Body weight (kg) | 57±3 | 53±3 | NS |
| Heart rate (beats/min) | 73±3 | 73±4 | NS |
| SBP (mmHg) | 107±4 | 108±5 | NS |
| DBP (mmHg) | 65±3 | 67±3 | NS |
| Drug therapy (%) | | | |
| Digoxin | 65 | 60 | NS |
| ACE inhibitors | 95 | 90 | NS |
| -blockers | 55 | 40 | NS |
| Diuretics | 95 | 100 | NS |
| Nitrates | 30 | 30 | NS |
| Antiarrhythmic drugs (%) | | | |
| Mexiletine | 50 | 50 | NS |

DCM, idiopathic dilated cardiomyopathy; ICM, ischemic cardiomyopathy; NYHA, New York Heart Association; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACE, angiotensin-converting enzyme; NS, not significant. All values are given as the mean ± SE.

10–48%). All patients were receiving maintenance doses of medications for heart failure and arrhythmias, including angiotensin-converting enzyme inhibitors, diuretics, -blockers, digitalis and antiarrhythmic drugs (mexiletine), and they were in a stable clinical condition for 1 month before entering the study. They also did not have symptomatic arrhythmias. Their medications were unchanged for at least 1 month before or during this study. Written informed consent was obtained from all patients prior to participation, and the protocol was approved by the Ethics Committee of the Faculty of Medicine, Kagoshima University.

Sauna Treatment

Thermal therapy with a far infrared-ray 60°C dry sauna was performed as previously reported.¹⁹ Patients remained supine on a bed during the sauna for 15 min, followed by 30 min of bed rest with a blanket to keep them warm. Patients were weighed before and after the sauna treatment. Oral hydration with water was used to compensate for lost weight. Patients in the non-treated group remained supine on a bed in a temperature-controlled room (24°C) for 45 min.

Assessment of Clinical Symptoms

Clinical symptoms, such as dyspnea, fatigue, sleeplessness, edema, appetite-loss and constipation, were evaluated by a self-assessment quality of life (QOL) questionnaire.²⁰ Each item had 4 grades: remarkably improved, improved, no change, or worsened. Patients were classified into 3 groups based on the results of the questionnaire. Patients who answered 'improved' to more than 3 items were defined as the improved group, those who answered 'worsened' for at least 1 item were defined as the worsened group, and the others were defined as the unchanged group.

Laboratory Examination

A fasting blood sample was obtained in the morning to measure plasma concentrations of neurohormonal factors, including catecholamines, atrial natriuretic peptide (ANP), and brain natriuretic peptide (BNP). Plasma catecholamine (norepinephrine, epinephrine, and dopamine) concentrations were measured with high-performance liquid chromatography,

and both plasma ANP and BNP concentrations were measured by radioimmunoassay. Chest radiography (CTR) and echocardiography (LVEDD, left ventricular end diastolic dimension; LAD, left atrial dimension; LVEF) also were performed.

Ambulatory ECG Recording

Ambulatory ECG monitoring was by 2-lead 24-h Holter monitoring (DMC-4502, Nihon Koden, Tokyo, Japan). The Holter tape recordings were analyzed on a full disclosure unit that printed out each individual QRS complex for subsequent visual examination. Complete determination of PVC frequency with a description and quantification of complex forms (multiform PVCs, couplets, and ventricular tachycardia) was undertaken by manual analysis of the full disclosure data. For the purpose of this study, PVCs were defined as any beat of ventricular origin faster than the sinus rate, including the premature beats in couplets and ventricular tachycardia. Ventricular tachycardia was defined as ≥3 consecutive premature beats at a rate of ≥100 beats/min. There was an excellent correlation between the 2 observers with respect to determining the total number of PVCs ($r=0.99$), and the number of episodes of ventricular tachycardia ($r=0.99$). The technician and physician were unaware of the clinical information associated with the recording. Reproducibilities of the results of 24-h Holter monitoring performed twice were assessed in 13 patients with CHF: total beats, $r=0.99$, $p<0.0001$; PVCs, $r=0.91$, $p<0.0001$; couplets, $r=0.95$, $p<0.0001$; ventricular tachycardia, $r=0.95$, $p<0.0001$.

Analysis of HRV

Time-domain parameters of HRV were analyzed on a MARS8000 analysis system (GE Medical Systems Information Technologies, Milwaukee, WI, USA) from 2-lead 24-h Holter recordings. All tapes were manually edited for exclusion of artifacts and premature beats. A minimum of 18 h of analyzable data and a minimum of 85% successive RR intervals were required for a tape to be accepted as valid. The time interval between 2 consecutive QRS complexes was calculated as the normal-to-normal (NN) interval. Abnormal QRS complexes and RR intervals

Table 2 Frequency of Ventricular Arrhythmias and Heart Rate Variability at Baseline and After 2 Weeks in the 2 Groups

| | Sauna-treated group | | Non-treated group | | Comparison with both groups | |
|--------------------------|---------------------|---------------|-------------------|---------------|-----------------------------|---------------|
| | Baseline | After 2 weeks | Baseline | After 2 weeks | At baseline | After 2 weeks |
| PVCs/24 h (beats/24 h) | 3,161±1,104 | 848±415** | 3,048±914 | 3,097±1,033 | NS | <0.0001 |
| Couplets (episodes/24 h) | 71±33 | 15±11** | 69±45 | 87±46 | NS | <0.005 |
| VT (episodes/24 h) | 20±9 | 4±3** | 21±18 | 24±20 | NS | <0.005 |
| Mean RR interval (ms) | 807±28 | 831±42 | 858±63 | 872±46 | NS | NS |
| SDNN (ms) | 113±8 | 142±10** | 111±10 | 112±11 | NS | <0.005 |

PVCs, premature ventricular contractions; VT, ventricular tachycardia; SDNN, standard deviation of NN interval; NS, not significant. All values are given as the mean ± SE; **p<0.01 vs baseline.

Table 3 Various Parameters at Baseline and After 2 Weeks in the 2 Groups

| | Sauna-treated group | | Non-treated group | | Comparison with both groups | |
|------------------|---------------------|---------------|-------------------|---------------|-----------------------------|---------------|
| | Baseline | After 2 weeks | Baseline | After 2 weeks | At baseline | After 2 weeks |
| NYHA (I/II/III) | 0/5/15 | 0/15/5** | 0/2/8 | 0/2/8 | NS | <0.005 |
| Body weight (kg) | 57±3 | 56±3 | 53±3 | 54±3 | NS | <0.05 |
| SBP (mmHg) | 107±4 | 100±3 | 108±5 | 108±4 | NS | NS |
| DBP (mmHg) | 65±3 | 62±2 | 67±3 | 67±2 | NS | NS |
| CTR (%) | 59±1 | 56±2** | 58±1 | 58±1 | NS | <0.05 |
| LVEDD (mm) | 64±2 | 61±2* | 64±3 | 64±3 | NS | NS |
| LAD (mm) | 46±2 | 44±2 | 47±2 | 46±2 | NS | NS |
| LVEF (%) | 29±2 | 33±2* | 29±3 | 31±3 | NS | NS |
| NE (pg/ml) | 431±56 | 415±76 | 414±42 | 455±84 | NS | NS |
| EP (pg/ml) | 25.3±4.1 | 25.0±3.4 | 24.9±4.3 | 28.3±6.0 | NS | NS |
| DOPA (pg/ml) | 13.7±3.1 | 13.7±3.0 | 14.2±4.2 | 14.2±3.2 | NS | NS |
| ANP (pg/ml) | 121±23 | 81±19** | 126±32 | 130±37 | NS | NS |
| BNP (pg/ml) | 425±102 | 229±54** | 415±98 | 419±110 | NS | <0.01 |

NYHA, New York Heart Association; SBP, systolic blood pressure; DBP, diastolic blood pressure; CTR, cardiothoracic ratio; LVEDD, left ventricular end diastolic dimension; LAD, left atrial dimension; LVEF, left ventricular ejection fraction; NE, norepinephrine; EP, epinephrine; DOPA, dopamine; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; NS, not significant. All values are given as the mean ± SE; *p<0.05 vs baseline, **p<0.01 vs baseline.

were replaced by a linear interpolation algorithm. The standard deviation (SD) of all normal beat intervals and the mean length of the NN intervals (SDNN) were used for time-domain measures from the entire recording period. We analyzed 24 patients; 6 patients with atrial fibrillation were excluded.

Study Protocol

Sauna treatment was performed daily for 5 days each week, for a total of 2 weeks. All examinations were performed before the first treatment and on the day after the last treatment.

Statistical Analysis

All data are expressed as the mean ± SEM. Differences in baseline characteristics were evaluated by the chi-square test and unpaired t-test. Within-group changes between baseline and after 2 weeks were evaluated by paired t-test or Wilcoxon signed rank test for variables that were not normally distributed. Between-group comparisons were evaluated by Mann-Whitney's U test using differences between baseline and after 2 weeks. A value of p<0.05 was considered statistically significant.

Results

Baseline Clinical Characteristics and Assessment of Clinical Symptoms

Baseline clinical characteristics are summarized in Table 1. There were no differences in age, gender, NYHA functional class, mean heart rate, blood pressure or use of drugs, such as digoxin, angiotensin-converting enzyme

inhibitor, -blockers, diuretics, nitrates, and antiarrhythmic drugs, at baseline between the 2 groups. All patients enrolled completed the study. In the sauna-treated group, no patient experienced dyspnea, angina pectoris or palpitations. Clinical symptoms related to dyspnea, fatigue, edema, appetite-loss, constipation and insomnia were improved in 17 of 20 patients and unchanged in 3 patients after the 2-week sauna treatment. However, no patients had worsening of clinical symptoms. In the non-treated group, clinical symptoms did not change after 2 weeks.

Cardiac Arrhythmias

At baseline, the total number of PVCs, couplets and episodes of ventricular tachycardia per day were similar between the 2 groups (Table 2). In the sauna-treated group, the total number of PVCs decreased in all patients 2 weeks after treatment. The total number of PVCs in the sauna-treated group was significantly decreased compared with the non-treated group after 2 weeks (p<0.01, Table 2). The total number of couplets and episodes of ventricular tachycardia per day also decreased significantly in the sauna-treated group compared with the non-treated group (Table 2). The prevalence of couplets and ventricular tachycardia in the sauna-treated group compared with the non-treated group was 45% vs 90%, p<0.05, and 20% vs 80%, p<0.01, respectively. The total number of PACs did not significantly change between the 2 groups after 2 weeks (170±102 vs 617±375, p=0.07).

HRV

There was no difference in SDNN at the baseline between the 2 groups, but after 2 weeks, SDNN was sig-

nificantly greater in the sauna-treated group compared with the non-treated group (Table 2).

Neuro-Hormonal Factors

At baseline, there were no differences in the plasma concentrations of ANP, BNP, or catecholamine between the 2 groups. After 2 weeks, there were no differences in the plasma concentrations of ANP or catecholamine between the 2 groups, but the plasma concentration of BNP in the sauna-treated group was significantly lower than in the non-treated group (229 ± 54 pg/ml vs 419 ± 110 pg/ml, $p < 0.05$; Table 3).

NYHA Functional Class, Chest Radiography, Echocardiography and Laboratory Parameters

At baseline, there were no differences in NYHA functional class, CTR or LVEDD between the 2 groups, but after 2 weeks, there was a significant difference in NYHA functional class, body weight, and CTR in the sauna-treated group; LVEDD did not change between the 2 groups. Laboratory parameters, including liver function tests (aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, γ -glutamyl transpeptidase etc), creatinine, electrolytes (Na, Cl, K) and hematocrit, did not change after 2 weeks in either group (data not shown).

Discussion

In the present study, we found that repeated 60°C sauna treatment improved ventricular arrhythmias. Furthermore, we observed that thermal therapy increased HRV and reduced the plasma concentration of BNP in patients with CHF.

The incidence of ventricular arrhythmias is extremely high in patients with CHF: approximately 80% or more of CHF patients have frequent ventricular premature beats and approximately 50% of them have runs of nonsustained ventricular tachycardia.^{3,28–30} Sudden death because of ventricular arrhythmias accounts for approximately half of all deaths in patients with CHF.^{4,31–33} Several studies have shown an association between ventricular arrhythmias and mortality in patients with CHF^{5–9,34–36} but unfortunately, current antiarrhythmic medications, such as class I drugs, have only limited efficacy in these patients and may even be associated with worsening ectopic activity and hemodynamic deterioration.^{10–12} In large randomized trials with amiodarone, a potent antiarrhythmic drug with additional sympatholytic and minor negative inotropic effects, the Group for the Study of Survival in Heart Failure in Argentina (GESICA) demonstrated that low doses reduced ventricular arrhythmias and mortality in patients with CHF;¹³ however, the Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure had conflicting results concerning mortality.¹⁴ Previous studies have demonstrated that β -blockers, which also have antiarrhythmic effects, reduce mortality and the risk of sudden cardiac death, as well as ventricular arrhythmias, in patients with CHF³⁷ and other studies have shown that ventricular arrhythmias in patients with CHF are improved by treatment with non-antiarrhythmic drugs, such as angiotensin-converting enzyme inhibitors^{16–18} and spironolactone.³⁸ Our present results demonstrated that thermal therapy reduced the total number of PVCs, couplets, and episodes of ventricular tachycardia in patients with CHF and we have already shown that thermal therapy reduced mortality in hamsters

with CHF.²² We suggest that improvement of ventricular arrhythmias may be one of the mechanisms by which repeated thermal therapy improves the prognosis in patients with CHF.

Although the mechanisms of ventricular arrhythmias occurring in patients with CHF are still unclear, experimental evidence suggests that the development of delayed and early afterdepolarization-induced triggered activity and automaticity, in addition to conditions favoring reentry, are related to arrhythmias in the setting of heart failure. Modulating factors, such as sympathetic activation, electrolyte disturbances and chronic left ventricular stretch, are also present in the setting of heart failure.^{39,40} It is well-established that the sympathetic nervous system is activated in patients with CHF^{41–43} and analysis of HRV provides important information about sympathetic nervous activity in these patients.^{25,44} Data from the recent United Kingdom-Heart failure Evaluation and Assessment of Risk Trial (UK-HEART) suggest that reduced HRV, analyzed by a traditional time-domain method (including SDNN), is related to the risk of ventricular arrhythmias and sudden death in patients with CHF.²⁴ and we suggest that one of the mechanisms by which repeated sauna treatment significantly improves ventricular arrhythmias is by increasing HRV, although we have not clarified the underlying mechanisms of that effect of thermal therapy. On the other hand, the self-assessment QOL questionnaire revealed 17 of 20 patients who answered 'improved' to more than 3 of 6 clinical symptoms that comprised dyspnea, fatigue, sleeplessness, edema, appetite-loss and constipation, and furthermore, none of the patient answered 'worsened' for any symptom. Therefore, the improvement may be related to better mood as a result of repeated sauna treatment. Further study is needed.

The chronic stretch of cardiac myocytes contributes to shortening of the action potential duration and mild decreases in the action potential amplitude and resting membrane potential.⁴⁵ These changes may be arrhythmogenic by increasing reentry and abnormal automaticity.⁴⁶ In patients with CHF, the ventricular wall is chronically stretched because of increases in ventricular volume and/or pressure overload. It is well-established that BNP is secreted predominantly by the ventricle in response to ventricular wall stretch.⁴⁷ On the basis of our findings, including previous data,²⁰ which showed significantly decreased plasma concentrations of BNP after 2 weeks of sauna treatment, we speculate that another mechanism responsible for decreased ventricular arrhythmias may be reduction of ventricular wall stretch.

Electrolyte disturbances, such as hypokalemia and hypomagnesemia, are prevalent in patients treated with diuretics and are implicated as a cause of ventricular arrhythmias associated with CHF. However, we did not observe significant changes in the electrolyte concentrations after 2 weeks (data not shown).

We have treated many CHF patients with sauna therapy and so far none of the in-hospital patients has shown any deterioration in their condition. However, thermal therapy does not appear to be indicated for CHF patients with aortic stenosis or obstructive hypertrophic cardiomyopathy because the pressure gradient is increased. In the present study, only CHF patients with NYHA functional class II or III underwent sauna treatment. It is well-known that the more severe the CHF, the more prevalent are ventricular arrhythmias. We evaluated the effects of sauna therapy on

ventricular arrhythmias at 2 weeks, but further studies of the long-term effects and benefit in CHF patients with NYHA functional class IV are needed.

In conclusion, repeated 60°C sauna treatment decreased ventricular arrhythmias in CHF patients with NYHA functional class II or III.

Acknowledgment

This study was supported in part by a Grant-in-Aid from the Japan Heart Foundation/Pfizer Grant for Cardiovascular Disease Research.

References

- Wilson JR, Schwartz JS, Sutton MS, Ferraro N, Horowitz LN, Reichel N, et al. Prognosis in severe heart failure: Relation to hemodynamic measurements and ventricular ectopic activity. *J Am Coll Cardiol* 1983; **2**: 403–410.
- Meinertz T, Hofmann T, Kasper W, Treese N, Bechtold H, Stienen U, et al. Significance of ventricular arrhythmias in idiopathic dilated cardiomyopathy. *Am J Cardiol* 1984; **53**: 902–907.
- Maskin CS, Siskind SJ, LeJemtel TH. High prevalence of nonsustained ventricular tachycardia in severe congestive heart failure. *Am Heart J* 1984; **107**: 896–901.
- Koseki Y, Watanabe J, Shinozaki T, Sakuma M, Komaru T, Fukuchi M, et al. Characteristics and 1-year prognosis of medically treated patients with chronic heart failure in Japan: Chronic Heart Failure Analysis Registry in Tohoku district (CHART). *Circ J* 2003; **67**: 431–436.
- Holmes J, Kubo SH, Cody RJ, Kligfield P. Arrhythmias in ischemic and nonischemic dilated cardiomyopathy: Prediction of mortality by ambulatory electrocardiography. *Am J Cardiol* 1985; **55**: 146–151.
- Dargie HJ, Cleland JGF, Leckie BJ, Inglis CG, East BW, Ford I. Relation of arrhythmias and electrolyte abnormalities to survival in patients with severe chronic heart failure. *Circulation* 1987; **75**(Suppl IV): IV-98–IV-107.
- De Maria R, Gavazzi A, Caroli A, Ometto R, Biagini A, Camerini F. Ventricular arrhythmias in dilated cardiomyopathy as an independent prognostic hallmark. *Am J Cardiol* 1992; **69**: 1451–1457.
- Doval HC, Nul DR, Grancelli HO, Varini SD, Soifer S, Corrado G, et al. Nonsustained ventricular tachycardia in severe heart failure: Independent marker of increased mortality due to sudden death. *Circulation* 1996; **94**: 3198–3203.
- Stevenson WG, Sweeney MO. Arrhythmias and sudden death in heart failure. *Jpn Circ J* 1997; **61**: 727–740.
- The Cardiac Arrhythmias Suppression Trial (CAST) Investigators. CAST mortality and morbidity: Treatment versus placebo. *N Engl J Med* 1991; **324**: 781–788.
- Pratt CM, Eaton T, Francis M. The inverse relationship between baseline left ventricular ejection fraction and outcome of antiarrhythmic therapy: A dangerous imbalance in the risk-benefit ratio. *Am Heart J* 1989; **118**: 433–440.
- Flaker GC, Blackshear JL, McBride R, Kronmal RA, Halperin JL, Hart RG. Antiarrhythmic drug therapy and cardiac mortality in atrial fibrillation: The Stroke Prevention in Atrial Fibrillation Investigators. *J Am Coll Cardiol* 1992; **20**: 527–532.
- Doval HC, Nul DR, Grancelli HO, Perrone SV, Bortman GR, Curiel R. Randomized trial of low-dose amiodarone in severe congestive heart failure. *Lancet* 1994; **344**: 493–498.
- Singh SN, Fletcher RD, Fisher SG, Singh BN, Lewis HD, Deedwania PC, et al. Amiodarone in patients with congestive heart failure and asymptomatic ventricular tachycardia. *N Engl J Med* 1995; **333**: 77–82.
- Julian DG, Camm AJ, Frangin G, Janse MJ, Munoz A, Schwartz PJ, et al. Randomised trial of effect of amiodarone on mortality in patients with left-ventricular dysfunction after recent myocardial infarction: EMIAT. *Lancet* 1997; **349**: 667–674.
- The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991; **325**: 293–302.
- Fletcher RD, Cintron GB, Johnson G, Orndorff J, Carson P, Cohn JN, for the V-HeFT II VA Cooperative Studies Group. Enalapril decreases prevalence of ventricular tachycardia in patients with chronic congestive heart failure. *Circulation* 1993; **87**(Suppl VI): VI-49–VI-55.
- Cohn JN, Johnson G, Ziesche S, Cobb F, Francis G, Tristani F, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991; **325**: 303–310.
- Tei C, Horikiri Y, Park JC, Jeong JW, Chang KS, Toyama Y, et al. Acute hemodynamic improvement by thermal vasodilation in congestive heart failure. *Circulation* 1995; **91**: 2582–2590.
- Kihara T, Biro S, Imamura M, Yoshifuku S, Takasaki K, Ikeda Y, et al. Repeated sauna treatment improves vascular endothelial and cardiac function in patients with chronic heart failure. *J Am Coll Cardiol* 2002; **39**: 754–759.
- Tei C, Tanaka N. Thermal vasodilation as a treatment of congestive heart failure: A novel approach. *J Cardiol* 1996; **27**: 29–30.
- Ikeda Y, Biro S, Kamogawa Y, Yoshifuku S, Kihara T, Minagoe S, et al. Effect of repeated sauna therapy on survival in TO-2 cardiomyopathic hamsters with heart failure. *Am J Cardiol* 2002; **90**: 343–345.
- Meredith IT, Broughton A, Jennings GL, Esler MD. Evidence of a selective increase in cardiac sympathetic activity in patients with sustained ventricular arrhythmias. *N Engl J Med* 1991; **325**: 618–624.
- Nolan J, Batin PD, Andrews R, Lindsay SJ, Brooksby P, Mullen M, 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.
- Fauchier L, Babuty D, Cosnay P, Fauchier JP. Prognostic value of heart rate variability for sudden death and major arrhythmic events in patients with dilated cardiomyopathy. *J Am Coll Cardiol* 1999; **33**: 1203–1207.
- Bilchick KC, Fetis B, Djoukeng R, Fisher SG, Fletcher RD, Singh SN, et al. Prognostic value of heart rate variability in chronic congestive heart failure (Veterans affairs' survival trial of antiarrhythmic therapy in congestive heart failure). *Am J Cardiol* 2002; **90**: 24–28.
- Koyama J, Watanabe J, Yamada A, Koseki Y, Konno Y, Toda S, et al. Evaluation of heart-rate turbulence as a new prognostic marker in patients with chronic heart failure. *Circ J* 2002; **66**: 902–907.
- Meinertz T, Hofmann T, Kasper W, Treese N, Bechtold H, Stienen U, et al. Significance of ventricular arrhythmias in idiopathic dilated cardiomyopathy. *Am J Cardiol* 1984; **53**: 902–907.
- Gradman A, Deedwania P, Cody R, Massie B, Packer M, Pitt B, et al. Predictors of total mortality and sudden death in mild to moderate heart failure. *J Am Coll Cardiol* 1989; **14**: 564–570.
- Podrid PJ, Fogel RI, Fuchs TT. Ventricular arrhythmias in congestive heart failure. *Am J Cardiol* 1992; **69**: 82G–96G.
- Brandenburg RO. Cardiomyopathies and their role in sudden death. *J Am Coll Cardiol* 1985; **5**: 185B–189B.
- Packer M. Sudden unexpected death in patients with congestive heart failure: A second frontier. *Circulation* 1985; **72**: 681–685.
- Olshausen KV, Witt T, Pop T, Treese N, Bethge KP, Meyer J. Sudden cardiac death while wearing a Holter monitor. *Am J Cardiol* 1991; **67**: 381–386.
- Romeo F, Pelliccia F, Cianfrocca C, Cristofani R, Reale A. Predictors of sudden death in idiopathic dilated cardiomyopathy. *Am J Cardiol* 1989; **63**: 138–140.
- Singh SN, Fisher SG, Carson PE, Fletcher RD. Prevalence and significance of nonsustained ventricular tachycardia in patients with premature ventricular contractions and heart failure treated with vasodilator therapy. *J Am Coll Cardiol* 1998; **32**: 942–947.
- Singh BN. Significance and control of cardiac arrhythmias in patients with congestive heart failure. *Heart Fail Rev* 2002; **7**: 285–300.
- Cice G, Tagliamonte L, Ferrara L, Lacono A. Efficacy of carvedilol on complex ventricular arrhythmias in dilated cardiomyopathy: Double-blind, randomized, placebo-controlled study. *Eur Heart J* 2000; **21**: 1259–1264.
- Ramires FJ, Mansur A, Coelho O, Maranhao M, Gruppi CJ, Mady C, et al. Effect of spironolactone on ventricular arrhythmias in congestive heart failure secondary to idiopathic dilated or to ischemic cardiomyopathy. *Am J Cardiol* 2000; **85**: 1207–1211.
- Vermeulen JT. Mechanisms of arrhythmias in heart failure. *J Cardiovasc Electrophysiol* 1998; **9**: 208–221.
- Wit AL, Rosen MR. Pathophysiologic mechanisms of cardiac arrhythmias. *Am Heart J* 1983; **106**: 798–811.
- Leimbach WN Jr, Wallin BG, Victor RG, Aylward PE, Sundlof G, Mark AL. Direct evidence from intraneural recordings for increased central sympathetic outflow in patients with heart failure. *Circulation* 1986; **73**: 913–919.
- Swedberg K, Eneroth P, Kjekshus J, Wilhelmson L. Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. *Circulation* 1990; **82**: 1730–1736.
- Meredith IT, Eisenhofer G, Lambert GW, Dewar EM, Jennings GL, Esler MD. Cardiac sympathetic nervous activity in congestive heart

- failure: Evidence for increased neuronal norepinephrine release and preserved neuronal uptake. *Circulation* 1993; **88**: 136–145.
44. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996. Heart rate variability: Standards of measurement, physiological interpretation, and clinical use. *Circulation* 1996; **93**: 1043–1065.
 45. Franz MR, Cima R, Wang D, Profit D, Kurz R. Electrophysiological effects of myocardial stretch and mechanical determinants of stretch-activated arrhythmias. *Circulation* 1992; **86**: 968–978.
 46. Hansen DE, Craig S, Hondeghem LM. Stretch-induced arrhythmias in the isolated canine ventricle: Evidence for the importance of mechanoelectrical feedback. *Circulation* 1990; **81**: 1094–1105.
 47. Yasue H, Yoshimura M, Sumida H, Kikuta K, Kugiyama K, Jougasaki M, et al. Localization and mechanism of secretion of B-type natriuretic peptide in comparison with those of A-type natriuretic peptide in normal subjects and patients with heart failure. *Circulation* 1994; **90**: 195–203.