Age and Sex as Determinants of Ventricular Arrhythmic Events in Patients with Decompensated Congestive Heart Failure

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Background: The propensity to develop specific arrhythmias varies between the sexes and is influenced by age. Patients with congestive heart failure (CHF) have a high prevalence of ventricular ectopy. However, in the setting of CHF, it is not known whether sex-related or age-dependent differences exist in the susceptibility to arrhythmias.

Methods: The study population included 134 men and 73 women (mean age 61 ± 14 years) admitted for decompensated CHF. The severity of ventricular arrhythmias was assessed by 24-hour Holter monitoring. None of the patients were on parenteral vasoactive therapy during Holter recording.

Results: All measures of ventricular ectopy were markedly lower in women. The average hourly premature ventricular contractions (PVCs), the frequency of ventricular pairs, the mean hourly repetitive ventricular beats, and the frequency of ventricular tachycardia episodes per 24 hours were 40%, 62%, 65%, and 78% lower in women, respectively. Multivariate logistic regression revealed that the risk of developing > 3 ventricular pairs per 24-hour period (OR = 2.2, CI = 1.1–4.2, P = 0.03), > 3 repetitive ventricular beats/hour (OR = 2.5, CI = 1.2-5.3, P = 0.01), or an episode of ventricular tachycardia (OR = 2.1, CI = 1.2–3.9, P = 0.01) were significantly higher in men. Patients in the higher tertile age group had a higher risk for the presence of > 3 ventricular pairs per 24-hour period (OR = 2.3, CI = 1.1–4.2, P = 0.03), and the presence of > 3 repetitive ventricular beats per hour (OR = 5.9, CI = 2.7–13.3, P < 0.0001), compared with patients in the lower age tertile.

Conclusion: Male sex and age are associated with complex ventricular ectopy in patients with CHF. Further understanding of the mechanisms involved in the relative protection conferred by female sex would advance our understanding about arrhythmias in heart failure. **A.N.E. 2002;7(3):234–241**

heart failure; gender; age; ventricular arrhythmias

The incidence and susceptibility to different types of arrhythmias varies between the sexes,[1,2] and different age groups.[3–5] Women have longer corrected QT intervals and are more likely to develop torsades de pointes.[1,2] Men have an increased prevalence of atrial fibrillation,[6] more supraventricular and ventricular ectopic beats, and more episodes of ventricular tachycardia.[5] Aging has been associated with increased ventricular arrhythmias in normal subjects and patients with structural heart disease.[3–5]

Cardiac arrhythmias are frequent among patients with congestive heart failure (CHF) and are considered a major mechanism causing death in these patients.[7,8] The presence of complex ventricular arrhythmias is associated with total mortality and arrhythmic death.[9–12] It is generally accepted that multiple mechanisms contribute to the occurrence of ventricular arrhythmias in patients with CHF including myocardial stretch, neuroendocrine factors, electrolyte abnormalities, and activation of the sympathetic and renin-angiotensin systems.[7,8,13,14]

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However, it is not known if age and sex are important factors in the susceptibility to arrhythmias in patients with CHF.

Several studies have shown that women with heart failure have a survival advantage compared with men, regardless of heart failure stage and severity.[15-18] These observations raise the possibility that lower susceptibility to arrhythmic events in women may explain their survival advantage. The primary aim of the present study was to assess potential gender-related differences in the occurrence of arrhythmias in patients with CHF. In addition, the effect of age on the frequency of ventricular arrhythmic events was determined.

METHODS

Patients

The study population was derived from subjects enrolled in the Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Nesiritide Therapy (PRECEDENT) study. This investigation was a randomized, multicenter trial comparing the proarrhythmic and chronotropic effects of nesiritide (human B-type natriuretic peptide) to dobutamine in patients with decompensated CHF for whom inpatient parenteral vasoactive therapy was considered appropriate. Eligible patients included subjects who were over 18 years of age and had a previous history of New York Heart Association Class III or IV heart failure. Exclusion criteria included recent myocardial infarction (< 48 hours), ongoing unstable angina, cardiogenic shock or baseline systolic blood pressure < 85 mmHg, stroke within the past month, significant valvular aortic stenosis, obstructive cardiomyopathy, or constrictive pericarditis. The investigational review committees of all participating study sites approved the study protocol, and informed consent was obtained in all patients.

As part of the study protocol, 24-hour ambulatory electrocardiographic (AECG) recordings were obtained in all patients prior to randomization to treatment with dobutamine or nesiritide. All clinical information and Holter tapes were submitted by individual investigators to the coordinating center for data entry and AECG analysis. Prespecified analysis of the AECG data were defined before the initiation of the study, and the present report consists of all patients in whom technically adequate AECG were available.

AECG Monitoring

Three-channel (V_1, V_5, and aVF) recordings were obtained and analyzed on a commercially available scanner (model 2010, Zymed Medical Instruments, Camarillo, CA, USA) by the core laboratory. Ectopic beats were quantified by creating templates of normally conducted QRS and complexes considered to be ventricular ectopic complexes that were displayed to and classified by an operator. Supraventricular ectopic complexes were those with QRS morphology matching the template of normally conducted complexes, detected strictly by their prematurity in the cardiac cycle.

Recordings were analyzed for the presence and hourly frequency of arrhythmic events, and measures of arrhythmic activity were calculated. Four measures of ventricular arrhythmic burden were prospectively defined: (1) average hourly number of single ventricular ectopic beats (premature ventricular contractions [PVCs]), (2) paired ventricular beats, (3) ventricular tachycardia events (3 or more consecutive ventricular ectopic beats with mean R-to-R cycle length < 600 ms), and (4) hourly repetitive ventricular PVCs.

Statistical Analysis

The baseline characteristics of the groups were compared by the *t*-test for continuous variables and by the chi-square statistic for noncontinuous variables. Because the distribution of continuous AECG variables was skewed and not normally distributed, the natural log transformation was applied before statistical analyses were performed as described by Sami et al.[19] and others.[4,20] Geometric mean values were calculated by exponentiation of the estimates obtained for transformed variables. Comparisons of arrhythmic events between male and female groups were made using the Mann-Whitney Rank Sum test. The frequency of ventricular arrhythmic events among age quartiles was analyzed by one-way ANOVA. If the ANOVA test revealed significant differences, subsequent pairwise analyses of individual group means were performed with the Bonferroni correction for multiple comparisons. In addition, univariate and multivariate logistic regression models were conducted to detect independent predictors of arrhythmic events. Factors associated with at least marginal ($P < 0.1$) univariate predictive values were entered into multiple logistic regression models using mea-

sures of ventricular arrhythmias as dependent variables. Differences were considered significant at the $P < 0.05$ level. All statistical analyses were performed using the StatView statistical software (SAS Institute Inc, Cary, NC, USA).

RESULTS

A total of 255 patients were enrolled at 46 clinical sites. Technical failure and excess artefacts resulted in the exclusion of 19 (7%) patients from analysis. An additional 29 (11%) patients were excluded because they were on amiodarone therapy. The remaining 207 patients (mean age of 61 ± 14 years) constituted the study population.

The study population was predominantly white and elderly with New York Heart Association Class III or IV heart failure (Table 1). Frequent, comorbid conditions included hypertension, diabetes mellitus, previous myocardial infarction, and significant cardiac arrhythmias. No difference in baseline clinical data was observed between the two groups with respect to clinical variables except that ischemic heart disease was more frequent as the primary etiology of CHF among men. Concomitant medications were not significantly different between the two groups.

Effect of Gender on Ventricular Ectopy

All measures of ventricular ectopy were markedly lower in women compared to men. The average hourly PVCs, the frequency of ventricular pairs, the mean hourly repetitive ventricular beats, and the frequency of ventricular tachycardia episodes per 24 hours were 40%, 62%, 65%, and 78% lower in women, respectively (Table 2).

To exclude the possible effects of clinical variables and drugs on the effect of the patient's sex on ventricular ectopic activity, simple and multiple logistic regression analyses were performed. The following measures of ventricular ectopy served as dependent variables: > 10 PVCs per hour, > 3 repetitive ventricular PVCs per hour, > 3 ventricular pairs per 24-hour period, and any episode of ventricular tachycardia per a 24-hour period. Variables considered as independent risk factor candidates for the model were clinical and historical variables that included age, sex, body weight, primary etiology of heart failure stratified as ischemic

Table 1. Baseline Clinical Characteristics

Characteristics	Men (n = 134)	Women (n = 73)
Age (years)	62 ± 15	61 ± 14
Primary Etiology of Heart Failure		
Ischemic	78 (58)‡	30 (41)
Idiopathic	27 (20)	21 (29)
Hypertensive	17 (13)	9 (12)
Valvular or rheumatic	3 (2)	6 (8)
Other*	9 (7)	7 (10)
New York Heart Association functional class		
Class III	99 (74)	51 (70)
Class IV	35 (26)	22 (30)
Laboratory data		
Serum sodium (meq/L)	137 ± 4	139 ± 5
Serum potassium (meq/L)	4.2 ± 0.5	4.2 ± 0.5
BUN (mg/dL)	35 ± 22	32 ± 21
Creatinine (mg/dL)	1.6 ± 0.8	1.4 ± 0.8
Cardiac Medications		
Digoxin	103 (77)	58 (79)
Angiotensin converting enzyme inhibitors	94 (70)	52 (71)
Angiotensin II receptor antagonists	14 (11)	12 (16)
β-Blockers	28 (21)	16 (21)
Other vasodilating drugs†	18 (13)	14 (19)

Numbers in parentheses are percent of the group. Continuous variables are mean ± SD.
* Other etiologic groups included myocarditis, alcoholic cardiomyopathy, and postpartum cardiomyopathy.
† Calcium channel blockers, nitrates, hydralazine, or α1-blockers.
‡ P = 0.02,

Table 2. Measures of Ventricular Ectopy in Men and Women

	Men (n = 134)	Women (n = 73)	P Value
PVCs/hr	178 ± 24	106 ± 18	0.06
Ventricular pairs per hour	11.8 ± 2.7	4.4 ± 1.3	< 0.05
Repetitive PVCs per hour	31.2 ± 9.4	6.9 ± 3.2	< 0.05
Ventricular tachycardia per 24-hour period	27.90 ± 6.7	9.90 ± 2.9	0.01

PVC = premature ventricular contraction.

or nonischemic, history of ventricular fibrillation, sudden cardiac death, or automatic implantable cardioverter defibrillator (AICD) implantation, New York Heart Association functional class, plasma potassium, plasma sodium, serum creatinine, and blood pressure. In addition, drug therapies (digoxin, angiotensin converting-enzyme inhibitors, and beta-blockers) were considered in the model.

In univariate logistic regression, no significant association was found between patient sex and the presence of > 10 PVCs per hour. However, a positive relationship was seen between male sex and the presence of > 3 ventricular pairs per 24-hour period (odds ratio [OR] = 2.3, confidence interval [CI] = 1.1–4.2, P = 0.03), the presence of > 3 repetitive ventricular beats per hour (OR = 1.9, CI = 0.9–2.4, P = 0.04), and ventricular tachycardia episodes (OR = 2.0, CI = 1.0–3.5, P = 0.02). Univariate logistic regression also identified beta-blocker use and higher plasma potassium level as negative independent correlates of all measures of ventricular ectopy (data not shown).

In a multivariate logistic regression, the positive association between male sex and the frequency of ventricular pairs, the mean hourly repetitive ventricular beats, and ventricular tachycardia episodes remained significant (Fig. 1). Ischemic heart disease was not a significant univariate predictor of any measure of atrial or ventricular ectopy, nor did it alter the multivariate models.

Effect of Age on Ventricular Ectopy

Patients were stratified into three groups according to tertiles of age. The ANOVA test indicated an overall significant difference among the three groups in the mean hourly PVCs (P = 0.0004), mean hourly ventricular pairs (P = 0.0005), mean hourly repetitive ventricular beats (P = 0.005), and the frequency of ventricular tachycardia episodes per 24 hours (P < 0.048). As shown in Figure 2, Bonferroni post hoc comparison revealed that patients in the lowest tertile of age had significantly less frequent ventricular arrhythmias compared with the patients in the upper tertile.

The results from univariate and multivariate logistic regression models, in which odds ratios are expressed as the risk of patients in the upper age tertile compared to patients in the lowest age tertile, are shown in Table 3. A significant independent association was found between the higher tertile age group and the presence of > 10 PVCs per hour, the presence of > 3 ventricular pairs per 24-hour period, and the presence of > 3 repetitive ventricular beats per hour, but not with the presence of ventricular tachycardia.

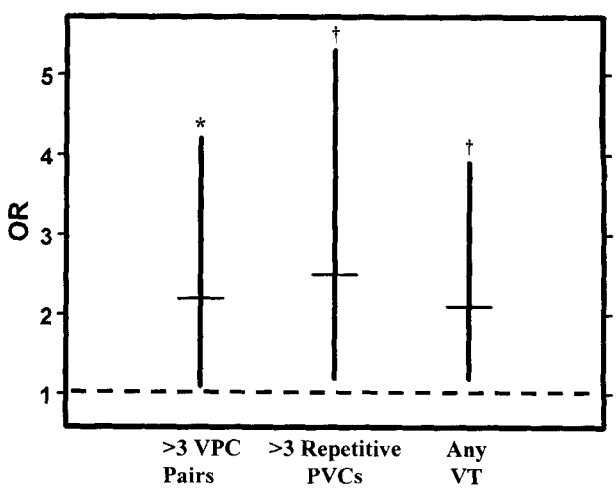

Figure 1. Logistic regression for association of sex and measures of ventricular ectopy. Adjusted odds ratios and 95% confidence intervals are shown for the risk of men to develop > 3 premature ventricular contractions (PVCs) pairs, > 3 repetitive PVCs, and any episode of ventricular tachycardia (VT) compared with women. *P = 0.02, †P = 0.01.

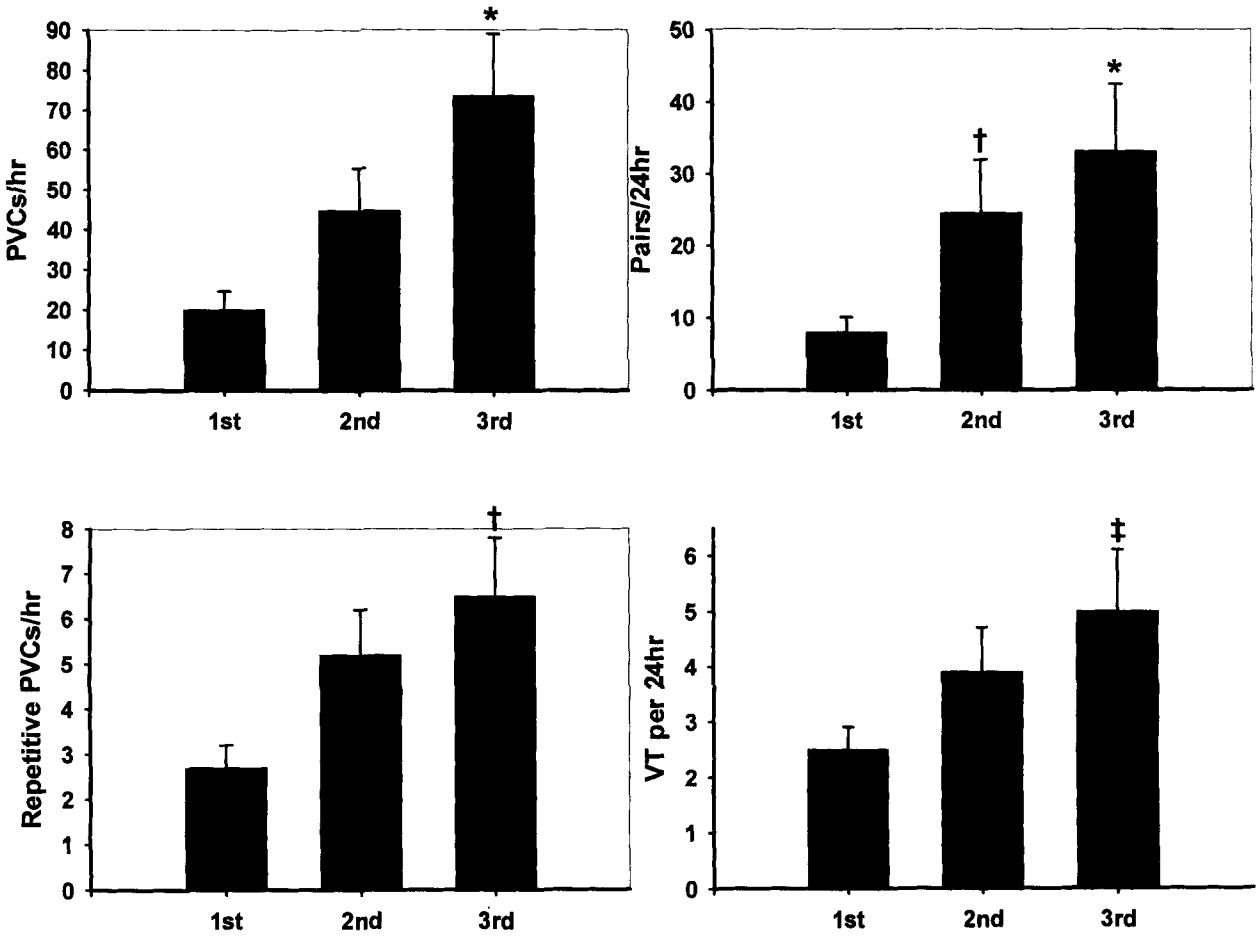

Figure 2. Bar graph showing geometric means of four measures of ventricular ectopy according to age tertiles. Age tertiles were compared by one-way ANOVA followed by Bonferroni post hoc comparison. *P < 0.001 compared with first tertile, †P < 0.005 compared with first tertile, ‡P = 0.01 compared with first tertile. VT = ventricular tachycardia.

Discussion

In patients with CHF, ventricular arrhythmia is a multifactorial event, preconditioned by structural abnormalities and modulated by functional factors that lead to triggering events.[21,22] Structural changes like cellular hypertrophy, myocardial stretch, interstitial fibrosis, scarring, and tissue re-

Table 3. Univariate and Multivariate Logistic Regression of the Relationship Between Age Quartiles (First Tertile vs Third Tertile) and the Occurrence of Ventricular Ectopy

	Unadjusted			Adjusted for Clinical Variables and Drug Therapies		
	OR	CI	P Value	OR	CI	P Value
PVCs > 10 per hour	3.9	1.7–8.8	0.001	6.7	2.6–16.9	< 0.0001
Ventricular pairs > 3 per 24-hour period	2.8	1.4–5.9	0.006	4.1	1.8–9.4	0.001
Repetitive PVC > 3 per 24-hour period	4.3	2.1–8.9	0.001	5.9	2.7–13.3	< 0.0001
Any ventricular tachycardia per 24 hours	1.3	0.7–2.6	NS	1.7	0.8–3.5	NS

PVC = premature ventricular contraction; OR = odds ratio; CI = confidence interval.

modeling produce an arrhythmic substrate.[22,23] Triggers for ventricular arrhythmias vary according to the clinical situation and are primarily electrical, ischemic, metabolic, and neurohormonal.[21-23] In the setting of decompensated heart failure, neurohormonal triggering mechanisms (like the magnitude of neuroendocrine responses, end-organ sensitivity to various neurohumoral modulators, or autonomic dysregulation) are believed to be especially important in determining the propensity to arrhythmias.

Despite the multiple factors that may promote ventricular ectopy in the setting of heart failure, the results of the present study suggest that men with heart failure are more likely to develop ventricular arrhythmias compared to women. In addition, age appears to be independently associated with ventricular arrhythmias. Multivariate regression analysis indicated a positive independent relationship between male sex and increased age with measures of ventricular arrhythmic events. The relative susceptibility conferred by male sex was especially striking for high-grade ventricular arrhythmias. The marked sex discordance in multivariate association with respect to ventricular arrhythmias in the setting of heart failure has not been previously reported.

Possible Mechanisms for the Gender Effect

Three major factors may account for the findings of the present study. First, sex-distinctive differences in the electrophysiological properties of the myocardium may exist. Several studies have demonstrated an antiarrhythmic effect of estrogens in the setting of ischemia, reperfusion, and catecholamine infusion.[24-26] The effect may be mediated through modulation of ion channel activation,[24,26] although this explanation is relevant only to premenopausal women or those on estrogen replacement therapy.

Second, sex-based differences in triggering events may explain the present findings. Heart failure entails complex neurohormonal responses including profound abnormalities in autonomic control, characterized by sympathetic overactivity and parasympathetic withdrawal,[27] together with activation of endogenous vasoconstrictor systems (e.g., renin-angiotensin, norepinephrine).[7,21] These humoral and neural alterations are thought to exert direct or indirect (e.g., parasympathetic withdrawal) proarrhythmic effects on the heart. Thus, differences in triggering mechanisms (like the magnitude of neurohormonal responses, end-organ sensitivity to various neurohumoral modulators, or autonomic dysregulation) may be especially important in determining the propensity to arrhythmias.

Third, gender-based differences in arrhythmic substrate may have been present due to differences in underlying cardiac diagnoses. This explanation, however, is not supported by the current data because the etiology of heart failure had no discernible effect on the severity of ventricular ectopy. In addition, all patients in the study had advanced heart failure, and therefore, the possibility of a major difference in arrhythmic substrate is unlikely.

Attenuated neurohumoral and sympathetic activation of a variety of stressors has been described in women and may confer protection from arrhythmias during heart failure decompensation. For example, women exhibit diminished adrenergic response to psychological stress,[28] hypoglycemia,[29] exercise,[30] and greater vagal activation during abrupt coronary occlusion.[31] Women with nonischemic heart failure seem to have an attenuated sympathetic activation and parasympathetic withdrawal compared with men.[32] Furthermore, the sensitivity of peripheral adrenergic receptors is lower in women than in men,[33] which may be related to estrogen mediated desensitization of beta-adrenergic receptor activation of adenyl cyclase.[34]

Possible Mechanisms for the Effect of Age

Increased age was independently associated with a higher incidence of all measures of ventricular ectopy. These findings are consistent with studies showing a relationship between ventricular ectopy and advancing age in subjects free of clinical cardiovascular disease,[5] in subjects undergoing treadmill exercise testing,[3] and in patients with prior myocardial infarction.[4,35] The age-dependence of ventricular arrhythmias in subjects without overt heart disease is thought to be related to a higher prevalence of subclinical heart disease.[5] However, the pathophysiological mechanisms underlying the effect of age on ventricular ectopy in patients with clinical structural heart disease are not well understood.[4] It has been suggested that age-dependent sinus pauses may initiate ventricu-

lar arrhythmias through early afterdepolarization-induced triggered activity.[36]

Implication of Gender Effect for CHF Prognosis

Although it is not easy to accurately determine the mechanism causing death in patients with severe heart failure, it is generally accepted that ~ 40% of these patients die suddenly.[10,37] Ventricular tachycardia and fibrillation have been reported as the culprits in ~ 80% of ambulatory patients[38,39] and 30% of in hospital patients[40] with CHF in whom Holter recordings were being obtained at the time of death. A number of studies in patients with heart failure have demonstrated the independent value of the presence of complex ventricular arrhythmias as predictors of sudden cardiac death.[9-12]

Natural history studies on patient populations with a broad spectrum of heart failure severity have shown that after the onset of CHF symptoms the prognosis of women is better than that of men.[15-18] Thus, the results of the present study raise the possibility that gender-dependent variability in CHF mortality might be related, at least in part, to a relative female protection from malignant ventricular arrhythmias.

CONCLUSION

The results suggest that women are relatively protected from the occurrence of ventricular arrhythmias in the setting of heart failure compared with men. These findings may be relevant to female survival advantage in the setting of heart failure. Better understanding of the mechanisms involved in the protection conferred by female sex would advance our understanding about arrhythmias in heart failure.

REFERENCES

1. Linde C. Women and arrhythmias. PACE 2000;23:1550-1560.
2. Larsen JA, Kadish AH. Effects of gender on cardiac arrhythmias. (comments) J Cardiovasc Electrophysiol 1998;9:655-664.
3. Mayuga R, Arrington CT, O'Connor FC, et al. Why do exercise-induced ventricular arrhythmias increase with age? Role of M-mode echocardiographic aging changes. J Gerontol A Biol Sci Med Sci 1996;51:M23-28.
4. Josephson RA, Papa LA, Brooks MM, et al. Effect of age on postmyocardial infarction ventricular arrhythmias (Holter Registry data from CAST I and CAST II). Cardiovascular Arrhythmia Suppression Trials. Am J Cardiol 1995;76:710-713.
5. Manolio TA, Furberg CD, Rautaharju PM, et al. Cardiac arrhythmias on 24-h ambulatory electrocardiography in older women and men: The Cardiovascular Health Study. J Am Coll Cardiol 1994;23:916-925.
6. Benjamin EJ, Levy D, Vaziri SM, et al. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. JAMA 1994;271:840-844.
7. Uretsky BF, Sheahan RG. Primary prevention of sudden cardiac death in heart failure: Will the solution be shocking? J Am Coll Cardiol 1997;30:1589-1597.
8. Bigger JT. Why patients with congestive heart failure die: Arrhythmias and sudden cardiac death. Circulation 1987;75:IV28-35.
9. Doval HC, Nul DR, Grancelli HO, et al. Nonsustained ventricular tachycardia in severe heart failure. Independent marker of increased mortality due to sudden death. GESICA- GEMA Investigators. (comments) Circulation 1996;94:3198-3203.
10. Chakko CS, Gheorghiade M. Ventricular arrhythmias in severe heart failure: Incidence, significance, and effectiveness of antiarrhythmic therapy. Am Heart J 1985;109:497-504.
11. Francis GS. Development of arrhythmias in the patient with congestive heart failure: Pathophysiology, prevalence and prognosis. Am J Cardiol 1986;57:3B-7B.
12. Gradman A, Deedwania P, Cody R, et al. Predictors of total mortality and sudden death in mild to moderate heart failure. Captopril-Digoxin Study Group. J Am Coll Cardiol 1989;14:564-570; discussion 571-562.
13. Packer M. Sudden unexpected death in patients with congestive heart failure: A second frontier. Circulation 1985;72:681-685.
14. Zipes DP, Wellens HJ. Sudden cardiac death. Circulation 1998;98:2334-2351.
15. Adams KF Jr, Dunlap SH, Sueta CA, et al. Relation between gender, etiology and survival in patients with symptomatic heart failure. J Am Coll Cardiol 1996;28:1781-1788.
16. Adams KF Jr, Sueta CA, Gheorghiade M, et al. Gender differences in survival in advanced heart failure. Insights from the FIRST study. Circulation 1999;99:1816-1821.
17. Ho KK, Anderson KM, Kannel WB, et al. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. (comments) Circulation 1993;88:107-115.
18. Simon T, Mary-Krause M, Funck-Brentano C, et al. Sex differences in the prognosis of congestive heart failure: Results from the Cardiac Insufficiency Bisoprolol Study (CIBIS II). Circulation 2001;103:375-380.
19. Sami M, Kraemer H, Harrison DC, et al. A new method for evaluating antiarrhythmic drug efficacy. Circulation 1980;62:1172-1179.
20. Teerlink JR, Jalaluddin M, Anderson S, et al. Ambulatory ventricular arrhythmias in patients with heart failure do not specifically predict an increased risk of sudden death. PROMISE (Prospective Randomized Milrinone Survival Evaluation) Investigators. Circulation 2000;101:40-46.
21. Packer M. The neurohormonal hypothesis: A theory to explain the mechanism of disease progression in heart failure. (editorial) J Am Coll Cardiol 1992;20:248-254.
22. Akhtar M, Garan H, Lehmann MH, et al. Sudden cardiac death: Management of high-risk patients (comments) Ann Intern Med 1991;114:499-512.
23. Sweeney MO. Sudden death in heart failure associated with reduced left ventricular function: Substrates, mechanisms, and evidence-based management, Part I. PACE 2001;24:871-888.
24. Nakajima T, Iwasawa K, Oonuma H, et al. Antiarrhythmic effect and its underlying ionic mechanism of 17beta- estra-

diol in cardiac myocytes. Br J Pharmacol 1999;127:429-440.
25. McHugh NA, Cook SM, Schairer JL, et al. Ischemia- and reperfusion-induced ventricular arrhythmias in dogs: Effects of estrogen. Am J Physiol 1995;268:H2569-2573.
26. Node K, Kitakaze M, Kosaka H, et al. Amelioration of ischemia- and reperfusion-induced myocardial injury by 17beta-estradiol: Role of nitric oxide and calcium-activated potassium channels. Circulation 1997;96:1953-1963.
27. Floras JS. Clinical aspects of sympathetic activation and parasympathetic withdrawal in heart failure. J Am Coll Cardiol 1993;22:72A-84A.
28. Frankenhaeuser M, Dunne E, Lundberg U. Sex differences in sympathetic-adrenal medullary reactions induced by different stressors. Psychopharmacology (Berl) 1976;47:1-5.
29. Claustre J, Peyrin L, Fitoussi R, et al. Sex differences in the adrenergic response to hypoglycemic stress in human. Psychopharmacology (Berl) 1980;67:147-153.
30. Sanchez J, Pequignot JM, Peyrin L, et al. Sex differences in the sympatho-adrenal response to isometric exercise. Eur J Appl Physiol 1980;45:147-154.
31. Airaksinen KE, Ikaheimo MJ, Linnaluoto M, et al. Gender difference in autonomic and hemodynamic reactions to abrupt coronary occlusion. J Am Coll Cardiol 1998;31:301-306.
32. Aronson D, Burger AJ. Gender-related differences in modulation of heart rate in patients with congestive heart failure. J Cardiovasc Electrophysiol 2000;11:1071-1077.
33. Freedman RR, Sabharwal SC, Desai N. Sex differences in peripheral vascular adrenergic receptors. Circ Res 1987;61:581-585.
34. Ungar S, Makman MH, Morris SA, et al. Estrogen uncouples beta-adrenergic receptor from the stimulatory guanine nucleotide-binding protein in female rat hypothalamus. Endocrinology 1993;133:2818-2826.
35. Kostis JB, Byington R, Friedman LM, et al. Prognostic significance of ventricular ectopic activity in survivors of acute myocardial infarction. J Am Coll Cardiol 1987;10:231-242.
36. Moise NS, Riccio ML, Kornreich B, et al. Age dependence of the development of ventricular arrhythmias in a canine model of sudden cardiac death. Cardiovasc Res 1997;34:483-492.
37. Wilson JR, Schwartz JS, Sutton MS, et al. Prognosis in severe heart failure: Relation to hemodynamic measurements and ventricular ectopic activity. J Am Coll Cardiol 1983;2:403-410.
38. Bayes de Luna A, Coumel P, Leclercq JF. Ambulatory sudden cardiac death: Mechanisms of production of fatal arrhythmia on the basis of data from 157 cases. Am Heart J 1989;117:151-159.
39. Nikolic G, Bishop RL, Singh JB. Sudden death recorded during Holter monitoring. Circulation 1982;66:218-225.
40. Olshansky B, Hartz V, Hahn E, et al. Location of death (in-hospital or out-of-hospital) and type of death (arrhythmic, nonarrhythmic, noncardiac) after inducible sustained ventricular tachyarrhythmias after syncope, sustained ventricular tachycardia, or nonfatal cardiac arrest (the ESVEM trial). Am J Cardiol 2000;86:846-851.