

Mean Frequency of Premature Ventricular Complexes As Predictor of Malignant Ventricular Arrhythmias

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Abstract

Aim: The aim was to test the hypothesis that mean frequency of premature ventricular complexes (PVCs) correlates with vulnerability to malignant arrhythmias such as ventricular tachycardia and/or ventricular fibrillation (VT/VF).

Methods: Patients with an implantable cardioverter defibrillator (ICD) device for underlying ischemic or non-ischemic cardiac pathology were selected from a database. Availability of total count of single (s) PVCs and runs (r) of PVCs was the only inclusion criterion. Forty-four subjects (6 females and 38 males) aged 18–74 years (mean 57.1 years), were eligible. All had a European Pacemaker Identification Card (EPIC) documenting left ventricular ejection fraction (LVEF). The frequency of recorded episodes of VT and VF was obtained from ICD memory.

Results: Among patients with ischemic heart disease (IHD) and those with IHD and an LVEF of less than 30%, the mean frequency of PVCs was significantly higher in those with subsequent episodes of VT/VF compared to those without subsequent episodes ($p < 0.05$ for sPVCs and rPVCs in both groups).

Conclusion: Among patients with IHD, mean frequency of PVCs is a useful marker of vulnerability to potentially fatal arrhythmias and may be a useful tool for the risk stratification of patients.

Key Words: Premature ventricular complexes, ventricular tachycardia, ventricular fibrillation, implantable cardioverter defibrillator.

Introduction

RE-ENTRY IN DAMAGED VENTRICULAR MUSCLE, automaticity in the His-Purkinje fibers, and triggered activity due to afterdepolarizations have been found to be the main mechanisms responsible for ventricular arrhythmias (1–3). Clinical and epidemiological associations between premature ventricular complexes (PVCs) and potentially fatal ventricular arrhythmias have been recognized for several years; much of the initial research was done by Lown and his colleagues in the 1970s (4–8). In the setting of the coronary care unit, he observed that PVCs invariably precede ventricular fibrillation (VF) and that suppression of PVCs reduces the incidence of VF (7). It is also known that almost 90% of patients with ischemic heart disease (IHD) exhibit ectopic activity. The mere presence of ectopic activity cannot, therefore, be a prognostic marker of risk (4, 9, 10). Using Holter monitoring, Lown proposed a grading system

for PVCs based on frequency, persistence, multiformity, repetitive pattern and degree of prematurity (5, 10). Only complex PVCs (R-on-T, runs of two or more, multiform or bigeminal) were found to impart an increased risk of sudden cardiac death (10, 11).

The development of third-generation implantable cardioverter defibrillator (ICD) technology, with enhanced storage capacity, has led to important advances in the understanding and treatment of potentially fatal arrhythmias. Studies of stored intracardiac electrograms (EGMs) from ICD devices have examined heart rate variability (HRV) and PVCs as predictors of arrhythmic events (1, 2, 12–14). The main purpose of our study was to examine the possibility of a relationship between mean frequency of PVCs and a predisposition to malignant ventricular arrhythmias in a group of patients who had received ICD devices for underlying structural, ischemic or electrophysiological cardiac pathology.

Methods

Forty-four subjects, selected from a database of 104 ICD patients, were included in this study. Of these, 6 were females aged 18–61 years (mean 47.9 years) and 38 were males aged 25–74 years (mean 58.9 years). Availability of total count of single PVCs

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Glossary

CAST = Cardiac Arrhythmia Suppression Trial

EGM = electrogram

EPIC = European Pacemaker Identification Card

EPS = electrophysiological studies

EURID = European Registry for Implantable Defibrillators

HRV = heart rate variability

IAPM = International Association of Prosthesis Manufacturers

ICD = implantable cardioverter defibrillator

IHD = ischemic heart disease

LVEF = left ventricular ejection fraction

MADIT = Multicenter Automatic Defibrillator Implantation Trial

MUSTT = Multicenter Unsustained Tachycardia Trial

PVC = premature ventricular complex

rPVC = runs of PVCs

sPVC = single PVC

VF = ventricular fibrillation

VT = ventricular tachycardia

VT/VF = VT and/or VF

(sPVC) and runs of PVCs (rPVC) was the only inclusion criterion. All subjects who satisfied the criterion had ICD devices of the GEM series (Medtronic Inc, Minneapolis, MN). This was actually coincidental, since the patients' choice of device had been independent of underlying pathology. The time interval over which PVC counts were registered in each patient varied between 21 and 1,073 days (mean 421 days). All patients in our series had European Pacemaker Identification Cards (EPIC) (IAPM/EURID, 1999).

Notes for each of the 44 subjects were reviewed. The total number of episodes of VT or VF and counts of PVCs over a defined period of time following implantation were obtained from records of the last interrogation of the ICD device. Left ventricular ejection fraction (LVEF), underlying pathology, main symptom, previous anti-arrhythmic treatment and device model were obtained from the EPIC. A correction to the total number of recorded episodes of VT and/or VF (VT/VF) was applied by subtracting the number of induced episodes of VT or VF during implantation. Mean frequency of PVCs was calculated for each patient and recorded in cycles per hour (cyc/hr).

Statistical analysis of data was performed using Minitab software (Minitab Inc, State College, PA). The Mann-Whitney test was used for non-parametric data and the χ^2 test was used for categorical data. A value of $p < 0.05$ was deemed significant.

Results

The table shows characteristics of the study population. Subjects with ischemic heart disease comprised the single largest group in terms of underlying pathology (at least 43% of the total) and at least 39% of the subjects had an LVEF of less than 30%. Cardiac arrest and syncope were the main modes of presentation in 82% of our study population. Twenty-two patients (50%) had received anti-arrhythmic medication, mainly amiodarone, before being considered for an ICD. Twenty-one subjects (48%) had had

TABLE

Characteristics of the Study Population and Its Subgroups

Characteristic	No of subjects (%)		
	Overall	IHD	IHD & LVEF < 30%
Underlying pathology			
Ischemic heart disease	19 (43.2)	-	-
Cardiomyopathy	4 (9.1)	-	-
Other (valvular heart disease, long QT syndrome)	2 (4.5)	-	-
Unknown	19 (43.2)	-	-
Left ventricular ejection fraction (%)			
< 30	17 (38.6)	11 (57.9)	-
30–50	13 (29.5)	5 (26.3)	-
> 50	8 (18.2)	1 (5.3)	-
Unknown	6 (13.6)	2 (10.5)	-
Main Symptom			
Syncope	15 (34.1)	4 (21.1)	3 (27.3)
Dizzy spells	2 (4.5)	0 (0.0)	0 (0.0)
Cardiac arrest	21 (47.7)	13 (68.4)	7 (63.6)
Palpitation	3 (6.8)	2 (10.5)	1 (9.1)
Other	3 (6.8)	0 (0.0)	0 (0.0)
Episodes			
At least one episode of VT and/or VF	21 (47.7)	9 (47.4)	6 (54.5)
At least one episode of VT only	6 (13.5)	0 (0.0)	0 (0.0)
At least one episode of VF only	3 (6.8)	2 (10.5)	2 (18.2)
Medication			
Amiodarone only	12 (27.3)	6 (31.6)	3 (27.3)
Amiodarone + other antiarrhythmic	5 (11.4)	4 (21.1)	2 (18.2)
Other anti-arrhythmic	5 (11.4)	1 (5.3)	1 (9.1)
None	10 (22.7)	3 (15.8)	2 (18.2)

IHD = ischemic heart disease, VT = ventricular tachycardia, VF = ventricular fibrillation.

at least one episode of VT/VF, 6 (13.5%) had had at least one episode of VT only and 3 (6.8%) had had at least one episode of VF only. The frequency of sPVCs in the overall population ranged from

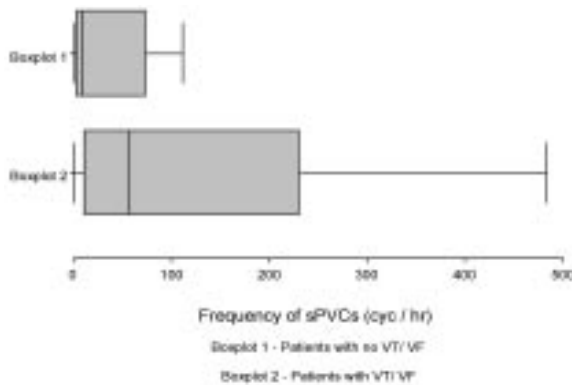


Fig. 1. Boxplots showing distribution of frequency of sPVCs in overall population.

sPVC = single premature ventricular complex, VT/VF = ventricular tachycardia and/or ventricular fibrillation.

0.1–791 cyc/hr (mean 103 cyc/hr), while the frequency of rPVCs ranged from 0–1,473 cyc/hr (mean 45.7 cyc/hr). The frequency of sPVCs was greater than that of rPVCs in all but 2 patients. As shown in Fig. 1, there was no statistically significant difference between the frequency of sPVCs in patients with VT/VF subsequent to implant compared to the frequency in patients with no VT/VF ($p=0.078$). A similar result was obtained for the frequency of rPVCs, where the Mann-Whitney test revealed $p=0.15$ (Fig. 2). There was no significant association between degree of impairment of left ventricular function and mean frequency of sPVCs and rPVCs ($p=0.747$ and $p=0.463$, respectively). Chi-squared test showed no significant association between LVEF, dichotomized at 30%, and presence or absence of VT/VF.

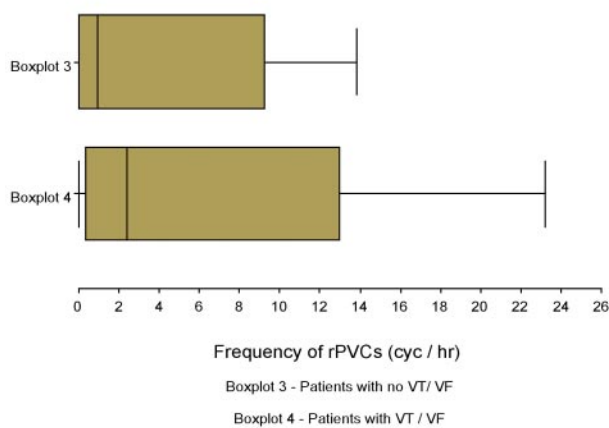


Fig. 2. Boxplots showing distribution of frequency of rPVCs in overall population.

rPVC = run of premature ventricular complex, VT/VF = ventricular tachycardia and/or ventricular fibrillation.

In the population subgroup having IHD as the underlying pathology, 18 subjects were male and 1 was female. The age range was 44–74 years (mean 62 years) and 11 subjects (57.9%) had an LVEF of less than 30%. Cardiac arrest and syncope were the main modes of presentation in nearly 90% of the patients (Table). The frequency of sPVCs in this subgroup ranged from 0.1–398 cyc/hr, while that of rPVCs ranged from 0.0041–237 cyc/hr. In contrast to the overall population, the frequency of sPVCs (Fig. 3) in the IHD subgroup was significantly lower in those with no VT/VF compared to those with VT/VF ($p=0.0305$). The frequency of rPVCs in the IHD subgroup, although having a lower predictive value ($p=0.0373$) compared to sPVCs, was also significantly lower in those with no VT/VF compared to those with VT/VF (Fig. 4). There was no significant association between degree of left ventricular impairment and mean frequency of sPVCs or rPVCs ($p=0.514$ and $p=0.802$, respectively).

Among the 11 patients with an LVEF of less than 30% and IHD as underlying pathology, the frequency of sPVCs ranged from 0.37–281 cyc/hr and that of rPVCs ranged from 0.0041–13 cyc/hr. Six patients had at least one episode of VT/VF (Table). The frequency of sPVCs and that of rPVCs within this subset were significantly lower in patients with no VT/VF compared to those with documented VT/VF ($p=0.0225$ in both cases). Fig. 5 summarizes the main findings.

Discussion

The progression of ventricular tachycardia (VT) to ventricular fibrillation (VF) and then to asystole is the most common sequence of events involved in fatal arrhythmias (15). While conventional risk factors such as

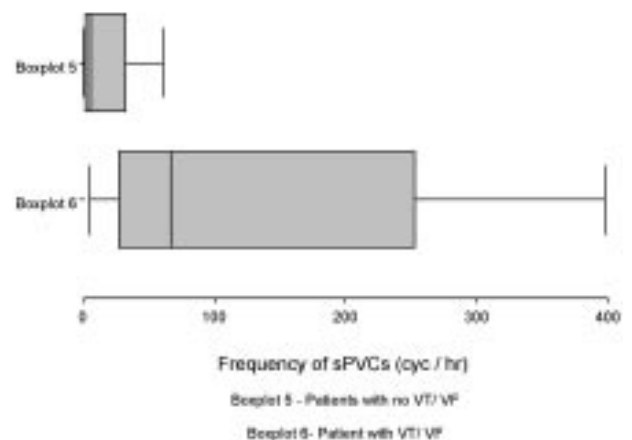


Fig. 3. Boxplots showing distribution of frequency of sPVCs in patients with IHD.

sPVC = single premature ventricular complex, VT/VF = ventricular tachycardia and/or ventricular fibrillation.

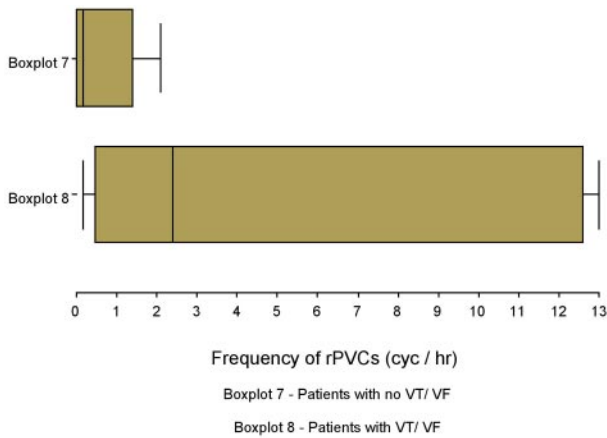


Fig. 4. Boxplots showing distribution of frequency of rPVCs in patients with IHD.
rPVC = run of premature ventricular complex, VT/VF = ventricular tachycardia and/or ventricular fibrillation.

	Median of sPVCs (cyc/ hr)		Median of rPVCs (cyc / hr)	
	No VT/VF	With VT/VF	No VT/VF	With VT/VF
Overall	9.4	55.8	0.95	2.4
	P=0.078		P=0.16	
IHD	4.9	66.2	0.2	2.4
	P=0.0306		P=0.0373	
IHD & LVEF < 30%	3.0	78.9	0.034	2.7
	P=0.0226		P=0.0226	

Fig. 5. Summary of predictive values of sPVCs and rPVCs as shown by the Mann-Whitney Test.
sPVC = single premature ventricular complex, rPVC = run of premature ventricular complex, VT/VF = ventricular tachycardia and/or ventricular fibrillation, IHD = ischemic heart disease, LVEF = left ventricular ejection fraction.

diabetes, smoking, hypertension and hyperlipidemia are invaluable in identifying high-risk subgroups, they have little predictive value in terms of the risk of a fatal arrhythmic event (16). Markers such as non-sustained VT, late potentials on signal-averaged ECG, T wave alternans, heart rate variability, baroreflex sensitivity, width of the QRS complex and QT dispersion have also been studied as indicators of an increased risk of death from arrhythmias and have been shown to have variable predictive power (15, 17–27).

A low left ventricular ejection fraction, caused by poor myocardial contraction, continuing ischemia or left ventricular dilatation, is a powerful predictor of the risk of death (15, 16, 28–31). However, the clinical use of LVEF as a specific marker of the risk of death due to arrhythmias has limitations. As LVEF decreases, both total mortality and the absolute number of sudden deaths increase, but the proportion of total deaths due to cardiac arrhythmias decreases (15, 32–34). Most randomized trials comparing antiar-

rhythmics to ICD therapy have included the measurement of LVEF in combination with other predictors for arrhythmia (35–37). In the Multicenter Automatic Defibrillator Implantation Trial (MADIT) and the Multicenter Unsustained Tachycardia Trial (MUSTT), patients underwent invasive electrophysiological studies (EPS) to determine inducibility of sustained tachyarrhythmias by programmed electrical stimulation (35, 37). In contrast, MADIT II and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) enrolled patients who had severely compromised LVEF (<36% and <30%, respectively) and no prior electrophysiological testing (38, 39). Both trials showed a significant reduction in mortality associated with the use of ICD therapy for primary prevention (38, 39).

Initially, it was thought that ambient forms of PVCs play a causal role in the genesis of malignant arrhythmias, and that the time and mode of the fatal event was fortuitous (31, 40, 41). This concept was fundamental to the early electrogenic theory for VF (41). However, with the development of a base of experimental information, the importance of structural and functional elements as major contributors to the pathophysiological evolution of fatal arrhythmias has been increasingly accepted. In the modified electrogenic theory, the interaction between structure and function is thought to convert pathophysiologically innocuous PVCs into triggering events for malignant arrhythmias (31, 41). Thus, the predictive value of PVCs in terms of risk of malignant arrhythmias depends on several conditioning factors, such as myocardial infarction, ventricular hypertrophy and cardiomyopathy (15, 41).

In our study population, which consisted of patients from several subgroups of structural and functional classification, there was no statistically significant difference between mean frequency of PVCs in patients with no VT/VF and those with VT/VF. However, in the IHD subgroup, where structural pathology was controlled, the difference between mean frequency of PVCs in those with VT/VF compared to those without VT/VF was statistically significant. This predictive power of mean frequency of PVCs was stronger for patients with IHD and an LVEF of less than 30%. We infer from these observations that the value of mean frequency of PVCs as a marker of risk of malignant arrhythmias is dependent on underlying structural factors. This is consistent with the modified electrogenic theory (41).

Several studies have assessed the significance of PVCs among patients with previous myocardial infarction and left ventricular failure. While some trials have suggested that higher frequencies of PVCs are associated with increased risk of sudden death (21, 30, 42–44), others have suggested that they are of

little independent prognostic significance (17). Assessing the relationship between mean frequency of PVCs and mortality was beyond the scope and methodology of this study. However, our findings suggest that the mean frequency of PVCs may be a useful measure for the risk stratification of ICD patients known to have either IHD only or IHD and an LVEF of less than 30%. As shown in Fig. 5, patients with no documented episodes of VT/VF in the "IHD only" and "IHD and LVEF < 30%" subgroups have significantly lower mean frequencies of sPVCs and rPVCs. Therefore, identifying low-risk patients from this subgroup, based on a mean frequency of PVCs less than the median, is likely to have a very high specificity with potential implications for therapy-oriented decision making. Moreover, as suggested by a recent study showing a statistically significant increase in the frequency of atrial ectopics over the hour preceding atrial fibrillation, we postulate that changes in the frequency of PVCs may be useful indicators of transient destabilization capable of progressing to malignant arrhythmias (45).

Since the involvement of PVCs in the genesis of malignant arrhythmias is supported by experimental evidence, it was hypothesized that their suppression could result in improved survival. However, large-scale studies like the Cardiac Arrhythmia Suppression Trial (CAST) have disproved this (46, 47). In the CAST study, although suppression of ventricular arrhythmias was achieved with flecainide, encainide and moricizine, there was no improvement in long-term survival (46). It was postulated that induction of early afterdepolarizations could have increased triggered activity. This paradoxical observation has prompted many to also consider PVCs as a marker of the degree of cardiac impairment (2, 33). In our study, no direct, significant association was found between mean frequency of PVCs and degree of left ventricular impairment in the overall population or in the IHD subgroup. Furthermore, our data did not show LVEF, dichotomized at 30%, to be a determinant of arrhythmia recurrence (42). Although these findings contradict previous reports, it is also likely that our study was not adequately powered with respect to these observations.

While this study did not specifically examine the electrophysiological characteristics of PVCs and their relationships with ventricular arrhythmias, some observations can be made. Among patients with IHD, re-entry of the sinus beat due to temporary impairment of conductivity or excitability in ventricular muscle is thought to be the main mechanism responsible for the initiation of ventricular arrhythmias (1–3, 14, 48). Previous studies of EGMs in patients with IHD have shown that single PVCs are most commonly involved in the onset of

ventricular arrhythmias (1, 3, 14). This observation is a possible explanation for the relatively higher predictive power of sPVCs compared to rPVCs, as illustrated in Figs. 3 and 4. However, we are unable to explain the consistently higher frequency of sPVCs compared to rPVCs observed in all but 2 of our patients.

There were several limitations to our study: (a) the overall study population was small, leading to an even smaller subgroup of patients with IHD; (b) the classification of patients into the IHD group was based on symptomatic presentation only, implying that some of the non-IHD patients with subclinical IHD may have been missed; (c) there was substantial variation in the number of days over which frequency of PVCs was calculated; (d) although our findings in relation to patients with IHD are statistically significant, we have been unable to characterize other trends, particularly in relation to LVEF; (e) the absence of categorical data, as is the case for underlying pathology in our overall population, implies that our figures are at best estimates; and (f) by examining only patients with an ICD, we excluded patients who are at risk of VT/VF but who did not receive ICDs. The correlation of PVCs with VT/VF in the latter group is likely to be very different.

Conclusion

The main finding of our study suggests that mean frequency of PVCs is a potentially useful marker of vulnerability to malignant arrhythmias in patients with IHD as underlying pathology. Elevated risk for sudden cardiac death clearly exists in clinical situations of left ventricular dysfunction, and has been extensively described. However, further risk stratification is needed. The challenge for clinicians is to identify those patients at the highest risk—individuals who would benefit from more extensive evaluation and more aggressive treatment.

References

1. Roelke M, Garan H, McGovern BA, Ruskin JN. Analysis of the initiation of spontaneous monomorphic ventricular tachycardia by stored intracardiac electrograms. *J Am Coll Cardiol* 1994; 23:117–122.
2. Saeed M, Link MS, Mahapatra S, et al. Analysis of intracardiac electrograms showing monomorphic ventricular tachycardia in patients with implantable cardioverter defibrillators. *Am J Cardiol* 2000; 85:580–587.
3. Bleiffer SB, Karpman HL, Sheppard JJ, Bleiffer DJ. Relation between premature ventricular complexes and development of ventricular tachycardia. *Am J Cardiol* 1973; 31:400–403.
4. Lown B. Sudden cardiac death. *Circulation* 1979; 60:1593–1599.
5. Lown B, Wolf MA. Approaches to sudden death from coronary heart disease. *Circulation* 1971; 44:130–142.

6. Lown B, Fakhro AM, Hood BW, Thorn G. The coronary care unit: new perspectives and directions. *JAMA* 1967; 199:188–198.
7. Lown B, Klein MD, Hershberg PI. Coronary and precoronary care. *Am J Med* 1969; 46:705–724.
8. Lawrie DM, Higgins MR, Godman MJ, et al. Ventricular fibrillation complicating acute myocardial infarction. *Lancet* 1968; 2:523–528.
9. Ryan M, Lown B, Horn H. Comparison of ventricular ectopic activity during 24 hour monitoring and exercise testing in patients with coronary heart disease. *N Eng J Med* 1975; 292:224–229.
10. Lown B, Calvert AF, Armington R, Ryan M. Monitoring for serious arrhythmias and high risk of sudden death. *Circulation* 1975; 52(Suppl III):189.
11. Calvert A, Lown B, Gorlin R. Ventricular premature beats and anatomically defined coronary heart disease. *Am J Cardiol* 1977; 39:627–634.
12. Lombardi F, Porta A, Marzegalli M, et al. Heart rate variability patterns before ventricular tachycardia onset in patients with an implantable cardioverter defibrillator. *Am J Cardiol* 2000; 86:959–963.
13. Meyerfeldt U, Schirdewan A, Wiedemann M, et al. The mode of onset of ventricular tachycardia. *Eur Heart J* 1997; 18:1956–1965.
14. Auricchio A, Hartung W, Geller C, Klein H. Clinical relevance of stored electrograms for implantable cardioverter-defibrillator (ICD) troubleshooting and understanding of mechanisms for ventricular tachyarrhythmias. *Am J Cardiol* 1996; 78(Suppl 5A):33–41.
15. Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. *N Eng J Med* 2001; 345:1473–1482.
16. Myerburg RJ, Interian A Jr, Mitrani RM, et al. Frequency of sudden cardiac death and profiles of risk. *Am J Cardiol* 1997; 80(5B):10F–19F.
17. 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 cardiac death. *Circulation* 2000; 101:40–46.
18. 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.
19. Rouleau J, Shenasa M, de Champlain J, Nadeau R. Predictors of survival and sudden death in patients with stable severe congestive heart failure due to ischemic and nonischemic causes: a prospective long term study of 200 patients. *Can J Cardiol* 1990; 6(10):453–460.
20. Szabo BM, van Veldhuisen DJ, Crijns HJ, et al. Value of ambulatory electrocardiographic monitoring to identify increased risk of sudden death in patients with left ventricular dysfunction and heart failure. *Eur Heart J* 1994; 15:928–933.
21. Doval HC, Nul DR, Grancelli HO, et al. Nonsustained ventricular tachycardia in severe heart failure: independent marker of increased mortality due to sudden death. *Circulation* 1996; 94:3198–3203.
22. Maggioni AP, Zuanetti G, Franzosi MG et al. Prevalence and prognostic significance of ventricular arrhythmias after acute myocardial infarction in the fibrinolytic era (GISSI-2 results). *Circulation* 1993; 87:312–322.
23. Nalos PC, Pappas JM, Nyitray W, et al. Prospective community evaluation of the signal-averaged electrocardiogram in predicting malignant ventricular arrhythmias: beneficial outcome with electrophysiology guided therapy. *Clin Cardiol* 1991; 14(12):963–970.
24. Breithardt G, Fetsch T, Reinhardt L, et al. [Ventricular late potentials—methods and clinical importance.] [German] *Ther Umsch* 1992; 49(8):550–558.
25. Breithardt G, Borggrefe M, Fetsch T, et al. Prognosis and risk stratification after myocardial infarction. *Eur Heart J* 1995; 16:10–19.
26. Steinberg JS, Regan A, Sciacca RR, et al. Predicting arrhythmic events after acute myocardial infarction using the signal averaged electrocardiogram. *Am J Cardiol* 1992; 69:13–21.
27. Kleiger RE, Miller JP, Biggar JT, Moss AJ; and The Multicenter Postinfarction Research Group. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol* 1987; 59:256–262.
28. Myerburg RJ, Kessler KM, Castellanos A. Sudden cardiac death: epidemiology, transient risk and intervention assessment. *Ann Intern Med* 1993; 119:1187–1197.
29. The Multicenter Postinfarction Research Group. Risk stratification and survival after myocardial infarction. *N Eng J Med* 1983; 309:331–336.
30. Bigger JT, Fleiss JL, Kleiger R, et al. The relationships among ventricular arrhythmias, left ventricular dysfunction, and mortality in the 2 years after myocardial infarction. *Circulation* 1984; 69:250–258.
31. Myerburg RJ, Kessler KM, Castellanos A. Sudden cardiac death. Structure, function, and time-dependence of risk. *Circulation* 1992; 85(Suppl I):I2–I10.
32. Luu M, Stevenson WG, Stevenson LW, et al. Diverse mechanisms of unexpected cardiac arrest in advanced heart failure. *Circulation* 1989; 80:1675–1680.
33. Packer M. Lack of relation between ventricular arrhythmias and sudden death in patients with chronic heart failure. *Circulation* 1992; 85(Suppl I):I50–I56.
34. Bigger JT. Role of left ventricular ejection fraction. In: Akhtar M, Myerburg RJ, Ruskin JN, editors, Sudden cardiac death. Philadelphia: Williams & Wilkins, 1994. pp. 190–201.
35. Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Eng J Med* 1996; 335:1933–1940.
36. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Eng J Med* 1997; 337:1576–1583.
37. Buxton AE, Lee KL, Fisher JD, et al. A randomized study of the prevention of sudden death in patients with coronary artery disease: Multicenter Unsustained Tachycardia Trial. *N Eng J Med* 1999; 341:1882–1890.
38. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure: Sudden Cardiac Death in Heart Failure Trial. *N Eng J Med* 2005; 352:225–237.
39. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction: Multicenter Automatic Defibrillator Implantation Trial II. *N Eng J Med* 2002; 346:877–883.
40. Wiggers CJ, Wegria R. Ventricular fibrillation due to single, localized induction and condenser shocks applied during the vulnerable phase of ventricular systole. *Am J Physiol* 1940; 128:500–505.
41. Myerburg RJ, Kessler KM, Bassett AL, Castellanos A. A biological approach to sudden cardiac death: structure function and cause. *Am J Cardiol* 1989; 63:1512–1516.

42. Caruso AC, Marcus FI, Hahn EA, et al. Predictors of arrhythmic death and cardiac arrest in the ESVEM trial. *Circulation* 1997; 96:1888–1892.
43. Maggioni AP, Zuanetti G, Franzosi MG, et al. Prevalence and prognostic significance of ventricular arrhythmias after acute myocardial infarction in the fibrinolytic era: GISSI-2 results. *Circulation* 1993; 87:312–322.
44. Ruberman W, Weinblatt E, Goldberg JD, et al. Ventricular premature complexes and sudden death after myocardial infarction. *Circulation* 1981; 64:297–305.
45. Grubb N, Stone N, Thornhill L, et al. Frequency of atrial premature beats in the pre-fibrillation period in patients with paroxysmal atrial fibrillation [abstract]. *Heart* 2001; 85(Suppl I):P10.
46. Echt DS, Liebson PR, Mitchell LB; and the CAST Investigators. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. *N Eng J Med* 1991; 324:781–788.
47. The Cardiac Arrhythmia Suppression Trial- II Investigators. Effect of the anti-arrhythmic agent moricizine on survival after myocardial infarction: Cardiac Arrhythmia Suppression Trial II. *N Eng J Med* 1992; 327:227–233.
48. Berger MD, Harvey L, Waxman M, et al. Spontaneous compared with induced onset of sustained ventricular tachycardia. *Circulation* 1988; 78:885–892.