Prevalence and Significance of Nonsustained Ventricular Tachycardia in Patients With Premature Ventricular Contractions and Heart Failure Treated With Vasodilator Therapy

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Objectives. This study sought to determine the prevalence and significance of nonsustained ventricular tachycardia (NSVT) in patients with premature ventricular contractions (PVCs) and heart failure treated with vasodilator therapy.

Background. Heart failure patients with ventricular arrhythmia and NSVT have a significantly increased risk of premature cardiac death. Recently there has been the question of whether these arrhythmias are expressions of a severely compromised ventricle or are they independent risk factors. We, therefore, determined the prevalence and significance of NSVT in patients with PVCs and heart failure and on vasodilator therapy.

Methods. Twenty-four hour ambulatory recordings were done at randomization, at 2 weeks, at months 1, 3, 6, 9 and 12 and then every 6 months in 674 patients with heart failure and on vasodilator therapy. The median period of follow-up was 45 months (range 0 to 54).

Results. Nonsustained ventricular tachycardia was present in 80% of all patients. Patients without (group 1) and with (group 2) NSVT were balanced for variables: age, etiology of heart disease, New York Heart Association (NYHA) functional class, use of amiodarone and diuretics and left ventricular diameter by echocardiogram. However, group 1 patients had significantly less beta-adrenergic blocking agent use and higher ejection fraction (EF) (p < 0.002 and p < 0.001, respectively). Survival analysis for all deaths showed a greater risk of death among group 2 patients (p = 0.01). Similarly, sudden death was increased in group 2 patients (p = 0.02, risk ratio 1.8). After adjusting for the above variables, only EF (p = 0.001) and NYHA class (p = 0.01) were shown to be independent predictors of survival. Nonsustained ventricular tachycardia showed a trend (p = 0.07) as an independent predictor for all-cause mortality but not for sudden death. Only EF was an independent predictor for sudden death.

Conclusions. Nonsustained ventricular tachycardia is frequently seen in patients with heart failure and may be associated with worsened survival by univariate analysis. However, after adjusting other variables, especially for EF, NSVT was not an independent predictor of all-cause mortality or sudden death. These results have serious implications in that suppression of these arrhythmias may not improve survival.

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Non-sustained ventricular tachycardia was defined as three consecutive premature beats in a row, at a rate of 100 beats/min. Fast NSVT were those episodes ≥120 beats/min while long NSVT was defined as episodes ≥15 consecutive premature ventricular contractions (PVCs). Ambulatory recordings were analyzed by a computerized system and arrhythmia density on 10% of all such recordings were hand-counted. A 90% correlation was considered acceptable. There was an excess of 90% correlation between the two methods.

Statistics. Baseline demographic data were expressed as mean and standard deviation values or percentages. The chi-square test was used to compare differences between groups for categorical variables, and similarly the t-test was used for continuous variables. Survival was calculated from randomization to death or last known follow-up using the Kaplan-Meier method. The log rank test was used to compare survival distributions; the risk ratio and respective 95% confidence interval (CI) for each survival comparison is provided. Using the PHREG procedure from the Statistical Analysis System (SAS) version 6.12 (SAS Institute, Cary, North Carolina), Cox proportional hazards modeling was conducted to identify independent prognostic factors. Variables entered into the model included those which were different between groups (ejection fraction, left ventricular external dimension [LVED], PVC density, beta-blocker use) and those previously identified as potentially associated with survival in similar patient groups (amiodarone, type of cardiomyopathy, New York Heart Association [NYHA] class and diuretic use). A two-sided alpha level of 0.05 was considered statistically significant.

Results

Characteristics of patients. There were 666 patients: 142 without (group 1) and 524 with NSVT (group 2) at baseline. There were no significant differences between the two groups with respect to age, race, NYHA functional class, presence of coronary artery disease, atrial fibrillation, hypertension or diabetes, previous bypass surgery, smoking and alcohol use, type of cardiomyopathy and use of diuretics, calcium channel blocking agents or angiotensin-converting enzyme (ACE) inhibitors. However, group 2 patients had significantly lower EF, larger left ventricular internal dimension, higher density of PVC per hour, and less beta blocker use. Fast NSVT was present in 82% and long NSVT was observed in 10% of the patients. Table 1 summarizes these baseline variables. The median follow-up period was 45 months (range 0 to 54).

NSVT and outcome. Non-sustained ventricular tachycardia showed an association with increased overall mortality and sudden cardiac death using a univariate model analysis (Fig. 1). However, after adjusting for EF, NYHA class, diuretic use, type of cardiomyopathy, LVED, PVC density and use of beta blocker or amiodarone, only EF (p = 0.001) and NYHA function class (p = 0.01) were independent predictors of all-cause mortality. Moreover, the suppression of NSVT by amiodarone had no effect on total survival nor on sudden cardiac death. Ejection fraction was the only independent predictor of sudden cardiac death.

There were no significant differences in all-cause mortality nor in sudden death mortality in patients with slow NSVT vs. fast NSVT (Fig. 2). Similarly, there were no differences in the group with long vs. short NSVT (Fig. 3).

Additional retrospective analyses were done to classify patients’ NSVT over time. There were 33 study patients in whom NSVT was never documented on a Holter; there were 162 patients in whom NSVT was documented on every study Holter; and the remaining 434 patients had NSVT documented on some of the Holters (ever). Overall mortality and sudden death rates of those 33 with no documented NSVT over time were similar to patients having NSVT (ever) (Fig. 4). In contrast, the overall and sudden death survival of patients never having VT was significantly better than that of patients who had persistent (always) VT (Fig. 5). After adjustment for other baseline variables, the survival related to sudden death was still not different between groups.

Discussion

Present study. Our findings show that in patients with PVCs and heart failure and on vasodilator therapy, the pres-
ence of NSVT on ambulatory recordings after adjusting for other variables, especially EF, is not an independent prognostic risk factor for all-cause mortality and especially for sudden cardiac death. This is true regardless of the rate or length of the NSVT runs. This was not only true for presence of NSVT on baseline recordings, but also for those patients who developed at least one episode of NSVT on subsequent recordings when compared to patients with no episode throughout the study period. Only EF and NYHA functional class independently predicted all-cause mortality. Most important, only EF predicted sudden cardiac death.

**Previous studies.** Previous trials in patients with left ventricular dysfunction or heart failure have shown that ventricular arrhythmias are associated with excess total and sudden cardiac death mortality (1–5). Bigger et al. (1) examined the relationship among ventricular arrhythmias, left ventricular dysfunction and mortality in the 2 years after a myocardial infarction, and in 766 patients there was a definite independent relationship among PVC frequency, PVC runs and LVEF. The instantaneous probability of dying in patients with LVEF <30% and PVC runs was almost seven times greater than in patients without any of the risk factors. However, it should be noted that this is in a population with prior myocardial infarction.

Maggioni et al. (12) in the Gruppo Italiano per lo Studio della Streptochiansi nell’Infarto Miocardico (GISSI-2) reported the prevalence and prognostic significance of ventricular arrhythmias after a myocardial infarction in the fibrinolytic era. While PVC frequency of ≥10/h independently predicted total and all-cause mortality, NSVT was not associated with worsened survival at 6 months after adjusting for other variables. This was also true for patients with congestive heart failure (CHF). For patients with fast NSVT (>120 beats/min), NSVT was still not associated with excess mortality. It is of interest to note in another trial that after adjusting for other variables, especially EF, PVC frequency was not predictive of mortality for patients with prior myocardial infarction in the 1990s (13).

Packer (9) showed a lack of relation between ventricular arrhythmias and sudden cardiac death. He noted that NSVT is a marker for hemodynamic and clinical instability and not a harbinger of sudden death. Moreover, in a large heart failure study, Massie et al. (10) showed that NSVT was predictive of cardiovascular mortality but not sudden cardiac death. Non-sustained ventricular tachycardia on ambulatory ECG had no independent prognostic value after adjusting for other variables in the Veterans Administration Heart Failure Trial II (14). And finally, in the Electrophysiologic Study Versus
Electrocardiographic Monitoring (ESVEM) trial (15), NSVT at baseline was not predictive of subsequent events.

Szabo et al. (16), on the other hand, examined the relationship between ventricular arrhythmias and outcome in patients with heart failure. They showed that ejection and presence of VT after adjustment had statistically prognostic value in predicting sudden death. By univariate analyses sudden death was predicted by VT $\geq 2$ s, VT rate $\geq 144$ beats/min. Our results differ perhaps because of patient selection bias. While all our patients had symptomatic heart failure, only some patients in Szabo’s study expressed symptoms. Our findings were based on three times the sample size, minimizing a beta error. Moreover, most of our patients were on ACE inhibitors and other vasodilator therapy that certainly can affect the mode of death (17).

Gradman et al. (18) studied 295 heart failure patients and the data were analyzed according to the presence and absence of NSVT episodes with respect to mortality. While EF was the best predictor of total mortality and sudden death, the presence of NSVT was independently associated with both total mortality and sudden death (18).

On the other hand, Wilson et al. (19) showed that only functional class independently predicted cardiac mortality and ventricular ectopic activity had no relation to prognosis.

Recently, Doval et al. (20), analyzing the data from the GESICA (Grupo de Estudio de la Sobrevida en al Insuficiencia Cardiaca en Argentina) trial, showed that NSVT was an independent risk factor for increased total and sudden death mortality. In this study, the presence of NSVT was determined from ambulatory recordings in 516 patients with heart failure. Patients with NSVT had an increased relative risk (RR = 1.69, CI 1.27 to 2.24, $p < 0.002$) of dying prematurely. Sudden death risk was also increased (RR = 2.77, CI 1.78 to 4.44, $p < 0.01$). This excess risk was also seen after adjusting for other variables and independent of the type (ischemic or nonischemic) of cardiomyopathy. While GESICA and CHF STAT share many similarities, there are differences. GESICA included a sicker population with severely depressed EF or higher NYHA functional class. Moreover, there were more patients with nonischemic cardiomyopathy. Our analyses according to types of cardiomyopathy or use of amiodarone did not change the results. Unlike GESICA, patients on the CHF STAT study were required to have $\geq 10$ PVCs/h at baseline.

**Limitations.** If it is true that the two major mechanisms for death in heart failure relate to arrhythmia and pump failure, then it is quite difficult to understand why the suppression of

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**Figure 3.** Kaplan–Meier estimates of (A) overall and (B) sudden death mortality according to NSVT length less than (short) or greater than (long) 15 consecutive beats. There are no significant differences.

**Figure 4.** Kaplan–Meier estimates of (A) overall and (B) sudden death rates according to the absence (never) or presence (ever) of NSVT on any ambulatory recording throughout the study. There are no significant differences.
arrhythmias with a “potentially benign drug” (amiodarone) and improvement in EF did not lead to an improvement in mortality (21). Because of the extremely high density of PVCs in the study groups, it is likely that the risk is already substantially high in these patients, and the mere presence of NSVT will not add any further risk. On the other hand, these arrhythmias could be merely markers for premature death and that any attempt to suppress them might not improve survival.

The use of beta-blockers in heart failure patients has been associated with some beneficial effects. The mechanisms of such benefit is unclear especially since beta-blockers are not potent suppressors of ventricular arrhythmias. The use of beta-blockers was very limited in our study. Perhaps it would have been more difficult to detect any beneficial effect of amiodarone if there were widespread and balanced use of beta-blockers. On the other hand, as in the EMlAT trial, the combined use of beta-blockers and amiodarone in patients with postmyocardial infarction and left ventricular dysfunction was much better than beta-blockers alone (22).

Conclusion. Our findings show that the prevalence of NSVT in CHF is high if the baseline PVC rate is >10/h. The presence, rate or length of NSVT in this population are not independent predictors for sudden death or all-cause mortality. These results have serious implications in that any attempt to suppress these arrhythmias may not change outcome. We feel that on the basis of our findings at this time, there is no need to treat pharmacologically patients on vasodilator therapy with asymptomatic NSVT episodes associated with heart failure and high density PVCs.

References


