Original articles

Prognostic role of non-sustained ventricular tachycardia in a large cohort of patients with idiopathic dilated cardiomyopathy

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Dilated cardiomyopathy; Prognosis; Sudden cardiac death; Ventricular tachycardia.

Background. **The identification of patients with idiopathic dilated cardiomyopathy (IDC) at higher risk of sudden death (SD) is still an unsolved issue, and the role of non-sustained ventricular tachycardia (NSVT) uncertain.**

Methods. **The effect of NSVT on total mortality, SD and life-threatening arrhythmias was evaluated in 554 patients with IDC on optimal medical treatment and at long-term follow-up (81 ± 58 months).**

Results. **At diagnosis, 240 patients (43%) had NSVT at Holter monitoring and 314 (57%) did not. During follow-up, 189 patients (5/100 patients-year) died or underwent heart transplantation; SD occurred in 53 patients (1.4/100 patients-year); SD + non-fatal ventricular arrhythmias occurred in 75 patients (2/100 patients-year). Patients with and without NSVT at diagnosis had the same 5-year transplant-free survival rate (76 vs 76%, p = NS) and a similar incidence of SD (10 vs 7%, p = NS). The length and rate of NSVT did not show any significant relationship with the outcome. Only heart failure symptoms (NYHA class III-IV) (hazard ratio [HR] 1.9, p = 0.015) and severe left ventricular impairment (left ventricular ejection fraction ≤ 0.30 and left ventricular end-diastolic diameter ≥ 70 mm) (HR 2.7, p < 0.0001) were independently associated with higher SD risk. At multivariate analysis the presence of frequent NSVT episodes (≥ 3 runs/day) was associated with an increased risk of total mortality (HR 1.68, p = 0.041) and of major ventricular arrhythmias (HR 2.11, p = 0.037), but only in the subgroup of patients with severe left ventricular impairment.**

Conclusions. **Patients with advanced heart failure symptoms, severe left ventricular dysfunction and dilation had a higher risk of SD independently of NSVT. The finding of more frequent NSVT was associated with an increased risk of all-cause mortality and of major ventricular arrhythmias in patients with severe left ventricular impairment.**

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Sudden death (SD) rate in idiopathic dilated cardiomyopathy (IDC), although reduced over the last decades, is still considerable and the identification of patients at higher risk remains an unsolved issue. In the first randomized controlled trials, the use of automatic implantable cardioverter-defibrillators (AICD) was not superior to conventional treatment[1] or amiodarone[2] in reducing mortality, while more recent studies involving larger populations showed a stronger benefit[3] or significantly improved survival in patients treated with these devices[4].

Non-sustained ventricular tachycardias (NSVT) are present in 30 to 50% of patients with non-ischemic dilated cardiomyopathy[1,5-7] and were considered as an inclusion criterion in some primary prevention trials of SD[2,3]. Despite NSVT are usually thought to be associated with a higher risk of SD, their role for risk stratification of patients with heart failure is still unclear and data are contradictory[1,7-9]. Moreover, it is unknown whether any characteristics of the arrhythmia (i.e. frequency, length, rate) may have additional prognostic value in the whole population or in specific subgroups of patients.

The aim of this study was to evaluate the role of NSVT in predicting the risk of total mortality and SD in IDC patients on optimal medical treatment and at long-term follow-up, enrolled in a large single-center registry.

Methods

From January 1, 1978 to December 31, 2002, 554 IDC patients were prospectively studied and enlisted in the Heart Muscle Disease Registry of Trieste (Italy).

According to the World Health Organization criteria[10], diagnosis of IDC is made when left ventricular ejection fraction (LVEF) is < 0.50 in the absence of any other known cardiac disease. Therefore, patients with moderate to severe hypertension (blood pressure > 170/100 mmHg), significant coronary artery disease (> 50% stenosis in at least one epicardial vessel), right ventricular arrhythmogenic cardiomyopathy, severe valvulopathies, high alcohol consumption (> 100 g/die in the previous 6 months), "tachycardia-induced" cardiomyopathies, systemic diseases potentially causing left ventricular dysfunction, severe pericardial and congenital diseases, cor pulmonale, and those with suspected cardiotoxicity were excluded from the study.

A complete physical examination, an electrocardiogram, an echocardiogram, an exercise stress test, and a hemodynamic evaluation were performed at enrolment. For patients with poor-quality echocardiogram, LVEF was quantified at radionuclide ventriculography. Until 1996, patients routinely underwent endomyocardial biopsy to exclude an active myocarditis (according to the Dallas criteria)[11]; more recently, myocardial biopsy was performed only in patients with heart failure of recent onset and/or clinical history suggesting active myocarditis.

Angiotensin-converting enzyme (ACE) inhibitors were introduced in the mid 1980s, initially in patients with more severe heart failure according to the published data[12]. Since the end of the 1980s, most patients were treated, unless contraindicated, with beta-blockers (metoprolol or carvedilol) at the highest tolerated dosages, on top of ACE-inhibitors, diuretics, and digoxin.

Starting from the mid 1990s, patients with sustained ventricular tachycardia, history of cardiac arrest due to ventricular tachyarrhythmias or syncope of unknown origin were treated with AICD. Since 2001, the device was implanted for primary prevention also in patients considered at high risk because of a long history of severe left ventricular impairment, family history of SD or frequent NSVT[13,14]. AICD interrogation was performed every 6 months.

Amiodarone was administered in the presence of non-sustained but frequent and/or symptomatic ventricular or supraventricular arrhythmias.

Arrhythmia definition and analysis. At enrolment, all patients underwent 48-hour Holter monitoring. NSVT were defined as ≥ 3 consecutive ventricular beats at a rate > 100/min, lasting < 30 s and hemodynamically not relevant. The number of ventricular ectopic beats/hour, the presence of couplets, the number of NSVT episodes/day, and their maximum length and rate were evaluated.

Patients were divided into two groups according to the presence (group A) or the absence (group B) of NSVT during Holter monitoring performed at the first evaluation.

In order to evaluate the significance of NSVT characteristics (frequency, length and rate), the median values were arbitrarily considered as cut-off values for subgroup analysis.

Endpoint definition. Total mortality + heart transplantation, unexpected SD, life-threatening arrhythmias, and related events (sustained ventricular tachycardia, aborted SD, appropriate AICD interventions) were considered endpoints of the study. SD was defined as "unexpected" when it occurred within 1 hour after new onset symptoms or during sleep in stable NYHA class I-III patients. Those who experienced "expected" SD, i.e. preceded by a significant worsening of heart failure, were therefore included only in the total mortality group.

December 31, 2002 (or the time of death/heart transplantation) was considered as the end of follow-up. Endpoint information was obtained from the patients, their relatives or referring physicians. For patients lost at follow-up, data were taken from the Register of Births.

Statistical analysis. Data are expressed as mean ± standard deviation or as percentage. Differences between groups were assessed by one-way analysis of variance for continuous variables and the χ^2 test with Yates correction for categorical variables. Changes from continuous to categorical variables were based on median values.

Survival functions from the time of enrolment were calculated for the different groups with the Kaplan-Meier method and compared with the log-rank test.

Cox proportional hazards model was used to analyze the relation between survival and prognostic indexes. Proportional hazard assumptions were carefully checked both visually (using the martingale residual plot) and using the Grambsch-Therneau test.

All analyses were performed with SPSS statistical package 10.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline findings. At the first evaluation, 240 patients (43%) had at least one run of NSVT on 48-hour Holter monitoring (group A) and 314 (57%) did not (group B). No episodes of sustained ventricular tachycardia were detected during Holter monitoring.

The baseline main clinical, Holter, echocardiographic and hemodynamic findings in patients with and without NSVT are summarized in table I. Patients in group A had a longer duration of the disease, a slightly lower systolic blood pressure, and worse left and right ventricular function. After the first evaluation, the majority of patients in both groups were treated with ACE-inhibitors and beta-blockers, while a minority with amiodarone (usually for paroxysmal/persistent atrial fibrillation) and digoxin. The proportion of patients on beta-blockers further increased during follow-up (83 and 75% after 24 months in group A and B, respectively, p = NS). As expected, the number of ventricular ectopic

Table I. Baseline findings in 554 idiopathic dilated cardiomyopathy patients enrolled in the Heart Muscle Disease Registry.

	Group A	Group B	p
No. patients	240 (43%)	314 (57%)	
Age (years)	45 ± 15	45 ± 14	NS
Symptom duration (months)	40 ± 60	30 ± 48	0.04
Syncope (%)	3	1	NS
NYHA class	2 ± 0.8	2 ± 0.9	NS
HR (b/min)	79 ± 16	79 ± 15	NS
SBP (mmHg)	122 ± 15	126 ± 16	0.004
LBBB (%)	32	30	NS
LVEF	0.29 ± 0.10	0.33 ± 0.11	0.0002
LVEDD (mm)	69 ± 10	66 ± 0.9	0.001
RVASF (%)	41 ± 17	45 ± 16	0.02
Exercise time (s)	618 ± 228	609 ± 251	NS
PCWP (mmHg)	13 ± 8	11 ± 7	NS
ACE-inhibitors (%)	81	83	NS
Beta-blockers (%)	57	53	NS
Metoprolol (mg/day)	109 ± 49	106 ± 54	NS
Carvedilol (mg/day)	35 ± 18	30 ± 21	NS
Amiodarone (%)	20	20	NS
Digitalis (%)	23	23	NS
VEB (/hour)	166 ± 269	49 ± 146	< 0.0001
Couplets (/hour)	7.4 ± 24	0.6 ± 3.6	< 0.0001
NSVT			
Frequency (median episodes/day)	2 (range 1-38)		
Max length (median beats/episode)	5 (range 3-170)		
Max rate (median b/min)	155 (range 103-290)		

ACE = angiotensin-converting enzyme; HR = heart rate; LBBB = left bundle branch block; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; NSVT = non-sustained ventricular tachycardia; PCWP = pulmonary capillary wedge pressure; RVASF = right ventricular area shortening fraction; SBP = systolic blood pressure; VEB = ventricular ectopic beats.

beats and couplets was higher in group A. The median values of NSVT frequency, length and rate were, respectively, 2 runs/day, 5 beats/episode, and 155 b/min.

Follow-up. The mean follow-up in the whole population was 81 ± 58 months. During this period, 32 patients underwent AICD implantation because of sustained ventricular arrhythmias (n = 9) or because considered at high risk according to clinical criteria (n = 23)[13,14].

One hundred and eighty-nine patients (5/100 patients-year) died or underwent heart transplantation. Death occurred in 150 patients, while 39 patients underwent heart transplantation; refractory heart failure was the indication for heart transplantation in all subjects.

Fifty-three patients (1.4/100 patients-year) died suddenly and 22 patients (0.6/100 patients-year) had non-fatal major ventricular arrhythmias: 4 were resuscitated from cardiac arrest due to ventricular fibrillation, 6 had sustained ventricular tachycardia requiring electrical cardioversion, and 12 patients with AICD (implanted for primary prevention of SD) had appropriate interventions (with antitachycardia pacing in 6 patients, shocks in 3 patients, and both in 3 patients).

As shown in figure 1, survival curves were similar in groups A and B. More in detail, patients with and without NSVT had the same 2, 5, and 10-year heart transplantation-free survival rates (89 vs 88%, 76 vs 76%, and 61 vs 60%, respectively; p = NS), as well as similar 2, 5, and 10-year rates of SD (3 vs 3%, 10 vs 7%, and 22 vs 18%, respectively; p = NS) and of life-threatening ventricular arrhythmias (5 vs 4%, 10 vs 8%, 23 vs 20%, respectively; p = NS).

In group A, longer (> 5 beats/episode) and faster (> 155 b/min) NSVT were not associated with worse total mortality, SD or life-threatening ventricular arrhythmia rates. Only patients with more frequent NSVT episodes (exceeding the median value of 2 runs/day) had higher 5-year rates of SD (15 vs 4%, p = 0.05 at log-rank test) and of life-threatening ventricular arrhythmias (21 vs 5%, p = 0.02), as compared to those with more sporadic episodes (Fig. 2). Heart transplantation-free survival did not differ between these two subgroups.

As shown in table II, lower systolic blood pressure values (hazard ratio [HR] 2.12 for every 5 mmHg), advanced heart failure symptoms (NYHA class III-IV) and severe left ventricular impairment (defined by the presence of LVEF ≤ 0.30 + left ventricular end-diastolic diameter ≥ 70 mm) were independent predictors of all-cause mortality or heart transplantation at multivariate analysis. NYHA functional class III-IV and the association of LVEF ≤ 0.30 + left ventricular end-diastolic diameter ≥ 70 mm were the only statistically significant variables predicting SD and life-threatening ventricular arrhythmias. In the whole population of our

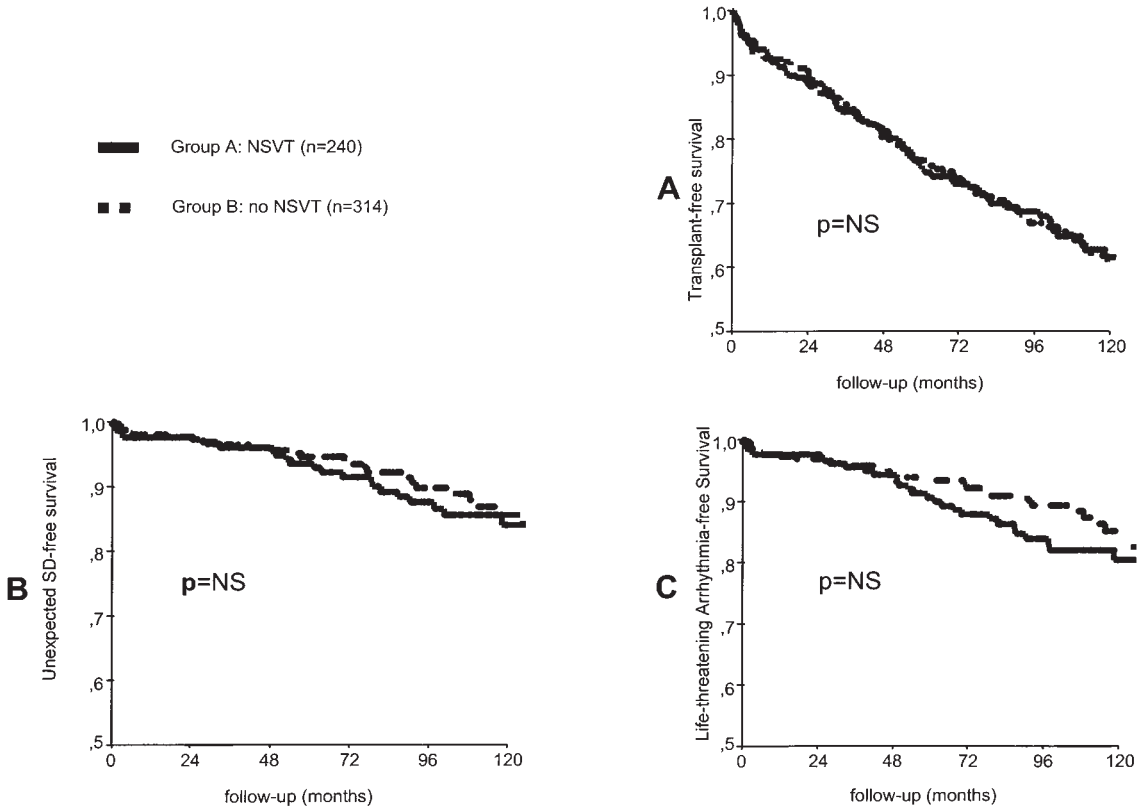

Figure 1. A: *survival freedom from heart transplant in patients with (group A) and without non-sustained ventricular tachycardia (NSVT) (group B).* B: *survival freedom from sudden death (SD) in patients with (group A) and without NSVT (group B).* C: *survival freedom from life-threatening ventricular arrhythmias in patients with (group A) and without NSVT (group B).*

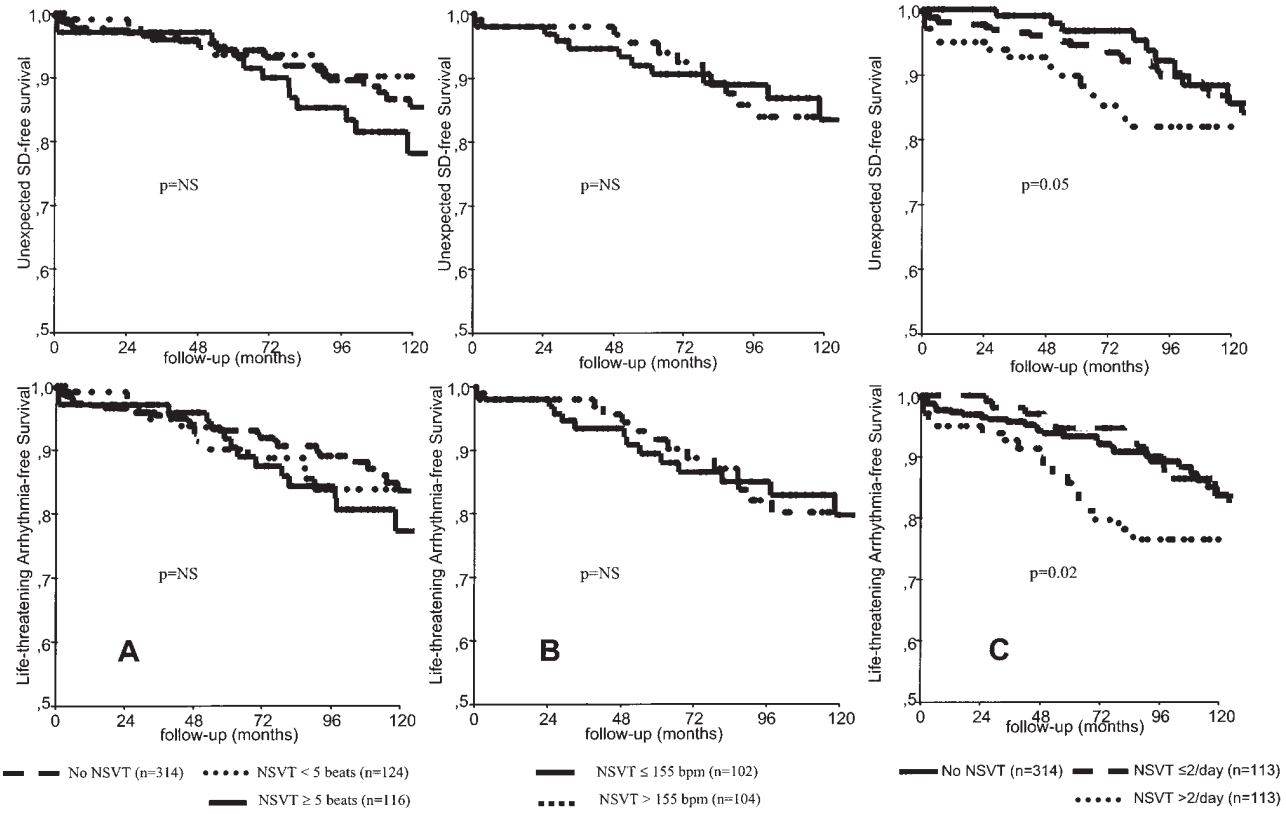

Figure 2. *Unexpected sudden death (SD)-free survival* (upper panels) *and life-threatening ventricular arrhythmias-free survival* (lower panels) *in patients according to the length of non-sustained ventricular tachycardia (NSVT)* (A), *to heart rate during NSVT* (B), *and to frequency of NSVT runs* (C).

Table II. Independent predictors of outcome in 554 idiopathic dilated cardiomyopathy patients enrolled in the Heart Muscle Disease Registry.

	Beta	SE	HR	95% CI	p
Death or heart transplant					
SBP (decrease of 5 mmHg)	0.15	0.005	2.12	1.91-2.33	0.004
NYHA class III-IV vs I-II	0.91	0.155	2.47	1.83-2.35	< 0.0001
LVEF ≤ 0.30 + LVEDD ≥ 70 mm	0.43	0.155	1.54	1.14-2.09	0.005
Unexpected SD					
NYHA class III-IV vs I-II	0.643	0.265	1.90	1.13-3.20	0.015
LVEF ≤ 0.30 + LVEDD ≥ 70 mm	1.004	0.254	2.73	1.66-4.49	< 0.0001
SD or life-threatening arrhythmias					
NYHA class III-IV vs I-II	0.624	0.269	1.87	1.10-3.16	0.020
LVEF ≤ 0.30 + LVEDD ≥ 70 mm	1.003	0.258	2.73	1.64-4.52	< 0.0001

CI = confidence interval; HR = hazard ratio; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; SBP = systolic blood pressure; SD = sudden death; SE = standard error.

study, no arrhythmic variable was associated with the outcome at multivariate analysis.

When we considered only patients with severe left ventricular impairment (i.e. LVEF ≤ 0.30 + left ventricular end-diastolic diameter ≥ 70 mm), the presence of ≥ 3 NSVT runs/day was significantly associated with a higher risk of all-cause mortality and of life-threatening ventricular arrhythmias, while it was of borderline significance in predicting the risk of SD at multivariate analysis (Table III).

Discussion

In this large single-center series of IDC patients on optimal medical treatment and long-term follow-up, we analyzed the variables predicting total mortality and SD, especially focusing on the role of NSVT detected at baseline Holter monitoring.

At present, it has not been well clarified yet which patients should be considered at higher risk of SD and, thus, should be more aggressively treated.

The CAT (Cardiomyopathy Trial)[1], the AMIOVIRT (Amiodarone Versus Implantable Cardioverter-Defibrillator)[2] and, partially, the DEFINITE (Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation)[3] trials failed to show any benefit from AICD in patients with severe left ventricular dysfunction[1] or left ventricular dysfunction plus NSVT[2,3]. These data were in contrast with those obtained in patients with severe left ventricular dysfunction of ischemic origin[15,16]. Explanations for such conflicting results might be, in part, the different mechanisms of SD[17] and of ventricular tachyarrhythmias[18] in patients with left ventricular dysfunction of ischemic and non-ischemic origin, but especially the insufficient statistical power of some trials evaluating non-ischemic patients, as total and especially SD rates were lower than expected in these studies. In the CAT trial[1], only patients with severe left ventricular dysfunction and recent-onset cardiomyopathy were enrolled. These patients may have a different, often better, outcome than those with a long history of disease[19,20] and the risk of SD tends to increase in the long period[13]. Also in the AMIOVIRT[2] and DEFINITE trials[3], evaluating patients with left ventricular dysfunction and NSVT, the total number of SD was probably too low and the follow-up too short to show any benefit from AICD; in the DEFINITE, enrolling > 500 patients, despite a 80% reduction of SD (p = 0.006), the 35% total mortality reduction was not statistically significant (p = 0.08). On the other side, in the recently published SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial)[4], where > 2500 patients with LVEF ≤ 0.35 were randomized to AICD vs con-

Table III. Independent predictors of outcome in 554 idiopathic dilated cardiomyopathy patients with left ventricular ejection fraction ≤ 0.30 and left ventricular end-diastolic diameter ≥ 70 mm enrolled in the Heart Muscle Disease Registry.

	Beta	SE	HR	95% CI	p
Death or heart transplant					
NYHA class III-IV vs I-II	0.84	0.23	2.31	1.46-3.66	0.000
NSVT (> 2 vs ≤ 2 runs/day)	0.52	0.25	1.68	1.03-2.71	0.041
Unexpected SD					
NSVT (> 2 vs ≤ 2 runs/day)	-0.69	0.41	1.99	0.89-4.45	0.09
SD or life-threatening arrhythmias					
NSVT (> 2 vs ≤ 2 runs/day)	-0.74	0.36	2.11	1.05-4.26	0.037

CI = confidence interval; HR = hazard ratio; NSVT = non-sustained ventricular tachycardia; SD = sudden death; SE = standard error.

ventional treatment or amiodarone, the 24% mortality reduction observed in the AICD group was statistically significant (p = 0.007), with similar results in patients with heart failure of ischemic (HR 0.79) and non-ischemic origin (HR 0.73). SCD-HeFT results will probably cause an increasing need of AICD for primary prevention of SD, but the economic impact is to be determined and costs are probably difficult to face. For this reason, also in the SCD-HeFT era, a further stratification of the patients to better identify those who may benefit more from AICD implantation will probably be necessary.

NSVT are usually associated with a higher risk of SD, and were considered inclusion criteria in some trials evaluating AICD for primary prevention of SD[2,3]. However, the value of spontaneous ventricular arrhythmias, including NSVT, for the identification of patients at higher risk is not established. Some studies suggested a worse prognosis and a higher risk of SD in patients with these arrhythmias[6,7,21,22], but this was not confirmed by other studies. In an extensive analysis of a large single-center population with non-ischemic dilated cardiomyopathy[5], NSVT were predictive of SD at univariate but not at multivariate analysis. Furthermore, in the CAT trial[1] the survival curves of patients with and without NSVT detected at baseline Holter monitoring were not statistically different.

Our study suggests that the presence of NSVT are of little value in predicting the risk of total mortality, SD and life-threatening ventricular arrhythmias in patients with IDC. The most significant predictive factors were the presence of advanced NYHA functional class and of severe left ventricular impairment. Also in the CAT[1] and in the MACAS (Marburg Cardiomyopathy Study)[5], the only significant variable predicting total mortality and SD was left ventricular dysfunction (LVEF ≤ 0.30).

Larger trials evaluating patients with heart failure of both ischemic and non-ischemic origin showed conflicting results. In the GESICA (Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina)[22], patients with NSVT had higher total mortality and SD rates. In the subgroup of patients with heart failure of non-ischemic etiology, those with NSVT showed a higher mortality rate (relative risk 1.51, 95% confidence interval 1.06 to 2.15) but the independent predictors of SD were not analyzed.

In the CHF-STAT (Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure)[23], the prognostic value of NSVT was assessed in 674 placebo patients with ischemic (70.7%) or non-ischemic (29.3%) heart failure, LVEF ≤ 0.40 and ventricular ectopic beats ≥ 10/hour. The presence of NSVT, after adjustment for other variables, including LVEF, was not an independent prognostic risk factor for all-cause mortality and SD. Interestingly, this was true regardless of the length (≥ 15 vs < 15 beats) and rate (≥ 120 vs < 120 b/min) of the NSVT runs. Also in our population we compared patients according to the median value of ventricular tachycardia length (5 beats) and rate (155 b/min), with similar results.

In the PROMISE (Prospective Randomized Milrinone Survival Evaluation)[24], the number of NSVT episodes/day was the most powerful parameter predicting SD at multivariate analysis in a population of 1080 patients with left ventricular dysfunction (LVEF ≤ 0.35) and severe heart failure (NYHA class III-IV) of ischemic (54%) or non-ischemic origin (46%), randomized to milrinone or placebo. However, the contribution of arrhythmic parameters in discriminating patients who died because of intractable heart failure from those who died suddenly was limited. In our analysis, patients with ≥ 3 NSVT episodes/day had a higher rate of SD and life-threatening ventricular arrhythmias during follow-up, but this variable at multivariate analysis was significant only in the subgroup of patients with severe left ventricular impairment.

Study limitations. To our knowledge, this is the largest single-center series of IDC patients on optimal medical treatment and long-term follow-up analyzed so far to identify variables predicting SD. However, several limitations of this analysis must be underlined.

First, it was a retrospective analysis including also patients studied in the 1970s and in the early 1980s; however, patients enrolled before 1988 (when we started to treat all our patients with beta-blockers, if tolerated, together with ACE-inhibitors) were a minority (< 20% of the whole population); for this reason, the great majority of patients, and not only those enrolled more recently, could be considered at the top of modern medical treatment.

Second, it cannot be ruled out that changes occurring over time in arrhythmic pattern as a treatment effect may have any prognostic value. However, the purpose of this study was specifically to evaluate the role of NSVT detected at the time of diagnosis before optimizing medical treatment rather than during follow-up.

Finally, a potential limitation which affects all studies evaluating spontaneous ventricular arrhythmias is their variability after repeat recordings. For this reason, a 48-hour Holter monitoring was performed in an attempt to attenuate the risk of missing some patients with NSVT because of a shorter registration[25].

In conclusion, in our series of IDC patients, the presence of NSVT at baseline Holter monitoring did not have any prognostic significance, while advanced NYHA class and severe left ventricular impairment were predictive markers of outcome. Recently, the SCD-HeFT trial[4] confirmed that patients with left ventricular dysfunction and moderate heart failure (independently of the presence of NSVT) improved their survival if treated with AICD, while in other trials[1-3], probably including too few patients for a relatively short follow-up, this was not evident, even when NSVT were considered as an inclusion criterion[2,3].

Nevertheless, frequent episodes of NSVT, regardless of their length and rate, may be correlated with a worse outcome, especially in patients with severe left ventricular impairment. In conjunction with other variables such as a long duration of the disease, left ventricular dilation[13], advanced NYHA functional class[3], and T-wave alternans[26], this may further improve the risk assessment of patients with IDC, to reduce unnecessary AICD implantations.

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