Idiopathic dilated cardiomyopathy: prognostic significance of electrocardiographic and electrophysiologic findings in the nineties

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Key words:
Electrophysiology; Idiopathic dilated cardiomyopathy; Prognosis; Sudden cardiac death.

Background. **With the exception of a few cases such as aborted sudden cardiac death, sustained ventricular tachycardia, and syncope of unexplained origin, there is no consensus on the clinical findings identifying patients with idiopathic dilated cardiomyopathy with an increased risk of sudden cardiac death or malignant ventricular arrhythmias.**

Methods. **To verify whether electrocardiographic and arrhythmologic features could be useful for prognostic stratification, 78 consecutive patients with an invasive diagnosis of idiopathic dilated cardiomyopathy, but without symptomatic ventricular arrhythmias, were enrolled in a prospective study. Signal-averaged ECG, 24 to 48 hour ECG monitoring and electrophysiologic study were performed at the time of diagnosis to identify arrhythmogenic predictors of outcome. Transplant-free and arrhythmic event-free survival was evaluated on the basis of initial parameters.**

Results. **During a mean follow-up of 85 months, 9 patients died (6 of sudden cardiac death and 3 of congestive heart failure), 10 patients underwent cardiac transplantation for refractory heart failure, and 3 presented with sustained ventricular tachycardia. The independent predictors for death and cardiac transplantation were an HV interval > 55 ms and the combination of frequent repetitive ventricular ectopics with a poor left ventricular function. A strong index of arrhythmic events proved to be the association of a prolonged HV interval with a wide (> 110 ms) QRS complex (odds ratio 4.53, 95% confidence interval 1.57-13.04, p < 0.005).**

Conclusions. **An accurate measurement of the HV interval and QRS duration at baseline evaluation may add prognostic information in patients with idiopathic dilated cardiomyopathy. In our experience, abnormal values of both parameters identified a group of patients with a very high risk of late occurring arrhythmic events.**

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Background

As reported in the literature between 1978 and 1989, the prognosis of patients with idiopathic dilated cardiomyopathy (IDCM) seems to be poor. During mean periods of follow-up of approximately 4 years, the mortality rate approaches a value of 40%. The corresponding figure for sudden cardiac death (SCD) was 12%, accounting for about one third of all the patients who died[1].

Since the end of the 80s a significant improvement in survival has been reported in this condition, mainly as a consequence of an earlier detection of the disease and of a widespread use of new effective treatments, such as ACE-inhibitors and beta-blockers[2,3]. In spite of this improvement, however, some authors[4] noted that the incidence of SCD remained almost unchanged when compared to that recorded in the previous decade.

With the exception of a few cases (such as aborted SCD, sustained ventricular arrhythmias or syncope of unexplained origin[5]), the prevention of SCD still remains a complicated problem in IDCM, mainly due to the lack of consensus on the clinical findings identifying patients at a higher risk of lethal or life-threatening arrhythmic events. Once identified, these patients might benefit from an implantable cardioverter-defibrillator (ICD), a beneficial procedure in ischemic cardiomyopathy[6-8]. The ICD, however, has not yet been shown to be effective in IDCM[9,10].

At the beginning of the 90s patients with IDCM, included in the Heart Muscle Disease Registry of Trieste, were enrolled into a prospective study to verify whether ECG and arrhythmologic and electrophysiologic parameters, collected at baseline evaluation, might be useful for prognostic purposes, with special reference to the risk

of SCD and malignant ventricular arrhythmias. The purpose of the present study was to identify the predictors of both mortality/heart transplant and arrhythmic events in a population with IDCM, extensively treated with effective drugs during the 90s.

Methods

Patient selection. From March 1989 to May 1996, all patients enrolled in the Heart Muscle Disease Registry of Trieste for suspected primary myocardial disease were prospectively included in this study if they had an invasive diagnosis of IDCM and satisfied the following two criteria:
1) no previous history of sustained and/or symptomatic ventricular tachycardia (VT) or aborted SCD;
2) no previous therapy with antiarrhythmic drugs and/or beta-blockers. Amiodarone, if previously assumed, had to be stopped for at least 6 months before baseline evaluation.

A diagnosis of IDCM was made, in accordance with the World Health Organization criteria[11], when the left ventricular ejection fraction (LVEF) was ≤ 45% and no significant (≥ 50%) coronary artery stenosis was evident at coronary angiography. A specific heart muscle disease was excluded by histological examination of left ventricular endomyocardial samples in 94% of the study population. We also excluded patients with an alcohol intake ≥ 100 g/day in the previous 6 months or a history of systemic blood pressure > 170/100 mmHg.

Before arrhythmologic evaluation, patients had to be in stable clinical conditions with an optimal medical treatment including ACE-inhibitors (all cases), digitalis and diuretics according to the clinical judgment of the cardiologists. Electrolytes and digoxin plasma levels, frequently monitored during hospitalization, were kept within the normal/therapeutic levels during the study.

Baseline evaluation. A total of 78 patients with IDCM were studied. After clinical evaluation, all patients underwent serial ECG recordings and M-mode and two-dimensional echocardiographic examination with measurements of the left ventricular end-diastolic (LVEDD) and end-systolic (LVESD) diameters according to the guidelines of the American Society of Echocardiography[12]. Right and left cardiac catheterization and coronary angiography were performed in all patients, followed in 67 cases by left ventricular angiography. Left ventricular volumes were calculated using the Kennedy's formula[13] in a 60° right anterior oblique projection and LVEF was determined. In the remaining 11 cases, LVEF was derived from nuclear ventricular angiography or echocardiography.

In 71 out of the 74 cases in which left ventricular endomyocardial biopsy was performed, a quantitative assessment of the fibrosis volume fraction was obtained from the left ventricular endomyocardial samples, using previously described methods[14].

The arrhythmologic evaluation included signal-averaged ECG (SAECG), prolonged ECG monitoring and electrophysiologic study for the induction of VT and conduction measurements.

Micropotential analysis was performed in the time domain by means of a 183 Cardiac Early Warning system (Del Mar Avionics) in patients without complete bundle branch block. The SAECG parameters were considered abnormal when they exceeded the mean value ± 2 SD of a reference normal population previously studied in our laboratory (QRS complex filtered [QRS-f] > 117 ms, root mean square voltage of signals in the last 40 ms of the QRS-f [RMS 40] < 15 μV, and duration of low amplitude signals < 40 μV of the QRS-f [LAS 40] > 37 ms were considered abnormal values for 25 Hz filtering, whereas QRS-f > 115 ms, RMS 40 < 11 μV, and LAS 40 > 44 ms were considered abnormal values for 40 Hz filtering). The presence of late potentials was confirmed when at least two parameters were abnormal at 25 and/or at 40 Hz filtering. With the same equipment, an accurate measurement of the non-filtered QRS complex duration was performed utilizing amplified (50 μV/mm) high speed (50 ms/cm) averaged QRS complexes obtained in the 3 Frank leads (x, y, z).

A two-channel Holter recording was obtained at baseline evaluation. It lasted 48 hours in 70 patients and, for technical reasons, only 24 hours in the remaining 8 cases. Holter recordings were analyzed by computer, supervised by an experienced nurse, and confirmed by senior investigators. VT was defined, according to the recognition algorithm of the computer, as three or more consecutive ventricular ectopic beats with a rate > 100/min.

Following the non-invasive arrhythmologic procedures, an electrophysiologic study was performed to evaluate cardiac conduction and ventricular irritability. The PA, AH and HV intervals were measured. Then, incremental atrial pacing was performed to determine the sinus node recovery time and the Wenckebach point. The protocol for induction of VT consisted of a maximum of three extrastimuli delivered at three levels of basic ventricular pacing at the right ventricular apex and outflow tract. When sustained ventricular arrhythmias were not obtained with previous methods, a short-long sequence of stimulation was used (8 driven beats at 150/min and then a pause of 600-800 ms) followed by 1, 2 and 3 extrastimuli.

The following definitions have been applied:
• VTs were episodes lasting > 5 beats at a rate > 120/min;
• non-sustained VTs were episodes lasting < 30 s without the intervening occurrence of hemodynamic compromise;
• sustained VTs were episodes lasting > 30 s or requiring rapid termination for worsening of the hemodynamic status.

Monomorphic VTs are those with a uniform QRS configuration not preceded by His bundle deflection and with cycle lengths > 200 ms. Polymorphic VTs or ventricular fibrillation (VF) were characterized by continuously changing QRS morphologies and cycle lengths generally ≤ 200 ms.

Bundle branch reentry VTs showed a uniform (left or right bundle branch block) QRS pattern preceded by a His bundle deflection with an HV interval equal or superior to that recorded during sinus rhythm. In addition, the diagnosis of bundle branch reentry VT required at least one of the following criteria[15]:
1) onset of VT after progressive VH prolongation in the course of premature ventricular stimulation;
2) spontaneous termination of VT with the last ectopic beat not followed by a retrograde His bundle deflection;
3) variation of the RR intervals parallel to the preceding HH interval changes.

Follow-up. All patients were monitored prospectively in the Heart Muscle Disease Outpatient Clinic of Trieste. Clinical-instrumental evaluation, including clinical examination, ECG, Holter monitoring and echocardiography, was repeated every 6 months during the first 2 years and then every 12-18 months, depending on the patient's clinical status. Follow-up, lasting a mean period of 85.0 ± 32.5 months, was ended in December 2001 or at the time of death/cardiac transplantation or at the documentation of life-threatening ventricular arrhythmias. None of the patients was lost during follow-up.

A stepwise increase of beta-blocker therapy (generally metoprolol or carvedilol) up to the target or to the maximum tolerated dose was tried in every case. Overall, beta-blocker treatment was continued in the long term in 91% of patients.

Amiodarone was initially prescribed to patients with inducible monomorphic or bundle branch reentry sustained VTs and to those with frequent repetitive ventricular ectopics (couplets or VTs > 20/24 hours). Twenty-seven cases (35%) received amiodarone for variable periods of time.

Cardiac transplantation was considered in all cases with relapses of congestive heart failure requiring new hospitalizations for intravenous infusion of inotropic and/or diuretic drugs in spite of optimal medical therapy.

During follow-up a third-generation ICD with ECG storage capabilities was implanted for the primary prevention of SCD in 5 cases. The indications were: syncope of unexplained origin in 2 patients, and worsening of asymptomatic non-sustained VTs despite chronic amiodarone treatment in 2 other cases. The fifth patient had a familial history of SCD and a persistent inducibility of sustained VTs in spite of long-term amiodarone treatment. A severe left ventricular dysfunction was documented in all patients at the time of ICD implantation.

Eleven patients underwent permanent atrioventricular sequential pacing, either prophylactically, before starting drugs which could worsen a previously known compromised conduction system (4 cases), or after the documentation of severe bradyarrhythmias (sick sinus syndrome in 3 cases or asymptomatic 2nd or 3rd degree atrioventricular block in 4 cases).

During follow-up, the endpoints were cardiac death, transplantation and arrhythmic events. Cardiac death was classified as due to progressive heart failure or sudden and unexpected (that is death within 1 hour of symptom onset in a previously stable patient, death during sleep or unwitnessed death).

Arrhythmic events were defined as follows:
• documented spontaneous sustained VT or VF;
• appropriate ICD shocks for spontaneous VT or VF with documentation of the rhythm leading to the shock on ECG stored within the device;
• Unexpected SCD.

Statistical analysis. Data are expressed as mean ± SD or as percentage. Difference between groups was assessed by one-way analysis of variance for continuous variables and using the χ^2 test with Yates correction for categorical variables. The changes from continuous into categorical variables were based on median values or clinically significant values.

Transplant-free survival and freedom from arrhythmic events were analyzed on the basis of the following factors collected at baseline evaluation: age, sex, a familial history of IDCM, NYHA functional class gradation, LVEDD, LVEF, the presence of complete left bundle branch block (a QRS complex ≥ 0.12 s with a morphology characterized by the absence of Q waves and by late intrinsic deflection in the left precordial leads), the presence/absence of late potentials in patients without major intraventricular conduction defects, the QRS and HV durations, the number of ventricular ectopic beats, couplets and VTs during a 24 hour period of ambulatory ECG monitoring, the induction of VT at premature electrical stimulation, the percentage of the fibrosis volume fraction at endomyocardial biopsy.

The influence of amiodarone treatment during follow-up was also analyzed.

The survivor functions from the time of control evaluation were calculated for the different groups using the Kaplan-Meier method and compared using the log-rank test.

The Cox proportional hazards model was used to analyze the relation between survival and prognostic indexes. Statistical significance was established at a p value < 0.05.

All analyses were performed with SPSS statistical package 10.0.

Results

Patient characteristics. Seventy-eight patients with IDCM and variable degrees of left ventricular impairment and functional status were enrolled in the study

(59 males and 19 females, mean age 41.4 ± 12.1 years, range 16-62 years). Their baseline characteristics are shown in table I.

Except for 2 cases with permanent atrial fibrillation (associated in one of them with advanced atrioventricular block and permanent VVI-R pacing), all patients were in sinus rhythm with 1:1 atrioventricular conduction.

Twenty-four to 48 hour Holter monitoring revealed the presence of non-sustained VTs (lasting from 3 to 30 beats) in 71% of cases.

A prolongation of the HV interval (> 55 ms) was evidenced at electrophysiologic study in 11 out of the 15 cases with left bundle branch block and in 22 patients without major intraventricular conduction defects. An additional case with infra-hisian conduction defects concerned the patient with atrial fibrillation and permanent VVI-R pacing.

During programmed ventricular stimulation 6 patients were found to have monomorphic VTs (5 sustained), 6 polymorphic VTs (1 sustained) and 4 bundle branch reentry VTs (2 sustained).

The modality of induction varied according to the category of VT. Bundle branch reentry VTs were easily inducible after 1 or 2 extrastimuli during ventricular-driven beats. Monomorphic and polymorphic VTs always required 3 extrastimuli or premature stimulation after a short-long sequence of ventricular pacing.

The duration of the QRS complex was inversely correlated with LVEF (Fig. 1).

The degree of fibrosis at endomyocardial biopsy was directly correlated with the duration of late potentials (r = 0.33, p = 0.018) and inversely correlated to LVEDD (r = -0.29, p = 0.036). A severe degree of fibrosis (> 20%) was frequently associated with the induction of sustained VT and particularly with monomorphic VTs (Table II).

The HV interval was directly correlated with LVEDD, but not with LVEF (Fig. 1). An important dilation of the left ventricle was generally associated with the induction of bundle branch reentry VTs (Table II). Both cases with sustained bundle branch reentry VTs had LVEDD ≥ 80 mm and HV interval > 65 ms and were characterized by the absence of stable and complete left bundle branch block during sinus rhythm.

Table I. Baseline characteristics of the study population.

No. patients	78
Age (years)	41 ± 12 (range 16-62)
Sex (M/F)	59 (76%)/19 (24%)
Familial IDCM	14 (18%)
Duration of symptoms (months)	23 ± 33
CHF history	47 (60%)
NYHA class I-II/III-IV	61 (78%)/17 (22%)
LVEDD (mm)	71 ± 10
LVEDD ≥ 70 mm	41 (53%)
LVEF (%)	29 ± 11
LVEF < 30%	42 (54%)
Endomyocardial fibrosis (%)	14.6 ± 8.4
Fibrosis > 20%	15 (19%)
Left bundle branch block	15 (19%)
Right bundle branch block	1 (1%)
QRS with LP	18 (23%)
QRS without LP	41 (52%)
Nf QRS duration (ms)	117 ± 27
Nf QRS > 110 ms	38 (49%)
HV interval (ms)	57 ± 12
HV interval > 55 ms	34 (44%)
VEB (no./hour)	138 ± 231
VC (no./24 hours)	91 ± 237
VT (no./ 24 hours)	3.4 ± 6.2
Patients with VT	55 (71%)
Max duration of VT (no. beats)	7 ± 5

It was not possible to measure the LVEDD and HV interval in 1 patient; percentage of fibrosis was determined on endomyocardial biopsy of 71 patients only; signal-averaged ECG was not performed in 2 cases and was rejected for excessive noise in another case. CHF = congestive heart failure; IDCM = idiopathic dilated cardiomyopathy; LP = late potentials; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; Nf QRS = non-filtered QRS; VC = ventricular couplets; VEB = ventricular ectopic beats; VT = ventricular tachycardia.

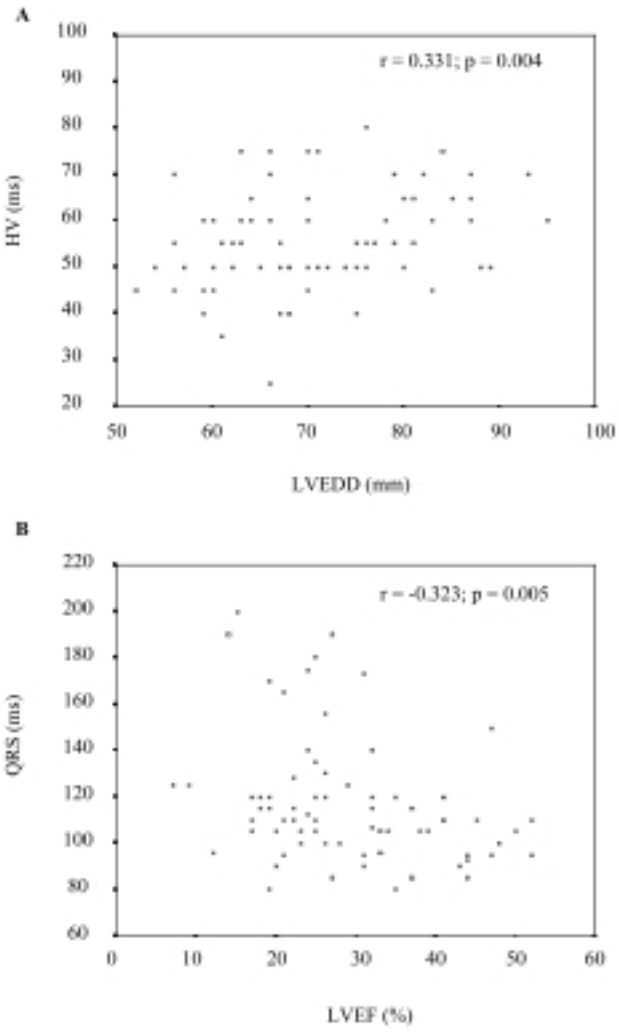


Figure 1. *Correlations between left ventricular end-diastolic diameter (LVEDD) and HV interval* (A) *and between left ventricular ejection fraction (LVEF) and QRS complex duration* (B).

Table II. Characteristics of patients with and without ventricular tachycardia (VT) (> 5 beats).

	Non-VT	VT					
		Holter	PES	Sustained	Monomorphic	Polymorphic	BBr
No. patients	42	20	16	8	6	6	4
LVEF (%)	29 ± 10	30 ± 13	30 ± 9	30 ± 10	32 ± 11	29 ± 10	28 ± 5
LVEDD (mm)	70 ± 10	75 ± 11	68 ± 9	67 ± 11	63 ± 5	66 ± 8	79 ± 9*
LBBB (% patients)	24	25	0	0	0	0	0
HV interval (ms)	55 ± 12	60 ± 12	57 ± 12	57 ± 10	50 ± 8	58 ± 12	66 ± 11
LPs (% patients)	12	15	62.5	87.5**	100**	33	50
Fibrosis (%)	13 ± 6	14 ± 10	21 ± 10	29 ± 7**	30 ± 7**	15 ± 8	13 ± 6

Patients are compared with the first group (non-VT). BBr = bundle branch reentry; LBBB = left bundle branch block; LPs = late potentials; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; PES = premature electrical stimulation. * $p < 0.05$; ** $p < 0.01$.

Predictors of transplant free-survival and arrhythmic events. During 85 ± 32.5 months of follow-up, 9 patients died (6 of SCD and 3 of cardiac pump failure), 10 underwent cardiac transplantation and 3 showed spontaneous episodes of sustained VT (one at telemetry performed a few weeks before cardiac transplantation and 2 at the time of appropriate ICD discharge). One of the last 2 cases died suddenly 1 year after ICD implant.

The cumulative transplant free-survival was 85% at 4 years and 76% at 8 years of follow-up respectively. The freedom from arrhythmic events (SCD + documented sustained VTs) was 95% after 4 years and 85% after 8 years from baseline evaluation respectively. Arrhythmic events (8 cases) occurred early during follow-up (within 6 months of baseline evaluation) in 2 cases, and at least after 3 years from diagnostic and arrhythmologic procedures in the others. Warning symptoms, such as syncope and/or palpitations, were recorded in only 2 of the 8 patients.

The findings associated with cardiac death and transplantation and to arrhythmic events are reported in table III.

At multivariate analysis, the independent variables of transplant free-survival were HV interval > 55 ms and

Table III. Relationship between the variables at baseline and the subsequent outcome. Univariate analysis.

	Death or transplant			Arrhythmic events		
	Yes	No	p	Yes	No	p
No. patients	19 (24%)	59 (76%)		8 (10%)	70 (90%)	
Males	18 (95%)	41 (69.5%)	0.026	8 (100%)	51 (73%)	NS
Age > 40 years	9 (4%)	32 (54%)	NS	5 (63%)	36 (51%)	NS
Familial DCM	5 (26%)	9 (15%)	NS	2 (2%)	12 (17%)	NS
NYHA class III-IV	7 (37%)	10 (17%)	NS	3 (37.5%)	14 (20%)	NS
CHF history	14 (74%)	33 (56%)	NS	6 (75%)	41 (59%)	NS
LVEDD (mm)	74 ± 11	70 ± 10	NS	76 ± 11	70 ± 10	NS
LVEDD ≥ 70 mm	12 (63%)	29 (49%)	NS	6 (75%)	35 (50%)	NS
LVEF (%)	26 ± 11	31 ± 11	NS	27 ± 12	30 ± 11	NS
LVEF < 30%	13 (68%)	29 (49%)	0.047	5 (63%)	37 (53%)	NS
Fibrosis > 20%	3 (16%)	12 (20%)	NS	0	15 (21)	NS
Left bundle branch block	3 (16%)	12 (20%)	NS	4 (50%)	11 (16%)	< 0.05
Late potentials	5 (26%)	13 (22%)	NS	1 (12.5)	17 (24%)	NS
Nf QRS (ms)	120 ± 33	116 ± 25	NS	153 ± 41	113 ± 22.5	0.0001
Nf QRS >110 ms	10 (53%)	28 (48%)	NS	7 (88%)	31 (44%)	0.027
HV interval > 55 ms	14 (74%)	20 (34%)	0.006	7 (88%)	27 (39%)	0.01
HV > 55 ms and QRS > 110 ms	8 (42%)	14 (24%)	NS	7 (88%)	15 (21%)	< 0.0001
VEB/hour > 45	9 (47%)	30 (51%)	NS	3 (38%)	36 (51%)	NS
VC > 11/24 hours	12 (63%)	27 (47%)	NS	3 (38%)	36 (51%)	NS
VT > 3/24 hours	8 (42%)	14 (24%)	0.032	3 (37.5%)	19 (27%)	NS
PES VT	4 (21%)	12 (20%)	NS	1 (13%)	15 (21%)	NS
Amiodarone	10 (53%)	17 (29%)	NS	5 (63%)	22 (31%)	NS
LVEF < 30% and VC > 11 and/or VT > 3/24 hours	11 (58%)	13 (22%)	0.003	3 (38%)	21 (30%)	NS

CHF = congestive heart failure; DCM = dilated cardiomyopathy; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; Nf QRS = non-filtered QRS; PES VT = VTs induced by premature electrical stimulation; VC = ventricular couplets; VEB = ventricular ectopic beats; VT = ventricular tachycardia.

the contemporary presence of LVEF < 30% and frequent repetitive ventricular ectopics (couplets > 11 and/or VTs > 3/24 hours). The freedom from arrhythmic events was independently associated with prolonged HV (> 55 ms) and QRS times (> 110 ms) (Table IV).

The curves for any independent variable are depicted in figures 2-4.

A prolonged HV interval identified the majority of patients (71%) with events of clinical interest for the study. The duration of the associated QRS complex determined the different type of outcome. Patients with a prolonged HV interval but a normal QRS duration (≤ 110 ms) had a 45% incidence of pump failure death or cardiac transplantation, while there was a high rate of arrhythmic events (32%) among patients with both a prolonged HV interval and QRS complex (Fig. 5). As predicted from echo-ECG correlations (Fig. 1), the last group showed a severe impairment of left ventricular function at presentation (LVEDD 76 ± 10 mm; LVEF 24.5 ± 8.7%) with an increasing incidence of major arrhythmic events evident only after the third year of a previously uneventful clinical course (Fig. 4).

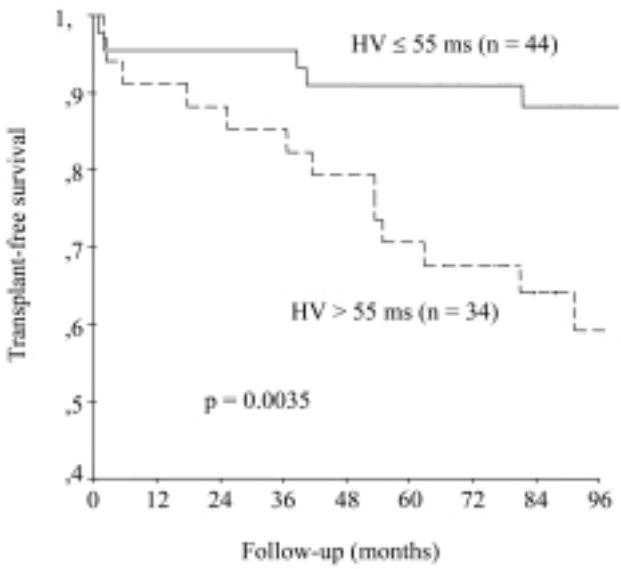


Figure 2. *Heart transplant-free survival in patients with and without HV interval prolongation.*

Discussion

The transplant-free survival in our series (85% at 4 and 76% at 8 years of follow-up) matches very favorably with the mean survival rate reported in historical controls of the previous decade[1]. The incidence of arrhythmic events, however, remained relatively high, affecting about one tenth of the entire population during follow-up. Arrhythmic events, occurring as late phenomena in the majority of cases, were usually not preceded by warning symptoms, such as syncope and/or palpitations, thus not being easily preventable.

Significance of spontaneous and induced ventricular arrhythmias. Spontaneous complex ventricular arrhythmias, a frequent finding in patients with IDCM, were the first characteristic attracting the attention of the researchers who tried to explain the high rate of SCD in this condition. The presence of a Lown class of ventricular ectopic beats ≥ IV[16-19], the prevalence of repetitive ventricular ectopics (couplets or VTs) during a 24 hour period of ECG monitoring[20,21], alone or in association with a depressed ventricular function, frequently proved to be independent risk factors for either total mortality[16,18] or SCD[17,20,21] or both[19].

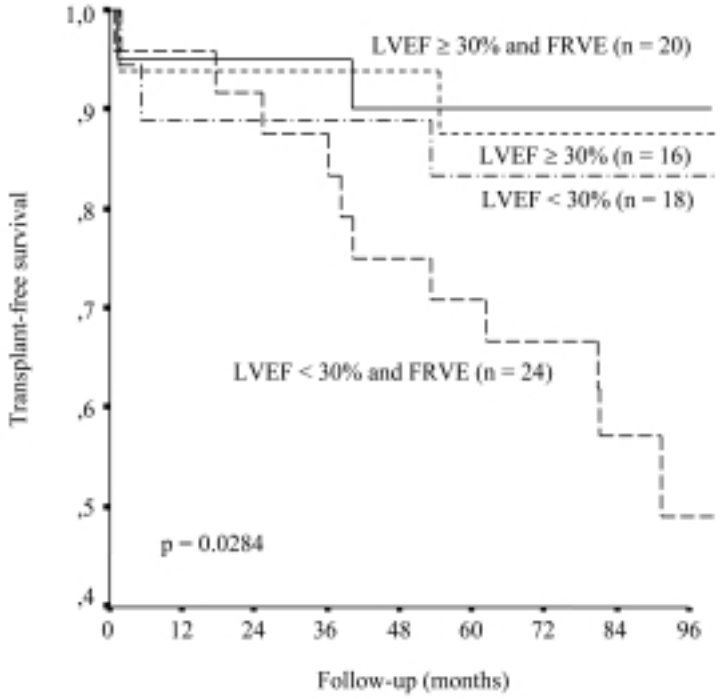
In our experience, the presence of non-sustained VTs was not in itself reliable for prognostic purposes, as it was a very widespread phenomenon among patients especially after an ECG monitoring period of 48 hours. A number of repetitive ventricular ectopics exceeding the median value (couplets > 11 and/or VTs > 3/24 hours) seemed more useful. In particular, the incidence of cardiac death or transplantation was almost 3 times higher whenever a poor left ventricular function (LVEF < 30%) was associated with complex ventricular arrhythmias. Frequent repetitive ventricular ectopics, on the contrary, had no prognostic value in patients with a relatively preserved left ventricular function (Fig. 3), nor predicted an increased incidence of arrhythmic events in the entire population.

Our experience and similar results reported in the literature[22,23] suggest that complex ventricular arrhyth-

Table IV. Independent variables of outcome. Multivariate analysis.

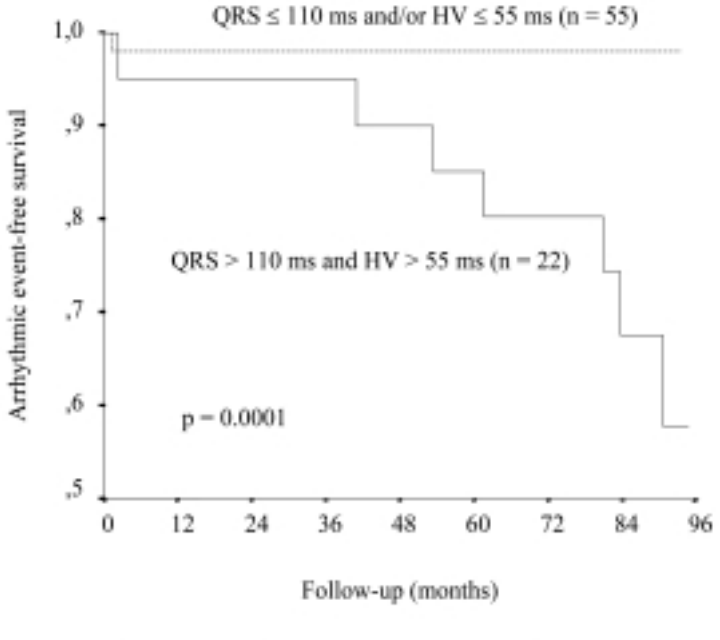
Variable	β	SE	95% CI	OR	p
Transplant-free survival					
HV interval > 55 ms	+0.51	0.27	0.98-2.83	1.67	0.062
LVEF < 30% and VC > 11 /24 hours and/or VT > 3/24 hours	+0.57	0.25	1.08-2.89	1.77	0.025
Arrhythmic events					
HV interval > 55 ms and QRS > 110 ms	+1.51	0.54	1.57-13.04	4.53	0.0049

CI = confidence interval; LVEF = left ventricular ejection fraction; OR = odds ratio; SE = standard error; VC = ventricular couplets; VT = ventricular tachycardia.



FE ≥ 30% + FRVE	100	95	95	95	90	90	90	90	90%
FE ≥ 30% - FRVE	100	94	94	94	94	88	88	88	88%
FE < 30% - FRVE	100	89	89	89	89	83	83	83	83%
FE < 30% + FRVE	100	96	92	88	75	71	67	57	49%

Figure 3. *Transplant-free survival according to left ventricular ejection fraction (LVEF, ≥ 30% or < 30%) and to the presence/absence of frequent repetitive ventricular ectopics (FRVE, ventricular couplets > 11/24 hours and/or ventricular tachycardias > 3/24 hours) in 78 patients with idiopathic dilated cardiomyopathy.*



n = 55	100	98	98	98	98%
n = 22	100	96	90	80	58%

Figure 4. *Arrhythmic events in the 22 patients with prolongation of both QRS complex and HV interval (QRS > 110 ms and HV > 55 ms) and in the 55 patients without these findings (QRS ≤ 110 ms and/or HV ≤ 55 ms). One patient is not included as he had no QRS measurement at signal-averaged ECG.*

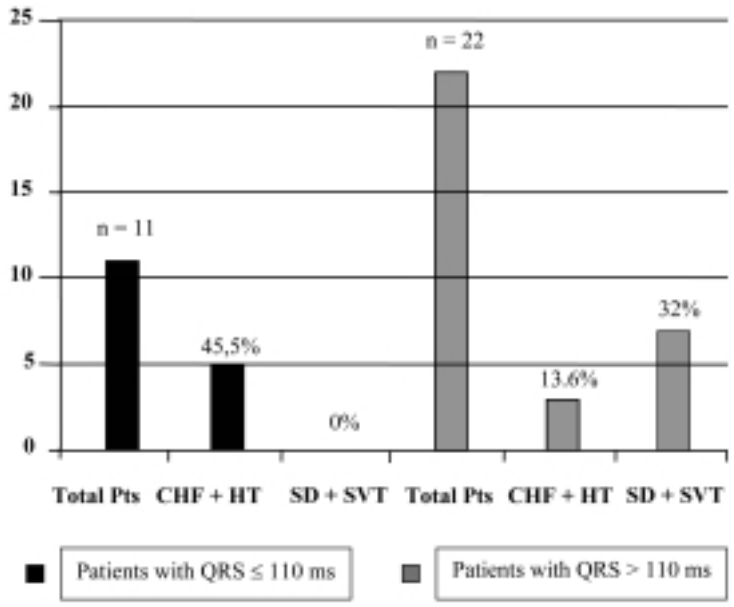


Figure 5. *Events in the group of 33 patients with HV interval prolongation (HV > 55 ms) according to the presence or absence of a wide QRS complex (QRS duration ≤ 110 ms or > 110 ms). CHF = congestive heart failure; HT = heart transplantation; SD = sudden death; SVT = sustained ventricular tachycardia.*

mias in patients with IDCM indicate a more advanced clinical status and compromised myocardium than one may presume on the basis of the values of left ventricular dysfunction alone.

A different opinion considers the enhanced electrical instability, evidenced at presentation, as a warning signal of an increased risk of malignant ventricular arrhythmias and SCD during the follow-up. This view has been proposed in 1988 by Hofmann et al.[21], showing that the frequency of repetitive ventricular ectopics may predict the type of death in patients with IDCM and a poor left ventricular function.

More recently, in a large cohort of patients with IDCM, Grimm et al.[19] found that the presence of non-sustained VTs was an independent predictor for both cardiac mortality/transplantation and for the occurrence of major arrhythmic events. Patients with non-sustained VTs, showing values of LVEDD ≥ 70 mm or values of LVEF ≤ 30%, had an arrhythmic risk 14-fold higher than other cases. The positive predictive accuracy of these combinations of factors was in the range of 36-40%.

Besides the characteristics of patients at presentation and the therapy used during the follow-up, the major difference between our study and that of Grimm et al.[19] lies in the timing of arrhythmic events, occurring early (within 3 years of follow-up) in the German study and generally late (beyond this temporal limit) in our population.

The question concerning the real significance of complex ventricular arrhythmias and the best treatment for the primary prevention of SCD in patients with early-onset IDCM has not yet been entirely solved. Indeed, the two small prospective trials focusing on these topics[9,10] failed to demonstrate a survival benefit from ICD implantation in IDCM patients with severe left ventricular dysfunction, regardless of whether the left ventricular impairment was associated or not with asymptomatic non-sustained VTs. Nevertheless, ICD implantation for the primary prevention of SCD in IDCM patients with a long history of severe remodeling and dysfunction could be effective[24].

As far as inducible VTs were concerned, we noted the possibility of inducing more categories of reentrant sustained VTs in a relatively small number of cases (10%) of the entire population.

Patients with monomorphic sustained VTs (6.4%) showed a histological substrate of severe fibrosis (> 20%), which, on the one hand, limits the extent of left ventricular dilation, while, on the other, determines the intramyocardial delay needed for reentry and the appearance of late potentials at SAECG.

Bundle branch reentry VTs, on the contrary, prevailed in patients with extremely dilated left ventricular cavities (Table II). Sustained VTs of this category were induced in only 2 patients, corresponding to 2.6% of the entire population. Characteristics suitable for induction were the presence of an HV interval > 65 ms, of a LVEDD ≥ 80 mm and of an enlarged QRS complex during sinus rhythm (> 110 ms), the morphology of which, however, does not resemble the typical pattern of a complete and stable left bundle branch block.

No prognostic weight of VTs induced by premature electrical stimulation was evident in our or in more recent studies[25,26]. Various hypotheses have been put forward to explain these negative results. It is possible that in IDCM, SCD could be unrelated to the response to

programmed ventricular stimulation. This possibility may be pertinent for malignant but non reentrant ventricular arrhythmias or for the most advanced stages of the disease, when bradyarrhythmias are the prevalent manifestation of SCD[27].

The very aggressive modes requested for the induction of monomorphic and polymorphic sustained VTs in our study may reflect a poor propensity for their spontaneous onset, a tendency further increased by the large use of amiodarone in inducible patients.

Finally, it is reasonable to assume that premature electrical stimulation may not be the best method to predict late occurring arrhythmic events, a frequent phenomenon in our series.

Prognostic factors for transplant free-survival. Independent variables of transplant free-survival were infra-hisian conduction defects (an HV interval > 55 ms, which approached statistical significance but did not reach it) and, as previously discussed, the combination of frequent repetitive ventricular ectopics with a poor LVEF.

In contrast to ventricular arrhythmias, the ominous prognostic significance of HV prolongation was independent of LVEF and reliable for any kind of cardiac event considered during the follow-up, including total cardiac mortality, heart transplantation and arrhythmic events.

The prolongation of the HV interval is a frequent finding in IDCM, even in patients without major intraventricular conduction defects at surface ECG[28]. To explain this finding several possibilities have been proposed, such as the presence of 1st degree atrioventricular block within the bundle of His, a more prolonged course of the intraventricular conduction system due to left ventricular dilation or a balanced conduction delay in both the right and the left bundle branches. In the presence of a close relationship between HV interval and LVEF, in their study, Probst et al.[28] favored the third hypothesis, which was more consistent with a diffuse and progressive involvement of both the working myocardium and the specialized conduction system. The same investigators[28] predicted a poor outcome in patients with IDCM and a prolonged HV interval, regardless of the presence or absence of a bundle branch block pattern during sinus rhythm.

To our knowledge, the present report is the first confirming their prognostic prevision. In our series, no correlation was found between LVEF and HV interval, while a direct correlation was evident between the latter and the extent of left ventricular dilation (Fig. 1).

Factors linking infra-hissian conduction defects to an increased incidence of arrhythmic events may be only hypothesized, although paroxysms of 3rd degree infra-hisian atrioventricular block and the occurrence of hemodynamically unstable ventricular arrhythmias seem likely. In this context, ventricular arrhythmias may take the form of "torsades de pointes", when the prolongation of the action potential in hypertrophic fibers[29] is further enhanced by spontaneous or drug-induced slowing of the heart rate, or the form of bundle branch reentry VTs, promoted by the atrioventricular conduction delay.

With reference to major arrhythmia documentation in our 33 patients with 1:1 atrioventricular conduction and a prolonged HV interval, we observed the occurrence of asymptomatic 2nd or 3rd degree atrioventricular block in 3 cases and that of sustained ventricular arrhythmias in 2 other patients. The precise location of atrioventricular block and the particular type of sustained VT, however, were not easily definable in our ECG recordings.

Prognostic factors for arrhythmic events. Mainly conduction defects, such as a prolonged HV interval, the presence of a left bundle branch block or simply of an enlarged QRS complex, were the variables linked to the arrhythmic risk (Table III).

Late potentials were relatively good predictors of VT inducibility in the present (positive predictive accuracy of 56%) as well as in other series[25], but were devoid of prognostic significance. The QRS complex duration, a parameter inversely related to LVEF in our population (Fig. 1), is more important from this point of view[30].

In other series, the prolongation of the R wave further increases the negative prognostic value of left ventricular dysfunction, thus predicting an increased incidence of mortality and SCD in patients with both ischemic and non-ischemic cardiomyopathy[31-33].

More pertinent to our data in linking the QRS enlargement with arrhythmic events are the results of the recently concluded MADIT II trial[8] and its non-invasive ECG substudy[34]. In this trial[8], testing the efficacy of ICD in patients with ischemic cardiomyopathy and severe left ventricular dysfunction, a QRS duration ≥ 120 ms was the only ECG parameter significantly associated with the occurrence of VT/VF and the most powerful variable identifying patients who may benefit from an ICD[34].

In the present study, the duration of the QRS complex proved to be useful in predicting the particular outcome modality of the patients with infra-hisian conduction defects. Indeed, those with prolonged HV intervals but normal QRS complexes (≤ 110 ms) frequently presented an accelerated course of refractory congestive heart failure, died or underwent heart transplantation. Patients with an increase of both the HV and QRS times, on the contrary, developed mainly arrhythmic events (Fig. 5), whose increasing incidence became clearly evident only after the third year of follow-up (Fig. 4).

As a consequence, the association of a prolonged HV and QRS duration proved a strong and independent predictor of arrhythmic events, showing an odds ratio of 4.5 and a positive predictive accuracy of 33%.

At least three factors may account for our results, namely: the particular electrophysiologic substrate characterized by HV and QRS prolongation, the degree of left ventricular impairment and the response to therapy.

Prolonged HV intervals and wide QRS complexes identify a pattern of diffuse intraventricular conduction defects, which is a very suitable substrate for the development of potentially lethal brady- and tachyarrhythmias.

On the basis of the echo-ECG correlations performed at baseline (Fig. 1), it may be seen that abnormal prolongation of both variables characterizes the patients with the most severe forms of left ventricular dilation and systolic dysfunction. The maintenance of such abnormalities was the major determinant of subsequent arrhythmic events in the series of Zecchin et al.[35], who performed periodic echocardiographic examinations in a large cohort of patients with IDCM enrolled in our Registry.

Finally, it is interesting to note that our patients with diffuse intraventricular conduction defects showed, in spite of a persisting severe left ventricular dysfunction, a good clinical response to treatment with ACE-inhibitors and beta-blockers, reporting a definite stabilization of congestive heart failure in the majority of cases. It seems, therefore, that the competitive risk existing between heart failure and arrhythmic death in patients with poor ventricular function may have favored the latter outcome in this particular subgroup of patients, whose signs and symptoms of heart failure were adequately controlled by therapy.

In conclusion, this study emphasizes the prognostic importance of an accurate measurement of the HV interval and QRS duration in patients with IDCM. To be valuable, measurements have to be performed at the time of baseline evaluation, in the absence of the confounding influence of antiarrhythmic drugs.

Accordingly, attention has been drawn on cases with diffuse intraventricular conduction defects, characterized by the contemporary presence of HV interval and QRS complex prolongation. These patients, showing severe degrees of left ventricular dysfunction at presentation, were usually stabilized by increasing the dosages of ACE-inhibitors and beta-blockers. The persisting mechanical and electrophysiologic abnormalities, however, were associated with a high incidence of lethal and life-threatening arrhythmias at long-term follow-up.

On the other hand, in our population arrhythmic events were not predicted by the other parameters measured at baseline evaluation, such as the severity of left ventricular dysfunction, the frequency of spontaneous repetitive ventricular ectopics, VT inducibility or the presence of late potentials. We cannot exclude that amiodarone, usually selected for cases with more severe spontaneous and induced ventricular arrhythmias, may have protected some of our patients from SCD and related arrhythmias. This possibility, however, seems unlikely in cases with diffuse intraventricular conduction defects, where drug-induced worsening of intraventricular conduction delay theoretically facilitates both high-degree atrioventricular block as well as reentrant ventricular arrhythmias.

We therefore think that, after a honeymoon period on optimal medical therapy, IDCM patients with HV interval and QRS complex prolongation at baseline could be considered good candidates for ICD implantation, which has proved to be a very effective therapeutic procedure for the primary prevention of SCD and related arrhythmias.

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