Characteristics of syncope in patients with dilated cardiomyopathy

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Abstract

Background: Syncope carries a poor prognosis among patients with dilated cardiomyopathy (DCM).

Objectives: To assess the prevalence, describe the underlying mechanisms and to identify risk factors for syncope in patients with DCM.

Methods: One thousand six hundred and ten medical files of 897 patients with a diagnosis of DCM were reviewed. Patients with syncope were identified and their clinical and paraclinical profiles were compared to an equal number of age- and sex-matched patients with DCM without syncope.

Results: Thirty patients (27 males) with an average age of 62.5 years were identified, corresponding to a prevalence of syncope of 3.3%. A cardiac origin of syncope was identified in 56% of patients (n = 17); ventricular arrhythmias in 33% (n = 10), and conduction disorders in 23% (n = 7). Other mechanisms of syncope were neurally mediated in 7% (n = 2) and orthostatic hypotension in 7% (n = 2). In 30% of cases (n = 9), the etiology was unidentified. There were no significant differences regarding the etiology of DCM, ejection fraction (35.3% vs 35.3%, p = 1.0), NYHA class (mild or advanced, p = 0.79) and associated conditions (hypertension, p = 0.36; diabetes, p = 0.75; atrial fibrillation, p = 0.43; and dyslipidemia, p = 0.33) between the two groups. However, among patients with syncope, patients with a noncardiac cause were more likely to have hypertension (61.53% vs 23.52%, p = 0.08) and diabetes (46.15% vs 5.88%, p = 0.03).

Conclusion: In patients with DCM, syncope is a relatively rare finding. Cardiac causes (arrhythmias and conduction disorders) are responsible for the majority of cases. Risk factors for syncope in these patients remain to be determined.

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1. Introduction

The occurrence of syncope in patients with congestive heart failure (HF) and left ventricular (LV) dysfunction is related to an increased risk of overall mortality and sudden cardiac death (SCD). 1, 2 The one-year risk of SCD can be as high as 45% in subjects with advanced HF and syncope, compared to a significantly lower SCD risk of 12% in patients with advanced HF but without syncope. 3 Several studies identified syncope to
be a negative prognostic factor for nonischemic dilated cardiomyopathy (DCM) patients.  

However, the occurrence of syncope in patients with DCM is not yet completely understood. The cause often remains undiagnosed after standardized evaluation and the relationship between syncope and death in HF patients remains vaguely characterized. The mechanisms of syncope in DCM patients are diverse, including cardiac diseases such as ventricular and supraventricular arrhythmias, bradycardia, conduction disorders, and valvular stenosis. Noncardiac causes are neurally mediated and those attributed to orthostatic hypotension (OH) or neurological pathology.

Since syncope is associated with an increased mortality in patients with DCM, identifying risk factors for the occurrence of syncope in these patients is important. In the general population, risk factors for syncope include advanced age, the presence of an underlying heart disease, autonomic dysfunction, drugs (vasodilators, diuretics, alcohol), and volume depletion. Whether patients with DCM have the same risk factors or whether there are other risk factors for syncope in these patients is less known. Therefore, the aim of this study was to assess the prevalence of syncope, to describe the underlying mechanisms and to identify risk factors for syncope in patients with DCM.

2. Methods

All data were collected retrospectively from the patients’ medical records. The medical files of 897 patients with a diagnosis of DCM, admitted for syncope from January 2008 to December 2013 to the Cardiology Department of the Rehabilitation Hospital in Cluj-Napoca, Romania were reviewed. Patients with syncope were identified and their clinical and paraclinical profiles were compared to an equal number of age- and sex-matched patients with DCM without syncope. Patients from the control group were chosen in a chronological order according to the admission date.

The studied parameters included DCM etiology, left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) class severity, and the presence of associated conditions: atrial fibrillation (AF), type 2 diabetes mellitus (DM II), hypertension, and dyslipidemia.

2.1. Patient workup for syncope

The protocol for the assessment of patients with syncope at our hospital includes:

- detailed history taking and a complete physical examination.
- blood pressure measurement in both arms, both in a supine position and during standing, to identify patients with orthostatic hypotension.
- a neurological exam performed by a certified neurologist, to rule out neurological causes of transient loss of consciousness.
- blood sample testing, including a complete blood count, blood glucose level, blood urea nitrogen, serum creatinine, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, aspartate amino transferase (ASAT), alanine amino transferase (ALAT), uric acid, Quick time, INR.
- a standard 12 lead ECG carefully assessed for the presence of brady- or tachy-arrhythmias, conduction disorders such as AV block or bundle branch block, the presence of ischemic changes, ventricular pre-excitation, QT prolongation or shortening, and Brugada-like changes.
- a trans-thoracic echocardiography using an Esaote MyLab 50 echocardiograph, to identify anatomical modifications such as atria or ventricular dilation, the presence of hypertrophy or cardiac masses, to quantify the LV ejection fraction (LVEF), to assess valve status, the presence of pericardial effusion, signs of cardiac tamponade, aortic dissection, and pulmonary embolism, to characterize the diastolic function, global and regional kinetics, and to measure the pulmonary artery pressure.
- a 24 h Holter ECG monitoring using a BTL CardioPoint H600 device, to assess the minimum, average and maximum heart rates, as well as the presence of arrhythmias and conduction disorders.
- a head-up tilt table test and carotid sinus massage, performed in patients in which history taking suggests elements in favor of a vaso-vagal syncope or carotid sinus hypersensitivity.
- an electrophysiological study (EPS), in patients in which an arrhythmia or a conduction disorder is suspected based on noninvasive tests.

Based on these clinical and paraclinical data, the clinician’s judgment established the cause of syncope.

2.2. Definitions

Syncope was defined as an episode of transient loss of consciousness with incapacity to maintain postural tone, with sudden onset, short duration and complete, and spontaneous recovery.

The definition of DCM was based on the existence of a progressive heart muscle disease with cavity enlargement and diminished performance of the left ventricle (LVEF < 55%), in the absence of left ventricular hypertrophy, with or without enlargement of the right ventricle. The upper limit of the normal left ventricular diastolic diameter for males and females was defined as 59 mm and 53 mm, respectively. The etiology of cardiomyopathy was differentiated into primary (idiopathic) and secondary causes. DCM was considered idiopathic after secondary causes (such as ischemia, severe valvular stenosis or regurgitation, a history of alcohol abuse, a history of myocarditis, general systemic diseases, muscular dystrophies, neuromuscular disorders, use of antracyclines, irradiation and peripartum cardiomyopathy) were excluded.

Atrial fibrillation was diagnosed using the 12 lead ECG or Holter ECG monitoring. Patients with all forms of atrial fibrillation: paroxysmal, persistent, and long-standing persistent were included.

Diabetes mellitus was defined as 2 values of fasting plasma glucose >126 mg/dl, or an abnormal oral glucose tolerance test, with a 2-h serum glucose after the ingestion of 75 g of glucose of >198 mg/dl.
Dyslipidemia was defined as an elevation of any of the following: plasma total cholesterol >190 mg/dl, low-density lipoprotein level cholesterol >115 mg/dl, triglycerides >150 mg/dl, or a high-density lipoprotein level <40 mg/dl in males and <46 mg/dl in females.\(^\text{12}\)

Patients were considered hypertensive, when known with arterial blood pressure levels of \(\geq 140/90\) mmHg\(^\text{13}\) or known with prescribed antihypertensive therapy.

### 2.3. Statistical analysis

Data are presented as average ± standard deviation for continuous variable and frequencies (%) for categorical variables.

The Mann–Whitney–U test was used for the comparison of quantitative variables and the chi-squared test for the comparison of qualitative variables. All statistical tests were performed using SPSS (Statistical Package for the Social Sciences). A \(p\)-value < 0.05 was considered statistically significant.

### 3. Results

The general characteristics of patients included in the study are presented in Table 1.

#### 3.1. Prevalence, median age and sex distribution

Twenty-seven men and three women were identified with DCM and syncope. The average age in the case group was 62.5 years and 62.6 years in the control group. The prevalence of syncope in patients with DCM was 3.3%.

#### 3.2. Dilated cardiomyopathy etiology

The etiologies of DCM in the two groups are presented in Fig. 1. Patients were considered to have idiopathic DCM, if secondary causes (ischemia, significant valve disease, alcohol abuse) were excluded. The encountered valve diseases were 1 case of severe aortic regurgitation and 2 cases of severe mitral regurgitation, all found in the case group. Ischemia was at least partially responsible for 63% of cases in both the syncope and control group. Alcohol abuse played a role in 37% of patients with and 24% without syncope. Six (20%) cases in the syncope group and 9 (30%) cases in the control group had no identifiable cause.

#### 3.2.1. Etiology of syncope in patients with DCM

A cardiac etiology was identified in 17 (56%) patients. Ventricular arrhythmias (sustained monomorphic ventricular tachycardia that either occurred spontaneously or was induced during the EPS and polymorphic ventricular tachycardia) were responsible for 10 (33%) cases and conduction disorders (second and third degree AV block) for 7 (23%) cases of syncope in patients with DCM. Seven percent of syncope were caused by orthostatic hypotension and an equal number were neurally mediated. In 9 (30%) cases no etiology was identified (Fig. 2).

### Table 1 – General characteristics of patients with dilated cardiomyopathy and syncope vs patients with dilative cardiomyopathy and no syncope.

| Patient characteristic | Patients with DCM and syncope | Patients with DCM but no syncope | \(p\) value |
|------------------------|-------------------------------|---------------------------------|-------------|
| Number of patients     | 30                            | 30                              | –           |
| Sex (males)            | 27                            | 27                              | –           |
| Age (years) age ± std dev | 62.53 ± 10.74                | 62.6 ± 10.06                   | 0.84        |
| Etiology of DCM        |                               |                                 |             |
| - Ischemia             | 12 (40%)                      | 14 (46%)                        |             |
| - Alcohol              | 2 (7%)                        | 2 (7%)                          |             |
| - Valve disease        | 1 (3.5%)                      | 0 (0%)                          |             |
| - Mixed (ischemia + alcohol) | 7 (23%)                     | 5 (17%)                        |             |
| - Mixed (Alcohol + valve disease) | 2 (7%)               | 0 (0%)                          | 0.55        |
| - Idiopathic           | 6 (20%)                       | 9 (30%)                         |             |
| Prevalence of syncope  | 3.3%                          | 0%                              | –           |
| LVEF: average          | 35.3%                         | 35.3%                           | 1.0         |
| \(\leq 35\), n (%)     | 18 (60%)                      | 12 (40%)                        | 0.19        |
| \(>35\), n (%)         | 1 (3%)                        | 0 (0%)                          |             |
| 15–25%, n (%)          | 1 (3%)                        | 4 (13%)                         |             |
| 25–35%, n (%)          | 16 (53%)                      | 8 (27%)                         |             |
| 35–45%, n (%)          | 10 (33%)                      | 17 (57%)                        |             |
| \(>45\), n (%)         | 2 (7%)                        | 1 (3%)                          |             |
| NYHA class: n (%)      |                               |                                 | 0.79        |
| - NYHA class I, II     | 11 (37%)                      | 12 (40%)                        |             |
| - NYHA class III, IV   | 19 (63%)                      | 18 (60%)                        |             |
| Associated conditions: |                               |                                 |             |
| n (%)                  |                               |                                 |             |
| - Hypertension         | 12 (40%)                      | 15 (50%)                        | 0.36        |
| - Diabetes mellitus    | 7 (23%)                       | 6 (20%)                         | 0.75        |
| - Atrial fibrillation  | 19 (63%)                      | 16 (53%)                        | 0.43        |
| Dyslipidemia           | 26 (87%)                      | 22 (73%)                        | 0.33        |

DCM, dilated cardiomyopathy; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; Std dev, standard deviation.

#### 3.3. LVEF distribution

In the DCM and syncope group, the LVEF varied between 15 and 51%. The average LVEF was 35.3%. The patient group with DCM and no syncope had LVEF between 20 and 49%, with an average LVEF of 35.3%. There was no statistically significant difference of LVEF distribution in the case and the control group. The distribution of the LVEF in the 2 groups is presented in Fig. 3.

#### 3.4. NYHA class severity distribution

The distribution of patients according to the NYHA class is presented in Fig. 4. The majority of patients in both groups were in NYHA class II and III. No patient with NYHA class I was found in either the case or the control group. Three (10%)
patients without syncope were found with NYHA class 4, whereas no patient with syncope was identified with this NYHA class.

There was no statistically significant link between NYHA class severity and the presence of syncope ($p = 0.79$).

### 3.5. Prevalence of associated conditions and risk factors

Arterial hypertension, type 2 diabetes mellitus, AF and dyslipidemia were relatively frequent findings in both groups of patients, with hypertension and dyslipidemia having a slightly higher prevalence in the syncope group: 40% vs 50%, $p = 0.36$ and 87% vs 73%, $p = 0.33$ respectively. Atrial fibrillation was more frequently encountered in the syncope group (63% vs 53%, $p = 0.43$), and DM II had a similar prevalence in both groups (23% vs 20%, $p = 0.75$). However, there were no significant differences in the presence of these associated conditions between the two groups.

### 3.6. Characteristics of patients according to the etiology of syncope: cardiac vs noncardiac

The general characteristics of patients with cardiac vs noncardiac syncope are presented in Table 2.

### 4. Discussion

#### 4.1. Prevalence of syncope in patients with DCM

In the present study, the prevalence of syncope is considerably lower than the one in the "Sudden Cardiac Death in Heart Failure Trial" (SCD-HeFT) study population (ischemic and nonischemic cardiomyopathy patients with NYHA class II and III and LVEF <35%). Olshansky et al. identified 19% of enrolled subjects with at least one episode of syncope during a median follow-up of 45.5 months. In 1993, Middlekauf et al. discovered a syncope prevalence of 12% among subjects with advanced HF.

#### 4.2. Age and sex distribution of patients with syncope and DCM

The average age in the study of Phang et al. was 59.5 years, which is very similar to the median age from the present study. However, the present male/female ratio differed greatly from the one of the syncope group described by Phang et al. (90%/10% vs 68%/32%). The results from the present study also correlate with the ones found by Middlekauf et al., a study population with 80% men. The same is true for Brembilla-Perrot's et al. study, where males made up 85% of each study group respectively. One group comprised subjects with a history of myocardial infarction and/or multiple coronary stenosis on coronary angiography and LVEF <40%. The other group included patients with idiopathic DCM and LVEF between 10 and 40%. Mean age in the former group was 65 years and 62 years in the latter.
4.3. DCM etiology

Ischemia was the most prevalent cause of DCM in both groups of patients, representing almost two thirds of causes in each group. Toxic cardiomyopathy was a relatively rare finding in each of the two DCM groups. Middlekauf et al.\(^2\) demonstrated 48% of advanced HF cases to be due to coronary artery disease. In his study, idiopathic DCM was responsible for 51%, a higher percentage than the one from the present study, and valvular heart disease for 5% of advanced HF cases, which is similar to the one from the present study.

4.4. Assessment of LVEF and NYHA class

In the present study, there was no correlation between the presence of syncope and the LVEF.

In their study, Middlekauf et al.\(^2\) compared the means LVEF of HF patients with syncope to HF patients without syncope. The syncope group contained 60 subjects and the control group 431 patients. No statistically significant correlation was obtained between the presence of syncope and the LVEF. Olshansky et al.\(^1\) compared HF patients with a LVEF < 25% to those with a LVEF > 25% regarding the occurrence of syncope, finding no correlation between the occurrence of syncope and the LVEF.

In the present study, almost two thirds with DCM and syncope were found in NYHA class III, comprising patients with a less advanced state of HF compared to the population included in the study of Middlekauf et al.\(^2\), where most of the patients with syncope were in NYHA class IV (58%).

We found no statistically significant correlation between the NYHA class severity and the prevalence of syncope in DCM patients. In contrast to our finding is the study of Olshansky et al.\(^1\), who compared the prevalence of syncope according to the NYHA class (class II vs class III) and established a statistically significant correlation between the NYHA class severity and the presence of syncope. One of the possible explanations might be the differences in the population characteristics (a larger population included in Olshansky's study, with all patients having an EF ≤35%).

4.5. Associated conditions and risk factors

No correlation between syncope and the presence of hypertension, AF, DM II and dyslipidemia was identified. We think

*Table 2 – General characteristics of patients with dilated cardiomyopathy and cardiac syncpe vs patients with dilated cardiomyopathy and noncardiac syncpe.*

|                          | Patients with cardiac syncpe | Patients with noncardiac syncpe | p value |
|--------------------------|------------------------------|---------------------------------|---------|
| Age (years)              | 62.07 ± 8.28                 | 62.88 ± 12.54                  | 0.84    |
| Sex (Males): n (%)       | 13 (100%)                    | 14 (82.35%)                    | 0.32    |
| NYHA class II: n (%)     | 3 (23.07%)                   | 8 (47.05%)                     | 0.33    |
| NYHA class III: n (%)    | 10 (76.93%)                  | 9 (52.95%)                     | 0.33    |
| DCM etiology: idiopathic| 3 (23/07%)                   | 3 (17.63%)                     | 0.71    |
| Associated conditions: n (%)|                            |                                 |         |
|   - Hypertension        | 8 (61.53%)                   | 4 (23.52%)                     | 0.08    |
|   - Diabetes mellitus   | 6 (46.15%)                   | 1 (5.88%)                      | 0.03    |
|   - Atrial Fibrillation | 5 (38.46%)                   | 11 (64.70%)                    | 0.28    |
|   - Dyslipidemia        | 11 (84.61%)                  | 15 (88.23%)                    | 0.77    |

DCM, dilated cardiomyopathy; NYHA, New York Heart Association. Bold value = statistically significant.
that there are two possible explanations for this finding: (1) the number of patients included in the study was not enough to reach statistical significance, or (2) there may be no relationship between these associated conditions and syncope in patients with DCM. This is in concordance with the results of the study by Olshansky et al., who compared the prevalence of syncope in HF patients with and without AF and found no statistically significant link.

In contrast to our results, Middlekauf et al. compared the prevalence of AF between patients with DCM and syncope and patients with DCM and no syncope and identified a statistically significant correlation between the presence of AF and syncope. Sanchez et al. assessed the frequency of HTN, DM II and dyslipidemia in patients with syncope and cardiomyopathy who had a negative EPS. This group comprised 19 subjects. HTN was present in 10 (53%), DM II in 6 (32%) and dyslipidemia in 8 (42%) subjects who received ICD therapy. Our values are congruent with these, except for dyslipidemia. The difference may be explained by the fact that in our study, patients with exclusive hypo-high-density-lipoproteinemia were considered to have dyslipidemia.

4.6. Etiology of syncope

Cardiac causes represent the most common etiology of syncope in congestive HF and primary DCM patients, with ventricular tachycardia being the most common cause. This is in concordance with our study, in which ventricular arrhythmias and conduction disturbances together made up more than half of syncope cases in DCM patients. Other cardiac causes encompass supraventricular arrhythmia, bradycardia, conduction disturbance, and valvular stenosis. Noncardiac causes are reflex-mediated syncope and those attributed to orthostatic hypotension (OH) or neurological pathology. Neurocardiogenic mechanisms also play a role in DCM patients with syncope of unknown cause. However, OH and reflex mediated syncope had a low prevalence in the present study. OH was found responsible in 6 (14%) out of 458 syncope events affecting the post randomization group of the SCD-HeFT and Middlekauf et al. established 15% of cases in patients with congestive HF and syncope to result from OH. The latter additionally established 48% of cases to be due to cardiac causes, which concords with our results.

It is important to note that no etiology could be identified in almost a third of the patients, which is in agreement with the study of Middlekauf et al., in which 30% of patients with advanced HF and syncope remained with no identified etiology. These percentages are higher than the one found in the SCD-HeFT trial, where only 19% of patients with syncope had no identifiable cause.

4.7. Characteristics of patients according to the etiology of syncope: cardiac vs noncardiac

There were no statistically significant differences between patients with cardiac syncope and patients with noncardiac syncope (neurally-mediated, orthostatic hypotension and unidentified cause) regarding age, sex, NYHA class, etiology of DCM (idiopathic vs other), LVEF, the presence of atrial fibrillation and dyslipidemia. However, patients with a noncardiac cause of syncope were more likely to have hypertension and diabetes mellitus compared to DCM patients with cardiac syncope, which is not surprising, since one of the most common causes of orthostatic hypotension is autonomic neuropathy due to diabetes mellitus. Also, it is known that hypertensive patients are more likely to have syncope due to orthostatic hypotension and neurally-mediated syncope, since most anti-hypertensive drugs (ACE inhibitors, angiotensin receptor blockers, diuretics, beta blockers, calcium channel blockers alpha central blockers) can cause orthostatic hypotension or excessive reduction in blood pressure values.

4.7.1. Current clinical situation and future directions

Our study contributes to the rather small amount of existing data in the field. As in previous studies, we established that the etiology of syncope in patients with DCM cannot be established in a significant number of cases. We did not find any significant correlation between the analyzed characteristics and the occurrence of syncope in DCM patients. As previously stated, other studies demonstrated a statistically significant relation between certain associated conditions (AF, NYHA class severity) and syncope. This implies the need for a larger study on the topic in the future in order to further understand not only the correlations of associated conditions with syncope, but also the mechanisms causing it. This is especially true since syncope is known to be a negative prognostic factor in patients with HF and the understanding of mechanisms and etiology is crucial in order to improve treatment options.

4.8. Limitations

This study is a retrospective study and carries all the disadvantages and bias possibilities of a retrospective study. The small number of patients included in the study might have influenced the results. The diagnosis was evidence-based in most cases. However, it was the clinician’s judgment who established the presumptive cause of syncope. In a few number of cases, the diagnosis was based mainly on the patient’s clinical history and arguments in favor of a specific condition. For example, in patients with inducible VT during the EPS, the cause of syncope was considered VT, even though this was not 100% certain, since no patient had ECG monitoring at the time of syncope.

5. Conclusions

Syncope in patients with DCM is a relatively rare finding. Cardiac causes (arrhythmias and conduction disorders) are responsible for the majority of the cases of syncope, even though up to a third of cases remain with an unidentified etiology. Risk factors for syncope in patients with DCM remain to be determined.

Conflicts of interest

The authors have none to declare.
Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ihj.2015.09.025.

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