Introduction

Over the past decade, syncope has become increasingly recognized as an indicator of poor prognosis in patients with nonischemic dilated cardiomyopathy (NIDCM). In several clinical series, patients with depressed ejection fraction in the absence of significant obstructive coronary artery disease who experience syncope have been shown to be at high risk for sudden death with a corresponding increased rate of ventricular arrhythmias and appropriate implantable cardioverter defibrillator (ICD) therapy. Furthermore, several studies have cast doubt on the prognostic value of electrophysiological studies in these patients. This review presents the body of evidence to date surrounding the clinical implications and management of syncope in this patient population.

Etiology of Syncope in Patients with NIDCM

The etiology of syncope in the patient with nonischemic cardiomyopathy includes a high incidence of ventricular arrhythmias. Middlekauff et al.1 found a cardiac etiology of syncope in 48% (29/60) of NIDCM patients with congestive heart failure, and spontaneous or induced ventricular tachycardia (VT) in 73% (21/29) of these individuals. Other cardiac causes of syncope included bradyarrhythmias in 8%, supraventricular tachycardia in 2%, and valvular stenosis in 3%. Noncardiac etiologies of syncope in this cohort included orthostatic hypotension (15%), neurological dysfunction (2%), and undetermined origin (30%).

Natural History

Observational studies of patients with left ventricular dysfunction and congestive heart failure who present with syncope have found a heightened risk of mortality from all causes, and in particular, a greater incidence of sudden cardiac death. Middlekauff et al.1 reported a 1-year actuarial sudden death risk of 45% in patients with advanced heart failure (51% due to NIDCM) and syncope versus 12% in patients with advanced heart failure who had not experienced syncope. A similar trend in all-cause mortality was noted, with a 1-year actuarial all-cause mortality risk of 65% in syncope patients versus 25% in nonsyncope patients. Multivariate analysis demonstrated an increased association of syncope with sudden death and all-cause mortality which was independent of age, cardiac index, serum sodium, absence of angiotensin converting enzyme inhibition, or history of atrial fibrillation. Tchou et al.,2 in a series of 50 NIDCM patients without documented ventricular arrhythmias found a significantly higher incidence of sudden death among those with syncope (5/16 [38%] patients) as compared with those who had no syncopal event (1/34 [3%]). Brembilla-Perot et al.3 described a high prevalence (70%) of prior syncopal events in NIDCM patients with sustained VT or cardiac arrest over a mean follow-up of 2 years. Finally, much of the mortality associated with NIDCM and syncope can be attributed to sudden cardiac death. Fruhwald et al.4 found a large proportion (83%) of deaths in patients with NIDCM and syncope were characterized as sudden.

Diagnostic Value of Electrophysiological Testing

The majority of existing clinical evidence indicates that electrophysiological testing has limited use in predicting sudden death due to sustained ventricular arrhythmias in patients with NIDCM and syncope. Multiple studies have demonstrated a poor correlation between clinical endpoints and induction of ventricular arrhythmias during programmed stimulation in patients with NIDCM and syncope.5–7 and a recent review highlights the relative lack of predictive value of electrophysiological testing across all patient subgroups with NIDCM. Brembilla-Perot et al.3 conducted electrophysiological testing with programmed ventricular stimulation in 103 NIDCM patients, 20 of whom had experienced syncope. Five of these patients who did not have inducible VT during programmed stimulation experienced sustained ventricular arrhythmias during follow-up. Furthermore, some authors have reported a high incidence of appropriate ICD therapy for VT in patients with NIDCM, syncope, and a negative electrophysiological study. Knight et al.8 found similar rates of appropriate ICD therapy between survivors of cardiac arrest and noninducible
NIDCM patients with syncope. Russo et al. found a high proportion of appropriate defibrillator therapy in a similar cohort of patients with syncope and no inducible arrhythmias.

**Antiarrhythmic Therapy in Patients with Syncpe and NIDCM**

Medical therapy for the prevention of sudden death due to ventricular arrhythmias in NIDCM patients who experience syncpe has been minimally effective at best. Fonarow et al. published a study of 147 patients with unexplained syncope, New York Heart Association (NYHA) Class III–IV symptoms, depressed ejection fraction (<0.35), and no obstructive coronary lesions who were randomized to ICD implantation (25 patients) or daily oral amiodarone (122 patients). In this trial, defibrillators were programmed for single zone ventricular fibrillation (VF) shock therapy, and amiodarone was dosed at 200 mg. The authors report a significant decrease in sudden death and total mortality among ICD patients versus those treated with amiodarone therapy only (0 vs 15% and 8 vs 25%, respectively). This translated into a hazard ratio of 0.46 between ICD implantation and conventional medical therapy.

**ICD Implantation and Sudden Death Prevention in Patients with NIDCM and Syncope**

The ICD has been shown to be effective in preventing sudden cardiac death and reducing mortality in populations with ischemic or NIDCM and documented spontaneous arrhythmias, like VT or VF. Randomized trials have shown survival benefit and successful treatment of ventricular tachyarrhythmias in this group of patients. In comparison, patients with NIDCM and syncope who have not had documented spontaneous arrhythmias have been excluded from large scale clinical trials.

The Cardiac Arrest Study Hamburg (CASH) trial was limited to survivors of cardiac arrest with documented sustained ventricular arrhythmias. The Antiarrhythmics versus Implantable Defibrillators (AVID) trial included a nontrivial proportion (13%) of patients with a prior clinical history of syncope and nonischemic cardiomyopathy (19%), but all patients were survivors of VF arrest or had documented sustained VT with significant symptoms. In the AVID Registry and AVID Substudy these patients with syncope and inducible VT/VF, who were excluded from the main trial, were found to have a mortality rate similar to survivors of cardiac arrest in the AVID trial (and a limited predictive utility of electrophysiological patients). The Canadian Implantable Defibrillator Study (CIDS) included patients with unmonitored syncope (14% of the cohort, if inducible at electrophysiological study), and also included patients with NIDCM (10%), but did not specifically focus on outcomes of patients with both of these conditions. Thus, data on ICD implantation in the population of patients with NIDCM and syncope of unknown etiology who have not had previously documented spontaneous ventricular arrhythmias has been essentially limited to smaller, uncontrolled observational clinical studies.

In June 1999, Knight et al. published a prospective analysis of 14 patients with NIDCM and unexplained syncope who underwent ICD implantation versus a comparator group of 19 survivors of cardiac arrest with NIDCM. All patients in the syncope cohort underwent electrophysiological testing with results classified as nondiagnostic. No patients received antiarrhythmic therapy, with the exception of three patients in the arrest survivor group. Asymptomatic nonsustained VT (NSVT) was present in 64% of patients. Fifteen of the 19 patients in the cardiac arrest group underwent electrophysiological testing, and 13% of these individuals had inducible sustained monomorphic VT. The authors report a high incidence (50%) of appropriate defibrillator shocks in the dilated cardiomyopathy patients with syncope. This was comparable to the rate of corresponding events (42%) in those who had survived cardiac arrest. Furthermore, Knight et al. found no significant difference in mortality (28% in those with syncope and 32% in cardiac arrest survivors) between the two groups. Kaplan-Meier analysis showed a mean survival time of 40 months in patients with syncope and NIDCM versus 86 months in NIDCM patients who survived cardiac arrest. Secondary analyses showed a trend toward lower ejection fraction and worse NYHA class in NIDCM patients with syncope who experienced an appropriate ICD shock.

Saeed et al. presented data on 61 patients with NIDCM and unexplained syncope, all of whom underwent electrophysiological testing. ICD implantation was performed in 28 of these patients. During a mean follow-up of 34 ± 25 months, 26% of the cohort experienced sustained ventricular arrhythmias with one patient experiencing sudden cardiac death. In this study the outcomes of patients also did not correlate with the results of electrophysiological testing.

Brilakis et al. performed a retrospective analysis of 54 patients with NIDCM and syncope from 1990–1998. Inclusion criteria were ejection fraction <0.35 and no history of coronary artery disease or myocardial revascularization. Thirty-seven (69%) of the patients underwent cardiac electrophysiological studies, with 10 of these patients inducible for sustained monomorphic VT, 8
of whom received an ICD. Of the 15 patients who had a negative or nondiagnostic electrophysiological study, 9 patients received an ICD. Twelve of whom ultimately received a permanent pacemaker. Results in the ICD group showed an 88% survival rate at 1 and 3 years, the pacemaker patients had an 86% and 76% survival rate at 1 and 3 years, and survival in those who did not receive any device was 72% and 48% at 1 and 3 years, respectively. The authors also reported on the effect of inducibility during electrophysiological studies on patient outcomes. Those individuals who had inducible sustained monomorphic VT had an increased incidence of appropriate ICD shocks at 1 and 3 years, and increased mortality at 1 year (but not at 3 years) compared with those patients who were noninducible. Overall, there was improved survival in those who underwent electrophysiological studies in this analysis with 1-, 3-, and 5-year survival of 86%, 76%, and 72% in the group that underwent an electrophysiology study versus 66%, 47%, and 35%, respectively, in the group who did not undergo such testing. However, it should be noted that 17 of these 37 patients who had electrophysiological evaluation received an ICD, which may have been responsible for this apparent protective effect of electrophysiological study in this cohort.

Incidence of Appropriate ICD Shocks in Patients with NIDCM and Syncope

Several authors have used the rate of appropriate ICD therapy for ventricular arrhythmias as a clinical endpoint for analyses of patients with NIDCM and syncope, particularly when the time horizon of such longitudinal studies makes total mortality an impractical endpoint.

Russo et al.10 conducted a prospective study of 46 patients with NIDCM who presented with syncope of unknown etiology and received an ICD during a 6-year period between January 1995 and January 2001. Patients with a history of sustained ventricular arrhythmias were excluded from the analysis. Of the cohort, 93% underwent electrophysiological studies, 21% had inducible sustained monomorphic VT, 16% developed sustained polymorphic VT or VF with premature ventricular stimulation, and the remaining 63% were noninducible. The mean follow-up in this analysis was 17 ± 15 months. ICD shocks occurred in 54% of the patients, 13% had antitachycardia pacing, and 50% experienced aborted shocks. Thirty-three percent of the patients experienced appropriate defibrillator therapy for sustained VT or VF (monomorphic VT in 22%, polymorphic VT or VF in 7%, and a combination of both in 4%).

As mentioned earlier, a lack of inducible ventricular arrhythmias with premature stimulation did not confer a low risk of subsequent events in this clinical series with 22% of the patients who were noninducible experiencing appropriate ICD therapy for sustained VT or VF. There was a twofold increase in events in patients who had a positive electrophysiological study. The authors also found on secondary analysis a trend toward a lower ejection fraction in those patients who received appropriate defibrillator therapy versus those who did not.

Rankovic et al.18 analyzed 54 patients with NIDCM who received an ICD from November 1993 until December 1999. Twenty-three of these patients had a Class I indication for ICD implantation (survivors of cardiac arrest, those with documented spontaneous ventricular arrhythmias or those with syncope and inducible VT or VF during electrophysiological testing). Overall, 54% of this cohort had experienced syncope (20% of patients had unexplained syncope). The authors report a trend toward higher rate of appropriate ICD discharges in those patients with prior syncope (61%) versus those without a history of syncope (48%). This study also indicated a statistically significant protective effect of beta-blocking agents in reducing the incidence of appropriate ICD therapy for ventricular arrhythmias in this cohort.

Recently, Grimm et al.19 reported results of a prospective analysis of 101 patients with idiopathic dilated cardiomyopathy who underwent ICD implantation between January 1993 and July 2000. This cohort included 26 patients who had syncope of unclear etiology, 49 patients who had proablytic ICD implantation with ejection fraction <0.30 with NSVT, and 26 patients who presented with sustained VT or VF. Patients received antiarrhythmic and other medical therapy at the discretion of their physician; β-blocker use was similar across all groups, and there was more amiodarone use in the patients who survived sustained VT or VF. The authors reported Kaplan-Meier survival, and in addition constructed a multivariate Cox proportional hazards regression model to predict ICD discharge. They found appropriate ICD therapy for ventricular arrhythmias in 37% of the patients who underwent prophylactic ICD implantation, 31% of the patients with syncope of undefined etiology, and 35% of the patients with prior documented sustained VT or VF. Multivariate regression modeling showed that ejection fraction, among baseline clinical variables, was strongly associated with increased events and was thought to be largely responsible for the similar event rates between the prophylactic and VT/VF survivor patients in the study. Based on these findings, the authors propose a potential role for prophylactic
ICD implantation in patients with NIDCM with a caveat that further primary data is needed.

Current Clinical Opinion and Future Directions

Although the body of published work surrounding the clinical implications of syncope in the patient with NIDCM is relatively small, much of the existing evidence points toward a potential survival benefit of ICD implantation in this patient population.20 Indeed, the updated 2002 ACC/AHA/NASPE (American College of Cardiology, American Heart Association, North American Society of Pacing and Electrophysiology) Guidelines classify ICD implantation in patients with advanced structural heart disease and syncope of undetermined etiology as a Class IIb indication, although with a low rank (C) of clinical evidence.21 Two currently ongoing large clinical trials, which include a significant cohort of patients with NIDCM, the Defibrillator in Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial and Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), have excluded patients with NIDCM who have experienced syncope. Until primary clinical trial data on this patient group becomes available, management of the NIDCM patient who has experienced syncope should likely include serious consideration of defibrillator implantation in this group of patients who have been found (albeit in small clinical series) to be at high risk for sudden death due to ventricular arrhythmias; furthermore, the predictive value of electrophysiology testing in these individuals remains controversial.

References