Sudden Death in Dilated Cardiomyopathy

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Summary: The purpose of this review is to examine the potential contribution of arrhythmia to the occurrence of sudden death in dilated cardiomyopathy (DCM) and to discuss current treatment options. We performed a search of the MEDLINE database from 1985 to the present and the reference citations of selected articles pertaining to the prognostic significance, management, and pathophysiology of arrhythmias in DCM. A large proportion of patients with DCM die suddenly, most secondary to ventricular arrhythmia and a smaller proportion due to bradyarrhythmia. The presence and severity of ventricular ectopy may predict risk for sudden death, but the role of electrophysiologic study and signal-averaged electrocardiography in further risk stratifying patients remains uncertain. Abnormalities of the autonomic nervous system and renin-angiotensin-aldosterone axis appear to promote the occurrence of ventricular arrhythmias. Angiotensin-converting enzyme inhibitors improve overall mortality in congestive heart failure, and the use of direct angiotensin-receptor antagonists is currently being studied. In addition, beta-receptor antagonists appear to improve morbidity and may prove to improve mortality in heart failure as well. Other interventions still under investigation include amiodarone and the implantable cardioverter-defibrillator. The underlying pathophysiology of sudden death in DCM involves primarily ventricular tachyarrhythmia. Angiotensin-converting enzyme inhibitors remain a mainstay of improving overall mortality, while further study on the roles for newer drugs and devices is ongoing.

Key words: heart failure, sudden death, beta-receptor antagonists, angiotensin-converting enzyme inhibitors, amiodarone, implantable cardioverter-defibrillator

Introduction

Dilated cardiomyopathy (DCM) is a syndrome of impaired systolic function characterized by many hemodynamic, neurohormonal, and electrical derangements that are the end point of a diverse array of pathologic processes not related to coronary artery disease (CAD). With an estimated 2-year survival rate of $\leq 50\%$,^{1,2} total mortality in DCM is dismal. As expected, many deaths are secondary to progressive pump failure, but even more alarming is the large proportion of patients who die suddenly or unexpectedly. Despite advances in medical management that reduce overall mortality associated with congestive heart failure (CHF), the mortality rate from sudden death has remained unchanged at 30 to 40% of all deaths.^{1–3} The key to reducing the high incidence of sudden death in this population is to understand the underlying pathophysiology, and investigation has focused primarily upon the role of arrhythmia. Although the presence of ventricular tachycardia (VT) identifies the patient with CAD who is at risk for sudden death,⁴ no such relation has been definitively established in the patient with CHF in the absence of CAD. Further complicating the issue and making comparisons among different studies difficult is the inconsistent and sometimes arbitrary definition of sudden death. Previously proposed definitions that have been utilized in various studies include classification by apparent etiology (circulatory failure or arrhythmia),⁵ death occurring within 24 h of symptom onset, and witnessed deaths within 1 h of symptom onset.⁶ The purpose of this review is to examine the potential contribution of arrhythmia to the occurrence of sudden death in the patient with DCM and to discuss current treatment options.

Sudden Cardiac Death

In several small series of unselected patients who experienced sudden death, VT or ventricular fibrillation (VF) is generally the most frequently encountered terminal rhythm, al-

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though roughly one quarter of events appears to be associated with bradyarrhythmias.⁷⁻⁹ In patients with and without CAD hospitalized for heart transplant evaluation, one series observed that bradycardia or electromechanical dissociation was in fact the predominant rhythm at the time of arrest, with no definite cause for arrest identified in approximately one half of those cases.¹⁰ The pathophysiology of bradyarrhythmic arrests is not well elucidated, although neural reflex activity has been implicated.¹¹

Predictive Testing: Electrophysiologic Study and Signal-Averaged Electrocardiogram

In patients with DCM, there is a high prevalence of ventricular arrhythmia. Nearly all patients demonstrate some form of ventricular ectopy on ambulatory electrocardiographic (ECG) monitoring, and at least half of these episodes qualify as non-sustained ventricular tachycardia (NSVT).¹²⁻¹⁴ Some observational studies have suggested that the occurrence of NSVT in patients with DCM identifies a subgroup at high risk for sudden death.^{5, 15} particularly in the setting of severely decreased left ventricular ejection fraction (LVEF).¹⁶ However, it is more likely that ventricular ectopy merely indicates globally impaired myocardial function rather than the presence of potentially arrhythmogenic foci, and the majority of studies have failed to demonstrate any correlation between either the presence or the severity of ventricular arrhythmias and the risk for sudden death.^{12, 14, 17}

Although inducibility of VT on electrophysiologic study (EPS) has been found to predict risk for sudden death in patients with ischemic heart disease,¹⁸ the role of EPS in the risk stratification of patients with impaired LVEF not associated with CAD remains controversial. Induction of ventricular arrhythmias does not correlate consistently with clinical or ECG criteria, including degree of LVEF dysfunction and severity of ventricular ectopy.^{19, 20} While the presence of polymorphic VT on EPS does not predict risk for sudden death in DCM, the induction of sustained monomorphic VT appears to identify high-risk patients.²¹ However, even if positive EPS were a useful prognostic indicator, the lack of inducible VT does not necessarily predict freedom from sudden death,²² as at least one third of patients with DCM with a history of sustained VT cannot be induced by EPS.^{23, 24} In addition, suppression or stabilization of induced arrhythmias by EPS-guided drug treatment does not lower risk of recurrent arrhythmia or sudden death.²⁵⁻²⁷

Another frequently studied prognostic tool is the signal-averaged ECG (SAE) as a measure of autonomic dysfunction in the patient with CHF. In the population with DCM, conclusions regarding the validity of SAE in predicting risk for sudden death have been contradictory, but SAE appears not to be a useful prognostic indicator. Heart rate variability correlates with severity of left ventricular dysfunction and risk for death secondary to pump failure²⁸ but does not significantly predict risk or sudden death.²⁸⁻³⁰ Some investigators have found a strong correlation between an abnormal SAE and inducible

VT on EPS, but the prevalence of both events was low²⁷ and, as noted previously, the significance of induced VT in patients with DCM is not well established.

Influence of the Autonomic Nervous System

Activation of the sympathetic nervous system is a well documented phenomenon associated with CHF. Plasma norepinephrine levels are significantly higher in patients with CHF than in normal controls,³¹ with levels in ischemic and nonischemic heart disease being similarly elevated,^{32, 33} although the level of plasma norepinephrine levels may³¹ or may not³² correlate with severity of heart failure. As has been observed in ischemic heart disease,³⁴⁻³⁶ heightened sympathetic activity may precipitate or predispose the patient with heart failure to potentially fatal arrhythmia.³⁴ Studies of unselected populations of sudden death victims have demonstrated a circadian pattern of events, with the highest incidence of events occurring during the morning hours,³⁷ a timing which appears to correspond to a daily rise in catecholamine levels³⁸ and associated platelet aggregability.³⁹ A similar diurnal pattern of sudden death incidence has been observed in patients with CHF without CAD.⁴⁰

The first large-scale multicenter trial examining the effect of beta blockers in DCM, the Metoprolol in Dilated Cardiomyopathy (MDC) Trial found that metoprolol was well tolerated and appeared to prevent clinical decline. However, the study was not large enough to demonstrate conclusively improved survival with metoprolol, and no significant effect on sudden death mortality was observed.⁴¹ Patients with heart failure treated with the beta-1 selective antagonist bisoprolol in the Cardiac Insufficiency Bisoprolol Study (CIBIS) demonstrated improved functional capacity, with possibly greater benefit in those patients without CAD, but again no survival benefit was observed.⁴² Newer beta blocker, carvedilol, possesses several unique properties: peripheral vascular resistance is reduced via alpha-1 blockade, while subsequent reflex tachycardia is prevented by its primary action of beta-1 antagonism. Furthermore, carvedilol also demonstrates a significant antioxidant action.⁴³ In a recent multicenter trial, the use of carvedilol in chronic CHF significantly reduced total as well as sudden death mortality. This effect was seen in all subgroups analyzed, including those with ischemic and dilated cardiomyopathy and with varying degrees of heart failure.⁴⁴ Smaller trials have shown slowing of disease progression in mild to moderate heart failure^{45, 46} and symptomatic and hemodynamic improvement in severe CHF.⁴⁷ Again, these benefits were seen to similar degrees in both nonischemic and ischemic populations, but in general these trials have been too small to judge mortality end points. Larger trials will be needed to assess the effect of beta blockers on mortality.

Influence of the Renin-Angiotensin-Aldosterone Axis

Angiotensin-converting enzyme (ACE) inhibitors have been shown to improve overall mortality in patients with

symptomatic CHF^{48–50} and to decrease the incidence of symptomatic heart failure in patients with decreased LVEF.⁵¹ The results of Vasodilator-Heart Failure Trial II (VHeFT II) suggest that there may be some benefit in sudden death mortality for patients with DCM and in general for those with less severe CHF. On the other hand, the significant mortality benefits seen in Studies of Left Ventricular Dysfunction (SOLVD)-Treatment and Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) and the trend in SOLVD-Prevention were primarily due to improvement in death rates from progressive pump failure. Differences in study groups and design may account for these findings. The study population of VHeFT II was roughly half with DCM, while those of SOLVD-Treatment, CONSENSUS, and SOLVD-Prevention were largely patients with CAD. Also, the two study arms of VHeFT II were vasodilator drug therapy rather than ACE inhibitor versus placebo.

In addition to their hemodynamic effects, ACE inhibitors may possess antiarrhythmic properties as well, although this finding has been better demonstrated in the population with ischemic CHF. Captopril prolongs ventricular refractoriness and repolarization on EPS in patients with ischemic CHF and inducible VT,⁵² and reduces both norepinephrine overflow and arrhythmias in the isolated rat heart during reperfusion.⁵³ Enalapril in comparison with placebo has been shown to reduce significantly the frequency of ventricular ectopy, including episodes of VT, in patients with DCM.⁵⁴ A small group of patients with CHF treated with an ACE inhibitor demonstrated restored heart rate variability, reflective of improved parasympathetic activity, which may be protective against fatal ventricular arrhythmias.⁵⁵

Angiotensin II type I receptor antagonists such as losartan have recently emerged as a new treatment option for CHF. The Evaluation of Losartan in the Elderly (ELITE) study compared treatment with losartan and captopril in elderly patients with symptomatic heart failure and in patients with DCM comprising approximately one third of the study population. There appeared to be a significant decrease in total mortality, primarily due to reduction in sudden deaths, a finding consistent in both ischemic cardiomyopathy and DCM subgroups.⁵⁶ Future trials using larger populations and longer follow-up periods will be required to establish any definite survival benefit.

Recent interest has also focused on the direct antagonism of aldosterone in the treatment of CHF, as aldosterone may contribute to potassium and magnesium loss and subsequent fatal arrhythmia, impaired myocardial norepinephrine uptake,⁵⁷ and increased myocardial collagen turnover and fibrosis.⁵⁸ The ongoing Randomized Aldactone Evaluation Study (RALES) will investigate the mortality benefit of adding aldactone to conventional heart failure therapy.⁵⁹

Amiodarone

Classified as a class III antiarrhythmic agent, amiodarone prolongs repolarization and the refractory period in all cardiac tissue. In addition to this fundamental action, amiodarone pos-

sesses an antifibrillatory effect, both alpha- and beta-blocking properties, and a minor negative inotropic effect.⁶⁰ Amiodarone has shown promise as an antiarrhythmic agent, but its role in the treatment of patients with impaired left ventricular function is still being studied. In a prospective, nonblinded design, the Grupo de Estudio de la Sobrevida en la Insuficiencia Cardíaca en Argentina (GESICA) trial demonstrated improved mortality in patients with severe CHF on low-dose amiodarone. Both sudden death and death due to progressive heart failure were reduced in all subgroups analyzed, including New York Heart Association (NYHA) functional class and presence or absence of NSVT on Holter monitoring. Although approximately 20% of the study population were patients with DCM, mortality in these patients was not analyzed separately.⁶¹ Singh *et al.*⁶² found no significant effect of low-dose amiodarone on sudden death or overall mortality, although there appeared to be a favorable trend toward survival benefit in the treatment of DCM. In smaller trials examining both ischemic and DCM populations, the use of amiodarone significantly reduced ventricular ectopy on ambulatory ECG monitoring,^{63,64} but suppression of ventricular arrhythmia has not been associated with improvement in overall or sudden death mortality.^{62,63}

Implantable Cardioverter-Defibrillators

Given the significant role of ventricular arrhythmias in sudden cardiac death, it would seem logical that the implantable cardioverter-defibrillator (ICD) would improve survival rates. Patients with DCM who have ICDs in place may have a rate of sudden death as low as 2% per year⁶⁵ and have similar sudden death rates as patients with ischemic CHF who have a history of cardiac arrest, a group with known survival benefit from ICD placement.⁶⁶ Several small nonrandomized studies investigating ICD placement in patients with a history of cardiac arrest or recurrent, refractory VT or VF have suggested a resultant decrease in the occurrence of sudden death in mixed populations of patients with both ischemic and nonischemic CHF^{67,68} and in those with DCM.²³ In comparing three treatment options for patients referred for cardiac transplant evaluation—ICD placement versus antiarrhythmic treatment versus no antiarrhythmic treatment—Sweeney *et al.*⁶⁹ found that sudden death rates were lowest in the ICD group regardless of the etiology of CHF, but that total mortality was similar in all three treatment groups. These findings raise the question of the ultimate utility of ICD use in prolonging survival in patients with CHF: the net result may be to reduce the occurrence of sudden death only to increase the number of patients living long enough to die of progressive heart failure.

Recent trials have compared ICD placement with antiarrhythmic treatment. In the Antiarrhythmics Versus Implantable Defibrillators (AVID) study, patients with a history of VF or hemodynamically significant VT in conjunction with LVEF ≤ 0.40 were randomized to ICD versus amiodarone or sotalolol. Patients treated with ICD demonstrated lower overall mortality than those treated with antiarrhythmic medication.

Mean LVEF for the two treatment arms were 0.32 and 0.31 (defibrillator and antiarrhythmic groups, respectively), and the proportions of subjects with CAD were identical (81%); a separate analysis was not performed for patients with DCM in this study.⁷⁰ Currently ongoing, the Cardiomyopathy Trial (CAT) will examine prophylactic ICD placement in patients with severe DCM who do not have a history of symptomatic ventricular arrhythmias.⁷¹

Conclusion

Sudden death in DCM remains a clinical problem of considerable importance. Ventricular arrhythmias play a prominent part in the pathophysiology of sudden death, and the optimal method of identifying patients at risk and improving prognosis is still undefined. The frequency of ventricular ectopy in patients with CHF may merely reflect the severity of left ventricular dysfunction and degree of sympathetic activation rather than represent an independent marker of risk. The exact role for EPS and SAE in the risk stratification of patients with CHF also remains to be established, particularly in light of data questioning the significance of inducible ventricular arrhythmias and the utility of suppressing induced arrhythmias in improving mortality. Angiotensin-converting enzyme inhibitors improve mortality secondary to progressive heart failure and remain a mainstay of medical treatment for CHF. Newer agents such as carvedilol and losartan, while showing promise in reducing heart failure morbidity and mortality, have not been definitively demonstrated in large, randomized control trials to affect incidence of sudden death. Initial data on the ICD suggest improved sudden death mortality, but use of this intervention may in turn result in increased incidence of death from progressive heart failure. Further study will be required to determine the effect of these treatment modalities on sudden death mortality in DCM.

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