DIAGNOSIS AND MANAGEMENT OF SUDDEN CARDIAC DEATH

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Sudden cardiac death (SCD) is an enormous public health problem with at least 300 000 deaths per year in the USA alone. The current state-of-the-art for treatment of SCD has several significant limitations. Because ventricular fibrillation (VF) quickly becomes irreversible, successful treatment requires immediate care. Even in metropolitan areas with excellent emergency medical services, survival of out-of-hospital cardiac arrest is extremely low. Attempts to prevent SCD with antiarrhythmic agents have had little success (and in some cases *increased* mortality). The development of implantable cardioverter-defibrillators (ICDs), which detect and treat VF almost instantly, has revolutionised the treatment of SCD. However, to be effective these devices must be implanted before cardiac arrest. This is the source of one of the major dilemmas in current SCD management: How to identify SCD victims *before* their first episode.

SCD is defined as unexpected, non-traumatic death within minutes of the onset of symptoms. Recordings obtained during spontaneous episodes of SCD (Holter, telemetry, etc) reveal that SCD results from ventricular arrhythmias in approximately 85% of cases (either primary VF or brief ventricular tachycardia (VT) degenerating to VF).[1] Table 1 lists the main causes of SCD.

Rational strategies for prediction, prevention, and treatment of SCD require an understanding of the mechanisms responsible for the initiation and maintenance of ventricular *fibrillation*. Many risk stratification tests and medical treatment regimens, however, have been predicated on the physiology of ventricular *tachycardia*. While there is clear overlap between VT and VF physiology, their mechanisms are not identical. The lack of specificity in testing and lack of efficacy in treatment stem in part from their predication on VT rather than VF physiology. There are ample articles detailing clinical studies of prediction, prevention, and treatment of SCD. Rather than recreate an exhaustive review of such literature here, we will explore current concepts of VF mechanisms and examine current management as it relates to this physiology.

RE-ENTRY

VF is a re-entrant arrhythmia; there is continuous electrical activity with each wave "recirculating" to produce the next wave. For activation waves to propagate continuously there must be at least two "paths" for conduction separated by unexcitable tissue. Activation must spread around one side of the unexcitable tissue allowing the other side time to recover from inactivation so it can be re-excited when the wavefront returns. Tissue refractory periods limit re-entry: the conduction time around the circuit must be greater than the refractory period of each component of the circuit. Therefore decreased conduction velocity or decreased refractory period facilitates re-entry by decreasing the likelihood that the activation wavefront will encounter its own refractory "tail" terminating tachycardia.

Re-entrant circuits can be divided into two types. In *fixed re-entry* a site of anatomic conduction block (for example, scar tissue post-infarction) provides an obstacle around which electricity must travel. Re-entry can also occur in the absence of anatomic obstacles. In this event the circuit path is determined by tissue refractoriness. A group of *transiently* unexcitable cells (secondary to refractoriness) create an obstacle to conduction around which a circuit can form. This latter type is referred to as *functional re-entry*.

A common example of ventricular re-entry is VT in the setting of ischaemic cardiomyopathy. Scar tissue from myocardial infarction forms a barrier to conduction; strands of living myocardium create channels for conduction through the scar. This forms an anatomically defined re-entrant circuit. The result, frequently, is stable monomorphic VT. SCD, however, rarely results from stable monomorphic VT but rather results from rapid polymorphic VT or primary VF.

MULTI-WAVELET RE-ENTRY

To understand VF we must examine the properties that create instability in VT leading to degeneration of VT into VF. Mapping studies of induced VF in animals reveal co-existence of multiple simultaneous wavefronts. In such multi-wavelet re-entry a "mother" wave divides

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Table 1 Causes of sudden cardiac death

- Coronary artery disease
- Ischaemic cardiomyopathy
- Non-ischaemic cardiomyopathy
- Hypertrophic cardiomyopathy
- Arrhythmogenic right ventricular cardiomyopathy
- Sarcoidosis
- Amyloidosis
- Myocarditis
- Valvar heart disease
- Congenital heart disease
- Cardiac tumours
- Long QT syndrome
- Brugada syndrome
- Wolff-Parkinson-White syndrome
- Electrolyte abnormalities
- Thyrotoxicosis
- Proarrhythmia from antiarrhythmic agents
- Cocaine

producing multiple ''daughter'' waves. The ''restitution hypothesis'' suggests a mechanism for development of instability in re-entry that may explain the predisposition for degeneration to fibrillation.

According to the restitution hypothesis the relation between heart rate and action potential duration is critical to the stability of re-entry. As heart rate increases action potential duration decreases. At fast heart rates oscillations of action potential duration can occur. If the refractory period and conduction velocity vary sharply with heart rate, oscillations tend to amplify causing wave break and degeneration to fibrillation.[2 3] When the action potential duration varies more slowly with heart rate, oscillation tends to decrease (dampen) resulting in stable single wave re-entry. According to the restitution hypothesis the slope of the restitution curve determines the risk of VF.[4] Animal and computer modelling studies have demonstrated that interventions which flatten the restitution curve reduce the inducibility of fibrillation.

SPECIAL CASE: ISCHAEMIA AND INFARCTION

Ischaemia and infarction notably alter tissue refractory and conduction properties, promoting arrhythmia. When cells become ischaemic they develop resting membrane depolarisation. This causes sodium channel inactivation. With modest depolarisation only a small percentage of sodium channels are inactivated; cells remain excitable but with reduced conduction velocity. In the setting of infarction, cells die and potassium leaks into the extracellular space. Local extracellular potassium concentration can be as high as 15 mEq during infarction. This potassium diffuses through the extracellular matrix increasing potassium concentration in the surrounding tissue. The raised extracellular potassium concentration alters Nernst forces leading to resting membrane depolarisation. Depending on the degree of depolarisation (and hence sodium channel inactivation) cells either fail to conduct or conduct with reduced velocity. Because infarction is regional and diffusion of potassium is non-uniform, there is an increase in heterogeneity of conduction velocity and conduction block. The combination of these factors increases the likelihood of VT and degeneration to VF. Under certain circumstances ischaemia can cause automatic and/or triggered firing. Thus ischaemia can provide both fertile substrate for, and the trigger to initiate, re-entry.[5]

Late after infarction there are several arrhythmogenic alterations in myocardial substrate which predispose the post-myocardial infarction (MI) patient to VF. One of these is the persistence of strands of surviving myocardium through areas of infarct scar. Following activation of ventricular tissue outside the scar, conduction spreads slowly through these channels, exiting the scar after healthy tissue has recovered from inactivation. This provides the substrate for re-entry. The electrical perturbations of acute ischaemia and infarction are particularly proarrhythmic when superimposed on the substrate of chronic ischaemic cardiomyopathy.

SPECIAL CASE: ELECTRICAL REMODELLING IN CARDIOMYOPATHY

It is well known that decreased LV function (from any cause) results in an increased incidence of SCD. The electrophysiologic effects of cardiomyopathy have been studied in several different animal models as well as in human tissue from biopsies and explanted hearts. These studies reveal that electrical remodelling occurs in myopathic hearts. Globally there is cell necrosis and replacement of myocytes with scar tissue. Remaining cells develop hypertrophy and altered ion channel and gap junction expression. I_{K1} current density is decreased, sodium calcium exchanger expression is increased, and expression of SERCA, the sarcoplasmic reticulum (SR) calcium pump, is decreased. These changes effect ventricular mechanical function (decreased SR calcium content reduces contractile force) as well as promoting arrhythmia. In the myopathic heart catecholamine responsiveness is preserved (until late in heart failure). In the presence of increased adrenergic tone the balance of forces on intracellular calcium result in transient SR calcium *overload*. With SR overload calcium can be spontaneously released (that is, not in response to an action potential). Calcium release alters the balance of electrochemical forces on the sodium calcium exchanger reversing current flow to produce an inward (depolarising) current, I_{ti}. The amount of membrane depolarisation from I_{ti} is greater in the myopathic heart because of reduced I_{K1}. Thus in the setting of heart failure catecholamine surges can produce spontaneous SR calcium release, I_{ti} and sufficient depolarisation to reach the sodium channel activation threshold.[6 7] An action potential is produced which can provide the trigger for ventricular arrhythmias.

CURRENT PRACTICE

Current management of SCD is shaped by two overriding problems:

- We have very limited ability to prevent SCD and must therefore depend upon risk prediction and prophylactic implantation of an ICD.
- We are unable to predict SCD risk in patients with preserved left ventricular function despite the fact that these patients account for approximately 50% of SCD victims.

RISK ASSESSMENT

Appropriate ICD utilisation is predicated upon accurate assessment of SCD risk. The most obvious indication of increased SCD susceptibility is a history of resuscitation from cardiac arrest. Unfortunately few are lucky enough to survive

such episodes, but of those that do up to 20% will have recurrent episodes by one year and 50% by three years. The goal of risk assessment is primary prevention. Certain groups have been identified as being at particularly high risk for development of VF. There is a clear relation between cardiomyopathy and VF susceptibility. Thus, perhaps the most potent determinant of risk is left ventricular dysfunction. In patients with ischaemic cardiomyopathy the presence of high grade ventricular ectopy and non-fatal ventricular arrhythmias such as non-sustained (or sustained) VT correlate with an increased likelihood of developing VF. In certain groups (for example, hypertrophic and non-ischaemic cardiomyopathy) ectopy is so common that it does not indicate an increased risk of SCD.

Attempts have been made to substratify patients in these groups. There are many studies that indicate autonomic abnormalities predispose to ventricular arrhythmias. Increased adrenergic tone and/or decreased vagal tone are associated with increased incidence of SCD. β Blockers have consistently been demonstrated to reduce mortality and arrhythmic death. Measurements of heart rate variability and baroreceptor sensitivity have been used to assess the balance of autonomic forces. However, these tests have only mediocre positive and negative predictive value.

Other studies seek to identify an underlying electrical substrate that predisposes to VF. In ischaemic cardiomyopathy scar tissue is sometimes traversed by channels of surviving myocardium as described above. In sinus rhythm spread of activation into these channels follows depolarisation of tissue outside of the scar. The magnitude of signal produced by depolarisation of these cells is so small that it is indistinguishable from background noise on the surface ECG. However, when averaging several hundred QRS complexes, noise (which is random) cancels out while the late potentials which are constant remain. Therefore signal averaging enhances the signal to noise ratio and late potentials (activation of channels) become apparent. These channels, however, provide the substrate for re-entrant single wave VT, not necessarily VF. This may explain the limited specificity of signal averaged ECGs.

In an electrophysiologic study, programmed ventricular stimulation is carried out to assess the inducibility of sustained monomorphic VT. A conditioning drive train (eight beats) is delivered to stabilise the action potential duration. Progressively earlier premature beats are then delivered in an attempt to cause unidirectional block and re-entry. Interestingly, despite the fact that electrophysiologic studies are performed to assess the risk of developing SCD, induction of VF is a non-specific finding while VT induction correlates with increased risk of cardiac arrest. The limited predictive value of these tests may reflect their predication on the substrate of VT rather than VF.

A novel approach to assessing SCD risk based more upon measurement of electrical instability than the substrate for VT is microvolt T wave alternans. Alternating action potential durations in a large population of cells can produce changes in T wave morphology. T wave variation (even in the microvolt range) can be discerned by computerised signal processing and has been correlated with risk of SCD. In animal models discordant alternans has been demonstrated to produce unidirectional block, re-entry, and fibrillation.[8] Clinical absence of T wave alternans has been shown to have an excellent negative predictive value in both ischaemic and non-ischaemic cardiomyopathies. The improved negative predictive value (compared with other tests) may result from a closer relation between T wave alternans physiology and vulnerability to fibrillation (not VT).

Table 2 Placebo controlled amiodarone trials

Trial	Population	Improved survival
Polish trial	Post-myocardial infarction, ineligible for β blockers	Yes
CHF-STAT	Congestive heart failure, asymptomatic ectopy	No
EMIAT	Post-myocardial infarction, low ejection fraction	No
CAMIAT	Post-myocardial infarction, asymptomatic ectopy	Yes

CAMIAT, Canadian amiodarone myocardial infarction arrhythmia trial; CHF-STAT, congestive heart failure: survival trial of antiarrhythmic therapy; EMIAT, European myocardial infarct amiodarone trial.

PREVENTION

Several studies have examined the possibility of reducing sudden death with antiarrhythmic agents. Early strategies for prevention of SCD were based on the hypothesis that if inducible VT was correlated with increased risk of SCD then medical treatment that rendered patients non-inducible at electrophysiologic study would reduce SCD. The CASCADE (cardiac arrest in Seattle: conventional versus amiodarone drug evaluation study) trial randomly compared electrophysiological (EP) guided therapy to empiric (non-EP guided) amiodarone in survivors of out-of-hospital cardiac arrest. There was a significant improvement in survival in the amiodarone group. The study had no placebo arm which was felt to be unethical in such a high risk population. There were subsequently several placebo controlled primary prevention trials of amiodarone in patients with (mostly ischaemic) cardiomyopathy with or without asymptomatic ectopy. The results of these trials were mixed although none showed a significant increase in mortality (table 2).[9–11]

Many attempts have been made to prevent episodes of VF with the prophylactic use of other antiarrhythmic agents. Unfortunately to date virtually all trials have demonstrated either no mortality benefit or *increased* mortality. It is useful to review two of the most blatant examples of antiarrhythmic failures; the CAST (cardiac arrhythmia suppression trial) and SWORD (survival with oral d-sotalol) trials.

CAST

In CAST, the class Ic agents flecainide, encainide, and morizicine were used to suppress ambient ventricular ectopy in patients with ischaemic cardiomyopathy.[12] The trial was stopped prematurely secondary to increased mortality with antiarrhythmics as compared with placebo. Class Ic agents bind sodium channels, reducing the number of channels available for depolarisation. Decreased rate of depolarisation (dV/dt) and hence reduced conduction velocity are the result. Such an electrophysiologic effect in isolation would tend to stabilise re-entry (*decreasing* the likelihood that a wavefront will encounter refractory tissue and extinguish). Drug binding is increased when the channel is inactivated. Thus under resting conditions there is little drug effect. When the cell is excited sodium channels open and rapidly inactivate, drug *then* binds to the channel—*after* an action potential has been initiated. Only following repolarisation does drug begin

to unbind from the sodium channel. Until the antiarrhythmic drug dissociates the channel cannot be reactivated. Class Ic agents therefore prolong refractoriness providing a less favourable substrate for re-entry. As long as the refractory period prolonging effects predominate over the conduction velocity slowing effects the net result is antiarrhythmic.

The exact mechanism of proarrhythmia in CAST remains a matter of speculation, but certain observations about the clinical characteristics of the events combined with relevant animal studies suggests a plausible hypothesis. Review of the CAST data demonstrated that SCD events occurred with a diurnal variation consistent with ischaemic events. Ischaemic events (increased angina and non-fatal MI) were similar in the drug and placebo groups. However, in the antiarrhythmic group an ischaemic event was more likely to be fatal. Animal data demonstrate increased flecainide binding during ischaemia. In ischaemic animals treated with flecainide there was an increased incidence of QRS prolongation (indicating reduced conduction velocity) and rapid sustained fatal VT.

SWORD TRIAL

Class III drugs are designed to prolong the action potential duration and thereby the refractory period. Moderate action potential duration prolongation has an antiarrhythmic effect but pronounced prolongation can result in torsade de pointes and SCD. Combined with the action potential prolongation of class III agents, the normal increase of action potential duration at slow heart rates increases the potential of proarrhythmia. The ideal antiarrhythmic drug prolongs refractory period at rapid heart rates (antiarrhythmic effect) but has no effect at slow heart rates (reduced proarrhythmia).

In the ventricle two potassium channels are largely responsible for repolarisation; I_{Kr} and I_{Ks}. The subscripts r and s (rapid and slow, respectively) refer to the kinetics of activation and deactivation. The slow kinetics of I_{Ks} deactivation contribute to the heart rate dependence of action potential duration (APD). With short diastolic intervals (rapid rates) I_{Ks} channels have not completely deactivated before they are activated again. Because there is substantial channel reserve (that is, not all I_{Ks} channels are activated under baseline conditions) I_{Ks} activation before complete deactivation results in ''stacking'' or accumulation of I_{Ks} current at fast heart rates. Thus outward current is increased at rapid rates (reducing APD). In addition, because I_{Ks} increases with increasing heart rate but I_{Kr} does not, I_{Ks} accounts for a greater proportion of the total repolarising current at faster heart rates.

In the SWORD trial the class III agent d-sotalol was used prophylactically against SCD in patients with ischaemic cardiomyopathy.[13] d-Sotalol is a relatively specific I_{Kr} blocker. Although d-sotalol binds I_{Kr} more avidly as heart rate increases, I_{Kr} accounts for less of the repolarising current at rapid rates. The result is a decreased significance (less effect on APD) of I_{Kr} block as heart rate increases. Thus, the antiarrhythmic effect of d-sotalol is diminished at fast rates while its APD prolonging effects are maximised at slow rates increasing its proarrhythmic effects.

Increased heterogeneity facilitates torsade de pointes as well as re-entry. Under normal circumstances there is transmural heterogeneity of APD (with the longest action potentials in the mid myocardium). This dispersion of refractoriness results from a transmural heterogeneity of I_{Ks} expression (reduced in the mid myocardium). Because there is regional variation in I_{Ks} expression the APD prolonging effect of I_{Kr} blockade is heterogeneous. d-Sotalol therefore not only increases APD but also increases the dispersion of refractoriness. This facilitates re-entry by creating voltage gradients between adjacent cells (epicardial cells with relatively short APD and mid myocardial cells with long APD). Interestingly amiodarone, which prolongs the APD, has not been associated with increased mortality. Amiodarone blocks I_{Kr} *and* I_{Ks} and *reduces* dispersion of refractoriness.

TREATMENT

There have been many studies of medical treatment for the prevention of SCD. As discussed above most traditional antiarrhythmic agents have either been ineffective or have increased sudden death. Several agents not typically considered to be antiarrhythmic have none-the-less been demonstrated to reduce arrhythmic death. β Adrenergic blocking drugs have been repeatedly demonstrated to improve both total mortality and arrhythmic death (CIBIS II, MERIT HF, CAPRICORN). Angiotensin converting enzyme (ACE) inhibitors have had more mixed results, but the TRACE and AIRE trials (trandolapril and ramipril, respectively) revealed decreased SCD. In the RALES trial (aldosterone versus placebo; New York Heart Association (NYHA) functional class II–IV patients, ejection fraction $\leqslant$ 40%, on ACE inhibitor, loop diuretic, $\pm$ digoxin) the aldosterone group experienced a 29% reduction in sudden death. Finally in both the Scandinavian simvastatin survival study and the long term intervention with pravastatin in ischemic heart disease study sudden deaths were lower in the treatment groups than in control (although statistical analyses of this end point were not performed). There are several potential ''antiarrhythmic'' effects of each of these drugs: beneficial alteration of autonomic balance, decreased deleterious remodelling following myocardial insult, and mild elevation of serum potassium (aldosterone). Perhaps most importantly, reduced ischaemic burden has profound antiarrhythmic benefits. Revascularisation is in fact the first line of intervention for reduction of sudden death risk in ischaemic patients.

In light of the limited efficacy of SCD prevention and the abysmal success of resuscitation from out-of-hospital cardiac arrest, ICD implantation has become the foundation of SCD management.

IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS

The advent of the ICD has made successful treatment of SCD possible. With the availability of this potent tool comes the question who should receive one? Initial ICD trials were secondary prevention trials: they required survival of SCD before ICD implantation. AVID, CIDS, and CASH all demonstrated the efficacy of ICD in secondary prevention of SCD.[14–16] Subsequent primary prevention trials have had progressively more inclusive entry criteria. The initial primary prevention trials (table 3) required inducibility at EP study in ischaemic cardiomyopathy patients (MADIT[17] and MUSTT). MUSTT suggested that even non-inducible ischaemic cardiomyopathy patients were at high risk for SCD.[18] MADIT II subsequently demonstrated mortality benefit from prophylactic ICD placement in post-MI patients with left ventricular ejection fraction $\leqslant$ 35% without requiring EP study or other positive risk markers.[19] The most recently completed trial, SCD-HeFT, which included patients with reduced left

Table 3 ICD trials

Trial	Comparison	Population	Improved survival
CABG Patch	ICD versus no ICD with CABG	EF <36%, planned CABG (positive SAECG)	No
MADIT	ICD versus ''conventional therapy''	CHF, post-MI, EF <35%, asymptomatic NSVT, inducible, non-suppressible	Yes
AVID	ICD versus class III	Resuscitated VF, CV of sustained VT, EF <40%	Yes
MUSTT	EP guided treatment versus ICD	CAD, EF <40%, asymptomatic NSVT, EP inducible	Yes
CIDS	ICD versus amiodarone	Cardiac arrest, symptomatic sustained VT, syncope, and inducible VT	No
CASH	ICD versus amiodarone versus β blockade	Cardiac arrest	Yes
MADIT II	ICD versus ''conventional treatment''	EF <30%, prior MI	Yes
SCD HeFT	ICD versus amiodarone versus placebo	EF <35%, NYHA II and III	Yes

AVID, antiarrhythmics versus implantable defibrillators study; CABG, coronary artery bypass graft; CAD, coronary heart disease; CASH, cardiac arrest study Hamburg; CHF, congestive heart failure; CIDS, Canadian implantable defibrillator study; CV, cardioversion; EF, ejection fraction; EP, electrophysiological; ICD, implantable cardioverter-defibrillator; MADIT, multicenter automatic defibrillator implantation trial; MI, myocardial infarction; MUSTT, multicenter unsustained tachycardia trial; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; SCD HeFT, sudden cardiac death heart failure trial; VF, ventricular fibrillation; VT, ventricular tachycardia.

ventricular function regardless of aetiology (and with no additional risk requirements), demonstrated mortality benefit from ICD implantation in the broadest group yet. The notable exception to this positive trend was the CABG patch trial in which ICDs provided no added benefit to surgical revascularisation (in ischaemic cardiomyopathy patients with positive signal averaged ECGs).[20] Among other things, this trial underscored the powerful ''antiarrhythmic'' effect of revascularisation.

There is a significant ''false positive'' rate using current implantation criteria. Some patients receive ICDs but never develop SCD, exposing them to unnecessary morbidity and producing a substantial financial burden on the health care system. Conversely almost half of SCD victims have normal left ventricular function with VF as the first manifestation of heart disease. We are currently unable to predict SCD in patients with normal left ventricular function (with the exception of small groups with primary electrical abnormalities—for example, Brugada, long QT syndrome, etc). Finally, even with prophylactic ICD implantation and best medical treatment, there is a 25% four year mortality.

FUTURE DIRECTIONS

There are several deficiencies in our current management of SCD. Risk assessment tools lack adequate sensitivity and accuracy, and while ICDs are an effective treatment they have not eliminated sudden death and to date SCD prevention has essentially been elusive. Future research should be directed toward elucidating the mechanisms specifically responsible for initiation and maintenance of VF. Diagnostic tests can then be developed to identify the electrical characteristics which predispose to development of VF. Finally we require a mechanism based strategy for prevention of SCD. Future paradigms for antiarrhythmic medication must have a higher specificity for the electrical properties that facilitate VF initiation or maintenance. Ultimately a better understanding of the factors responsible for adverse electrical remodelling may improve our chances of intervening to prevent the arrhythmogenic milieu that develops in the cardiomyopathic heart.

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Additional references appear on the *Heart* website—http://www.heartjnl.com/supplemental