The cardiac ventricular myocyte as a substrate for sudden death

The regional lecture in Bath 1993

A fresh approach to serious ventricular arrhythmias may offer a promise of progress in an area in which both prevention and treatment remain unsatisfactory. Three specific 'anti-arrhythmic' drugs have been shown to be pro-arrhythmic in patients who have had a myocardial infarct [1], and even amiodarone fails to prevent sudden death in patients with heart failure [2], although it has shown significant benefit after myocardial infarction [3,4]. Sudden cardiac death is common, affecting tens of thousands of people in this country each year. It is the fatal event in many patients with chronic heart failure. In this article I shall examine characteristics of patients with sudden death before describing recent electrophysiological studies on one of these characteristics, namely hypertrophied heart cells. I shall then show how it is possible that early afterdepolarisations, arising from hypertrophied heart cells, may serve as a trigger for fatal arrhythmias in the appropriate clinical setting.

Characteristics of patients liable to die suddenly

Sudden death has been defined as unexpected death taking place in less than one hour from the development of signs in a patient who has had no new symptoms for the preceding 24 hours [5]. Most of these individuals had hearts scarred from coronary disease, and many were asleep at the time of death [6,7]. The incidence of ST segment changes on the Holter record was low, except for bradycardia-related deaths, and their diurnal distribution, which is a characteristic of coronary events, is not a feature of sudden death [6]. Even though prior infarction is common in these patients, ischaemia, either induced or spontaneous, is not associated with the terminal arrhythmia in most cases. In 15–20% of sudden-death patients some other form of chronic heart disease, such as dilated cardiomyopathy or hypertensive heart disease, is present. In some of the very small group of patients dying suddenly with structurally normal hearts, a link has recently been found between the syndrome of congenital QT prolongation and the Harvey *ras*-1 locus on the short arm of chromosome 11 [8]. This DNA marker codes for one of the family of membrane G proteins that link membrane receptors to channel proteins. Channels for carrying ions are found in the sarcolemmal membrane surrounding each cardiac myocyte.

Cardiac arrhythmias in sudden death

Ventricular arrhythmias are a common feature on Holter recordings in patients with heart failure, and the prevalence of non-sustained ventricular tachycardia increases as left ventricular function deteriorates [9]. Nevertheless serious ventricular arrhythmias are poor predictors in the identification of sudden death. The best predictor for sudden death is systolic impairment of left ventricular function. This correlation between sudden death and mechanical rather than electrical properties has led some to question the long-held belief that sudden death is usually attributable to an arrhythmia [10]. An alternative explanation, of course, may simply be that most sudden deaths *are* attributable to ventricular arrhythmias, but that so far we have not found that electrical correlate of the impaired mechanical performance which is most closely linked to sudden death.

In the series of 157 patients reviewed by Bayés de Luna *et al* [6], 8% of patients died from primary ventricular fibrillation, 17% from a bradyarrhythmia, and 75% from ventricular tachycardia. Some attempt has been made to subdivide the latter group into those whose trace showed *torsade de pointes* and the remainder with 'classical' ventricular tachycardia. This subdivision is important because the aetiology of the terminal arrhythmia in the smaller *torsade* group may be different. Over half of the *torsade* group had no structural heart disease; few had coronary disease; and anti-arrhythmic drugs may play a more important role in this group, whose tachycardia usually starts from a lower baseline heart rate than in patients with classical ventricular tachycardia. However, the criteria for diagnosing *torsade* are not suited to Holter recordings, and lack of the characteristic twisting appearance on a Holter record does not exclude the possibility that in most cases the ventricular tachycardia or fibrillation may be a 'triggered' arrhythmia [11].

Cardiac hypertrophy and sudden death

The major structural change in surviving heart muscle in patients with impaired ventricular function is hypertrophy [12,13]. The Framingham study identified

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hypertrophy as an independent risk factor for sudden death even before the echocardiogram replaced the ECG in its assessment [14]. It is not widely appreciated that hypertrophy is the principal long-term response of the heart to overload from any cause, including myocardial infarction, valve lesions, myopathies, and the greater arterial stiffness which accompanies old age. Hypertrophy usually involves an increase in the heart:body weight ratio and an increase in the size (and probably not the number) of the muscle cells, or myocytes, making up the heart. It also gives rise to fibrotic scarring and myocyte loss. These changes may provide an important basis for arrhythmias because of abnormal impulse conduction, re-entry circuits, and increased dispersion of refractoriness [15]. Ultimately, though, any electric current which may be conducted over such circuits arises from ionic currents flowing across the sarcolemmal membrane. Therefore abnormalities in transmembrane current systems may initiate the fatal ventricular arrhythmias that characterise chronically damaged hearts; and given that impairment of mechanical function is the property most closely associated with a risk of sudden death, it would be reasonable to look for clues to the cause of the fatal arrhythmias in the source of electrical activity most closely linked to the contractile parts of the heart: in the myocyte membrane, the sarcolemma.

Electrical abnormalities in hypertrophied hearts

The most characteristic electrical abnormality in cardiac muscle tissue and in single myocytes from hypertrophied hearts is a prolonged ventricular action potential duration (APD), although this has not been found in every study [16]. Because the QT interval of the ECG reflects the APD of all the ventricular myocytes, one may expect the QT interval to be prolonged in patients with cardiac hypertrophy and failure. Survivors of out-of-hospital ventricular fibrillation have a higher incidence of prolonged QT interval than control patients with coronary disease [17]. We have shown that the QT interval is prolonged in patients with cardiac failure and hypertrophy, and that the QT interval is relatively more prolonged at lower heart rates [18]. The disparity in APD between normal and hypertrophied hearts is more easily seen in isolated heart muscle because isolated muscle can be driven much more slowly than would be possible in man. APD (and QT interval) increase at slower heart rates and this accentuates the differences [19,20].

The membrane action potential which precedes each heart beat is generated by electrical current flow through ionic channels, and these are controlled by the voltage difference on either side of the membrane. In order to examine channel properties it is necessary to manipulate the membrane potential, using the voltage-clamp technique. The heart is dissociated into single myocytes by enzyme perfusion, which is best delivered through the coronary arteries from an aortic cannula. In a model of mild left ventricular hypertrophy in the guineapig, which has a cardiac action potential closely resembling that of the human [21], the heart:body weight ratio was increased by 7%, and single myocytes from the hearts were larger than from control animals by a similar amount [22].

Calcium current in hypertrophied cardiac myocytes

Prolongation of the action potential in hypertrophied myocytes must be caused by an increase in inward membrane current, or a decrease in outward current, or a combination of both these possibilities. Over 20 current-carrying systems are known to be present in the cardiac myocyte membrane. The L-type calcium channel is of central importance in excitation-contraction coupling and this system has received most attention in studies of cardiac hypertrophy. This channel consists (in heart cells) of three protein subunits spanning the width of the membrane. The 165 kDa α_1-subunit contains the voltage-sensitive pore which, when opened by a reduction in membrane potential, allows calcium to flow into the cell down its electrochemical gradient. There are tens of thousands of calcium channels in the surface membrane of each ventricular myocyte and the 'whole-cell' current through these channels can be recorded by stepping the membrane potential to a more positive value from a holding level of -45 mV. When comparing currents in normal and hypertrophied myocytes it is necessary to standardise for surface area; the best way to do this is to express the current relative to the electrical capacity of the surface membrane. In the guineapig model of mild left ventricular hypertrophy, calcium current density is increased by approximately 30%. This will account in

Fig 1. *Photomicrograph of a single ventricular myocyte from the guineapig.* Magnification 804 times. The length of the cells is 159 μm. Note the cross-striations which mark the Z-bands between each sarcomere (courtesy Dr K O Ryder)
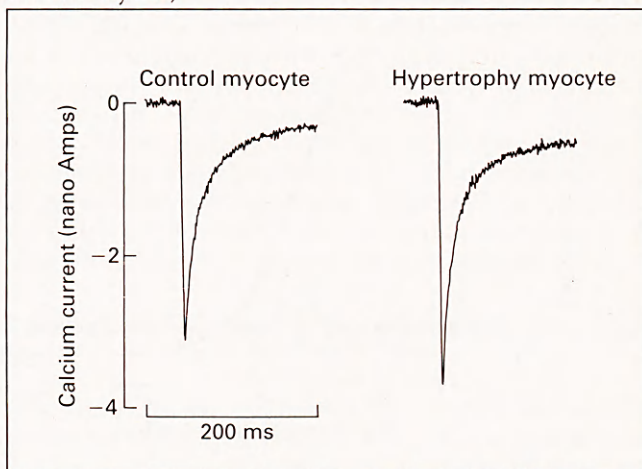
part for the prolonged APD; it signifies an increase in the density of membrane calcium channels in hypertrophied myocytes. Keung (1989) has described an even larger increase in calcium current density in left ventricular myocytes from the hypertensive (Goldblatt) rat model [23]. Hypertrophy does not give rise to the same change in all models, however. In severe cardiac hypertrophy associated with heart failure, calcium current density is reduced [24–27], and the prolongation in APD takes place through other mechanisms.

The control of calcium current gating

The L-type calcium current is switched on (or 'activated') by depolarisations more positive than approximately –40 mV, and the current increase continues as the voltage is increased up to about +10 mV. By recording the current at each voltage relative to the maximal current, the degree of activation can be expressed as a function from 0 (no activation) to 1 (complete activation). In the model of mild hypertrophy in the guineapig, no significant change was found in the activation curves from hypertrophied myocytes.

When the calcium current is switched on by a change in voltage, it reaches a peak within five milliseconds and then decays much more slowly. This decay is known as 'inactivation' and is a channel property separate from activation. Inactivation is also controlled by voltage. Using a two-pulse protocol the relative amount of inactivation can be expressed as a function of voltage. The amount of inactivation is expressed from a level of 1 (no inactivation) at negative potentials (which includes the normal resting potential of heart muscle) to 0 (complete inactivation) at approximately 0 mV. Figure 2 shows the activation and inactivation curves for the calcium channel of normal guineapig myocytes. The inactivation curve is shifted to more positive potentials in hypertrophied cells, and this shift may be of major significance for arrhythmia generation.

The calcium window current

Figure 2 shows that there is a range of voltages over which calcium current is partially activated and not completely inactivated; this range is indicated by the stippled part of the graph. If the membrane is held at a voltage within this range, current will flow for a long time. This current is called the 'window' current. The action potential passes slowly through the window range of voltages at the end of the plateau phase, and a positive shift of the inactivation curve means that window current flows for more of the plateau of the action potential than normal.

Shifts of the calcium current gating variables have also been described in hypertrophied right ventricular myocytes from the cat [28] and ferret [26], and we have found shifts of both activation and inactivation variables in a model of severe left ventricular hypertrophy in the guineapig, produced by banding the thoracic aorta [27]. Shifts in the gating variables have not been found in hypertrophied rat [23] or hamster [25] hearts, but the action potentials in rat and hamster hearts are very different in shape from those of the other species, including man [29,30]. The intracellular calcium-handling properties of these species also differ from the human pattern [30]. Intriguingly, shifts in the L-type calcium channel gating variables similar to those seen in hypertrophied cardiac myocytes have been found in hypertrophied smooth muscle cells from human bladder obtained from patients undergoing prostatic surgery [31]. These changes in calcium channel gating may be a fundamental biological feature of hypertrophied smooth muscle and cardiac muscle in these species.
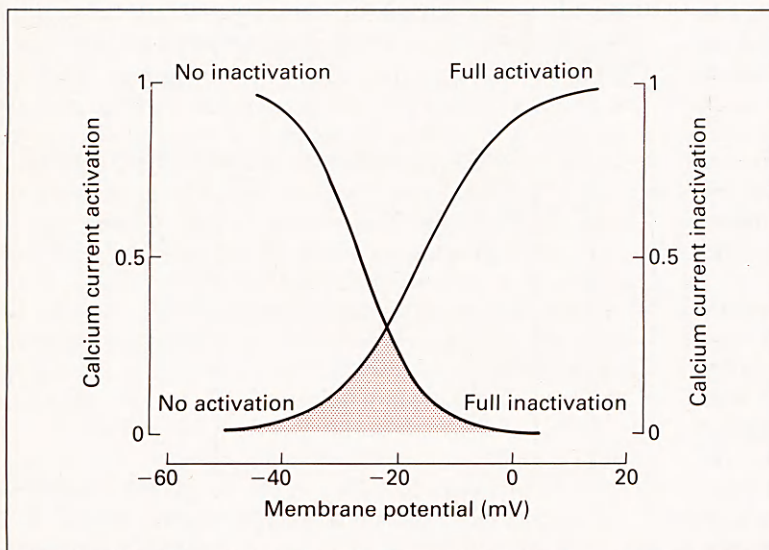

Fig 2. *The gating properties of the calcium current.* The current activates (curve upsloping to the right) and inactivates (curve downsloping to the right) as a function of voltage. The stippled area shows the voltage range over which steady state current flows; this is known as 'window' current and underlies the arrhythmia known as 'early afterdepolarisations'.

Early afterdepolarisations in hypertrophied heart cells

The increased calcium window current in hypertrophied heart cells underlies the cell and tissue arrhythmia known as 'early afterdepolarisations' [32–34]. These afterdepolarisations are low-voltage oscillations which usually occur during the later part of the plateau phase of the action potential, and are associated with known arrhythmic stimuli such as catecholamine or caesium administration, with 'antiarrhythmic' drugs, and with dihydropyridine calcium channel agonists such as Bay K8644. Hypertrophied hearts *in vivo* and isolated muscle from such hearts are much more likely to generate early afterdepolarisations than normal hearts [23,35]. Dogs with left ventricular hypertrophy display early afterdepolarisations and develop ventricular tachycardia after Bay K8644 administration more frequently than control animals. As yet there is no direct evidence linking early afterdepolarisations with clinical arrhythmias in man, but much circumstantial evidence points to their involvement in a variety of clinical situations [36].

The clinical setting for sudden death in the context of the cellular abnormalities.

If early afterdepolarisations based on the calcium window current are important in sudden death, other conditions must combine to determine the occurrence and timing of a fatal arrhythmia in an otherwise predisposed heart. Some clues in respect of the clinical setting may be apparent from studies of Holter recordings made at the time of sudden death. The mean basal heart rate immediately before the onset of classical ventricular tachycardia is approximately 90/min [6,7], and is significantly slower in the subgroup identified as having *torsade de pointes*. Early afterdepolarisations are suppressed at fast heart rates [36], when action potential duration and QT interval are shorter. More important still is the observation that in over half of the patients who die suddenly the fatal arrhythmia follows a pause which is usually post-extrasystolic. The *instantaneous* heart rate preceding the action potential which triggers the fatal tachycardia may therefore be much slower [11].

Triggered arrhythmias are much more likely to arise from a post-extrasystolic action potential than from steady state for several reasons. The duration of this action potential is longer than normal, principally because the calcium transient is larger [37], and this increases inward sodium-calcium exchange current and prolongs the plateau [38]. Thus the calcium window current will be larger during the prolonged action potential because the membrane is longer in the appropriate voltage range. More calcium channels will be recovering from inactivation (brought about by a larger calcium transient) during the late plateau of this action potential, which will further increase the

window current. Another arrhythmia mechanism which may contribute to afterdepolarisations during a post-extrasystolic beat is the sodium-calcium exchange current which gives rise to delayed afterdepolarisations. This current is also substantially increased in myocytes from guineapigs with mild left heart hypertrophy [21].

Resting heart rate increases by a small amount (6–19/min) in the one to three hours before sudden death [6,7]. This suggests a background of sympathetic activation which may be accompanied by parasympathetic withdrawal. Catecholamines increase the calcium current, particularly the window component of this current, by increasing the probability that calcium channels are open, and by favouring longer opening times [39].

The setting for sudden death therefore favours the generation of early and probably also delayed afterdepolarisations from hearts that are already predisposed to triggered arrhythmias because of hypertrophy-induced shifts in the calcium current gating variables and changes in cellular calcium handling. These interacting factors are brought together in an overall scheme in Figure 3. Other tissue mechanisms, such as slow conduction and re-entry, are also likely to be involved in maintaining ventricular arrhythmias once they have been triggered. Membrane current systems, such as the transient inward current and stretch-activated channels, may also help to initiate and maintain the arrhythmia.

These mechanisms may be relevant to hearts with mild and moderate degrees of left ventricular hypertrophy and impairment of systolic function. Patients with very severe degrees of heart failure are less likely to die suddenly than patients with somewhat better ejection fractions [5]. In a group of patients with very advanced heart failure, sudden death was less frequently attributable to ventricular tachycardia than in patients with better left ventricular function [40]. Some clues as to why this may be the case emerge from cellular studies on the calcium channel. In all the animal models of severe cardiac hypertrophy associated with failure, calcium current density is reduced [24,25,27], in contrast to mild and moderate degrees of hypertrophy in which the current density is unchanged [41] or increased [21,23]. Arrhythmias based on the calcium window current may therefore be less likely to occur in more severely hypertrophied hearts than in those with only mild or moderate degrees of hypertrophy, and similar considerations may also apply to the sodium-calcium exchange current which underlies delayed afterdepolarisations.

Therapeutic options for the prevention of sudden death

Given this knowledge, how can one devise worthwhile strategies to prevent sudden death? Local anaesthetic (class I) agents would seem to be unsuitable for pro-
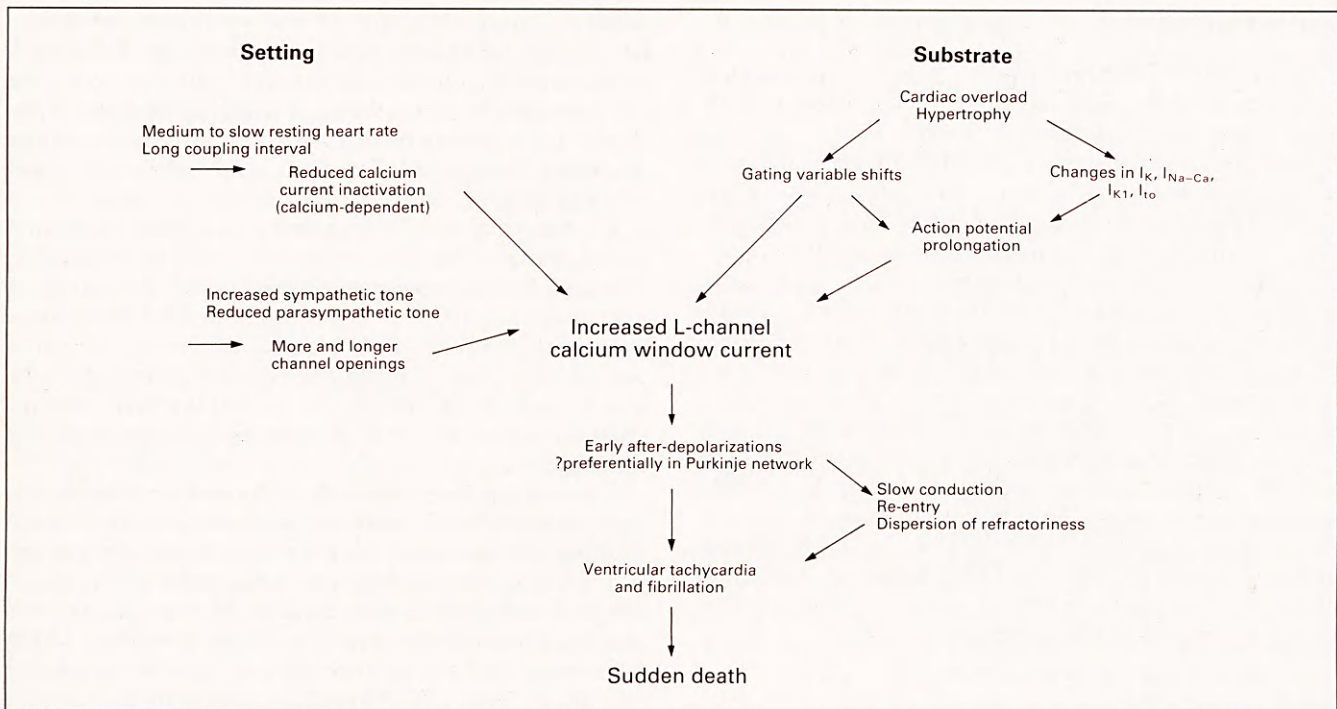
Fig 3. *Scheme showing a central role for the calcium window current in sudden death, in patients with cardiac hypertrophy following myocardial infarction, hypertension, cardiomyopathies, etc.* The substrate (myocyte hypertrophy) is acted on by an appropriate combination of heart rate, sympathetic tone (and probably other features not illustrated here, which may include stretch of the myocytes) to give rise to early afterdepolarisations. These cellular arrhythmias may act as a trigger for the initiation of ventricular tachycardia and fibrillation in the whole heart.

phylaxis against sudden death because of their pro-arrhythmic potential [42], and because the sodium channel does not appear to have a primary role in the pathogenesis of sudden death (Fig 3). Beta-blockers reduce overall mortality and the incidence of sudden death after myocardial infarction [43]. Part of their action in this respect may be attributable to a reduction in the calcium window current. Enalapril reduces sudden death in patients with heart failure [44], and the SAVE study has recently reported a reduction in sudden death with captopril in asymptomatic patients with impaired left ventricular function after myocardial infarction [45]. ACE inhibitors may act through several different mechanisms, including a reduction in the degree of hypertrophy, an improvement in autonomic tone, the effect of potassium conservation on the action potential, and alterations in calcium handling [46].

Unfortunately, conventional calcium channel antagonists are not likely to be useful in arrhythmias triggered by early afterdepolarisations because these arrhythmias can be triggered following recovery from inactivation of only a small fraction of the calcium current [32]. High doses of calcium antagonists would therefore be necessary but would produce an unacceptable reduction in cardiac contractility. Further-

more, calcium antagonists do not block calcium channels at all membrane voltages, or in all channel configurations. No benefit has been found from the use of calcium channel blockers after myocardial infarction [47], with the exception of verapamil in the DAVIT-II trial [48], and in this trial sudden death was significantly less in the subgroup of patients with good left ventricular function [48,49].

To reduce this current component we need a 'calcium antagonist' which will reduce the calcium window current while maintaining the phasic calcium current which acts as a trigger for contraction. Possible reasons for the shifts in the gating of the calcium current in cardiac hypertrophy include a change in the electric charge close to the channels, brought about by differences in intracellular ionic composition or in the degree of channel phosphorylation. Differences in membrane lipid composition in hypertrophy [50,51] may also play a part in the altered channel behaviour, and this may open up novel possibilities for altering arrhythmia risk by modifying plasma lipids. A rational basis for the prevention of sudden death in patients with cardiac hypertrophy may be within our grasp, and a physician's sense of helplessness over the problem of sudden death may eventually be conquered by the determined application of good clinical science.

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