Editorial

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QT and action potential duration

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Depolarisation of cardiac muscle is achieved by "fast inward current", carried by sodium ions, through channels which are inactivated within about one millisecond. When the cells are repolarised (by a net efflux of potassium ions) the process of inactivation of fast channels is rapidly reversed. The class 1 antiarrhythmic drugs delay the disappearance of inactivation until long after repolarisation is complete, and so reduce the probability of re-excitation at short intervals, thus suppressing premature extrasystoles and tachycardia. In theory, it should be possible to produce a similar extension of refractory period by delaying the repolarisation itself, and a drug with this property was sought for many years. Quinidine and disopyramide[1] caused minor delays of repolarisation, but both were primarily class 1 agents, and in addition had undesirable anticholinergic activity.

Eventually it was found that amiodarone, already in use for many years as an antianginal drug, prolonged action potential duration, and on theoretical grounds seemed worthy of trial as an antiarrhythmic agent. It was indeed shown to have an antiarrhythmic action in rabbits[2] and dogs,[3] but two important questions remained. Would the prolongation of action potential duration occur in man, and, if so, would this property be antiarrhythmic?

There was an understandable reluctance to accept that a drug which prolonged action potential duration could prevent or abolish cardiac arrhythmias. At the same meeting in Elsinore at which I proposed a classification of antiarrhythmic actions, which included the prolongation of action potential duration as "class 3", Ward[4] described the familial propensity to ventricular arrhythmias, precipitated by exercise or emotion, in association with a long QT interval, not unlike cases previously noted by Romano *et al.*[5] and by Ward himself.[6] The phenomenon of "R on T" has long been regarded as a harbinger of impending life-threatening arrhythmia, and a long QT has been proposed as a predictor of sudden death.[7]

It must be emphasised that QT is not a measure of action potential duration. Though a uniform prolongation of ventricular action potential duration can be detected as a lengthened QT interval, QT itself represents the time from the first depolarisation to the final repolarisation in the axis of the selected leads. It records the algebraic sum of millions of individual action potential durations and could conceal within itself a number of *short* action potential durations juxtaposed to long ones. The first successful use of amiodarone as an antiarrhythmic agent in man was reported in 1972 by Ferrero and Benabderhamane in atrial flutter.[8] Amiodarone was later shown to prolong action potential duration, monophasically recorded with suction electrodes.[9]

Long term treatment of rabbits with beta blockers induces several adaptive changes in the myocardium, which persist long after the drugs have been eliminated from the body.[10] This "adaptation syndrome" included a prolongation of action potential duration and QT, and both these effects have been shown to occur in man.[11–13] These observations could explain both the prevalence of arrhythmias in the long QT syndrome and the success of antisympathetic therapy by left stellate ganglionectomy or beta blockade. The long QT syndrome is said to be associated with a preponderance of sympathetic innervation from the left stellate ganglion, and a deficit on the right, accounting for a reduced tachycardia of exercise in patients, since the normal sinoatrial node is primarily innervated from the right side. The ventricular fibres deprived of their (right) sympathetic innervation, would adapt by having very long action potential durations (hence the long QT). During exercise or emotion the myocardial regions supplied by the left stellate would receive excessive sympathetic drive, since they would have to compensate for the failure of the non-innervated areas to increase their activity. The myocardium would thus be subjected to two highly arrhythmogenic influences, the juxtaposition of shortened action potential duration in the innervated fibres next to adapted and unresponding long action potential duration in the remainder, and the probability of the awakening of subsidiary pacemaking cells by the aggravated adrenergic stimulation. Abolition of the excessive sympathetic drive by

surgery or by adrenergic blockade would reduce the heterogeneity of action potential duration and though peak performance might be diminished this would be a reasonable price to pay for a lessened risk of sudden death.

In hypertrophic cardiomyopathy there is also evidence of augmented adrenergic innervation, and it is of interest that amiodarone has recently been reported to be of benefit in arrhythmias occurring in hypertrophic cardiomyopathy.[14] It would be rational, therefore, to investigate whether amiodarone could reduce the incidence of arrhythmias in the long QT syndrome.

In spite of the above evidence, it is still unproven that a prolongation of action potential duration, uniform and homogeneous though it may be, can truly be regarded as responsible for an antiarrhythmic effect. Amiodarone has an acute antisympathetic action, of a non-competitive type,[15] and it restricts transmitter release[16]; both these properties could exert an acute (class 2) antiarrhythmic effect. Similarly, the protection afforded by prolonged beta blockade against reinfarction and sudden death could be attributed to an oxygen sparing effect or even to an increased myocardial capillarity,[17] rather than to a class 3 antiarrhythmic action. The drug sotalol could provide a useful tool for testing whether prolongation of action potential duration does contribute some antiarrhythmic efficacy, because it not only prolongs action potential duration at clinical concentrations, but is devoid of class 1 direct membrane action, which might otherwise be a complicating factor. Two papers in the current issue of this journal suggest that sotalol has a more potent antiarrhythmic action than could be attributed to beta blockade alone. Another compound recently shown to prolong action potential duration in cardiac muscle is melperone,[18] already in use as a tranquilliser.

Amiodarone has no direct negative inotropic action and, provided that it is given orally to reduce the hypotension which can occur on acute administration intravenously, there seems to be no reason why it should not be tested in combination with beta blockers for the treatment of life threatening arrhythmias occurring in hypertrophic obstructive cardiomyopathy, long QT syndrome, or pre-excitation syndromes. With several drugs now available which prolong action potential duration in atrial and ventricular muscle in a reasonably homogeneous manner, class 3 antiarrhythmic action may, perhaps, progress from unproven theory to practical reality.

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