Dispersion of repolarization. A basic electrophysiological mechanism behind malignant arrhythmias

See page 1329 for the article to which this Editorial refers

To understand the present paper, some knowledge of basic electrophysiology is necessary.

Monophasic action potentials were recorded for this study. The shape and the duration of monophasic action potentials correlate with those of neighboring action potentials of heart muscle cells. Human ventricular cardiac cells have long action potentials and thus long refractory periods, which can be considered as a safety mechanism protecting the heart against excessively high rates. It has been known for a long time that the refractory period is not constant, but is dependent on the heart rate and also adapts gradually to an increase in heart rate. Han and Moe showed that differences in refractory periods in adjacent areas could be responsible for the occurrence of arrhythmias especially fibrillation. Spatial inhomogeneity of the repolarization phase of action potentials (dispersion of repolarization) can be caused by different durations of the action potentials and also by some action potentials appearing late due to slow conduction. Therefore, dispersion of refactoriness may be due to the presence of non-homogeneous refractoriness, non-homogeneous conduction or both. Dispersion of refactoriness may be classified as 'maximal', which is the difference between the earliest and the latest repolarization recorded. Local or adjacent dispersion is observed between two sites with a certain distance apart in the myocardium. Adjacent dispersion was measured in the present study. The normal beating heart has a certain dispersion of refractoriness. Action potentials in the endocardium last longer than in the epicardium. This can be observed in the normal ECG as concordant QRS and T deflections (similar QRS and T wave axes). Gradients of long to short repolarization durations from the apex to the base have also been demonstrated.

The development of ventricular fibrillation seems to be dependent on several electrophysiological mechanisms, for instance the timing and the starting point of an extrasystole. When the distance to the preceding action potential is short, a marked shortening of the following action potential is observed. This phenomenon is observed as the proximity effect and has been described in man. There is reason to believe that an early extrasystole induces ventricular fibrillation, when it starts in an area with short action potentials and moves to an area with long action potentials, or moves from an area with normal conduction to an area with delayed conduction. Animal experiments show that an extrasystole in an area with short action potentials often creates ventricular fibrillation, while an extrasystole in an area with long action potentials does not induce fibrillation when conduction is normal. The dispersion of premature monophasic action potential durations is determined by the factors which regulate the duration of premature action potentials, namely the cycle length, the duration of the preceding action potential and the proximity to the repolarization of the preceding action potential. In the normal dog or human heart, aggressive electrical stimulation can induce ventricular fibrillation but not monomorphic sustained ventricular tachycardia. This indicates that a prerequisite for ventricular tachycardia is structural heart disease.

The present paper proposes that dispersion of monophasic action potentials should be given a specific sign, and when this is combined with the dispersion of activation the relative contribution of differences in activation and the difference in action potential duration to the inducibility of ventricular arrhythmias becomes more evident.

The limitations of this study are many and are stated in the paper. One obvious one is that malignant arrhythmias commonly start in the left ventricle while monophasic action potentials are obtained in the right ventricle. Increase in local dispersion in the right ventricle was recorded in patients with monomorphic ventricular tachycardia, but to an even greater extent in patients with ventricular fibrillation. As discussed previously, dispersion of refactoriness increases both by differences in monophasic action potential duration and activation time differences. In these patients, where structural heart disease was common, the local dispersion in the right ventricle was
increased mainly due to activation time differences. This was evident both during ventricular pacing and when premature extrastimuli were given. When two action potentials are associated with slow conduction, the dispersion will be largely dependent on the distance between the recording sites because the difference in action potential duration is often a relatively small contributing factor to the dispersion.

In patients with induced ventricular tachycardia, monophasic action potential duration differences did not contribute to the local dispersion of repolarization. This is in agreement with the common theories that non-homogeneous conduction is the most important factor for induction of ventricular tachycardia. In patients with polymorphic ventricular tachycardia or ventricular fibrillation induced during the electrophysiological study, the monophasic action potential duration differences contributed to the increase in dispersion of refractoriness. This study therefore points to the possibility that differences in action potential duration may play a more important role in patients with ventricular fibrillation than in those with monomorphic ventricular tachycardia. In the long QT time syndromes where large differences in action potential duration have been found, the clinical arrhythmias are commonly polymorphic ventricular tachycardia and ventricular fibrillation.

What causes differences in action potential duration in ventricles? The lack of knowledge is large. Neural influences on ventricular repolarization are, however, definite and significant. This was demonstrated in animal models more than 20 years ago and refractoriness may change locally, by at least 25 ms, by neural stimulation. Studies in man produce similar results. From a theoretical point of view beta-blockade should be beneficial and some of the effect on mortality seen in patients with coronary heart disease may be due to a decrease in dispersion of refractoriness. In patients with long QT time syndromes where the monophasic action potential dispersion is large, beta-blockade reduces malignant ventricular arrhythmias markedly, as well as sudden cardiac death.

Ischaemia and myocardial infarction increase the local dispersion mainly by a decrease in conduction velocity but also by action potential differences, as shown by Janse and co-workers. In agreement with this, it has recently been shown that ischaemia increases QT dispersion. From a theoretical point of view, antiischaemic therapy should be important in patients with coronary artery disease to avoid malignant arrhythmias. This is also indicated by the reduction in mortality in patients after surgical revascularization. From a practical point of view, patients who have survived an episode of ventricular fibrillation should preferably have a coronary angiogram. Little is known about antiarrhythmic drugs, but some of them seem to increase dispersion of refractoriness and thus increase the risk of ventricular fibrillation.

While an electrophysiological test is a reliable test in patients with monomorphic ventricular tachycardia it is less so in predicting ventricular fibrillation. The reason for that may be that dispersion of action potentials plays a larger role in the development of ventricular fibrillation, while dispersion caused by differences in activation times is most important in patients with ventricular tachycardia, as indicated by the present study. However, more studies both in experimental animals and man, are needed.

At present, automatic defibrillation seems to be the only reliable therapy for patients who have survived ventricular fibrillation with coronary artery disease where ischaemia is not an obvious cause and in patients with cardiomyopathy. At present we have no drugs, except for possibly beta-blockers that may decrease dispersion of refractoriness. DL-sotalol, with both beta-blocking and action potential prolonging effects, reduces the number of spontaneous ventricular tachycardias after appropriate testing, but even after treatment with that drug, defibrillators are more effective in reducing mortality and probably ventricular fibrillation. D-sotalol, besides its antiarrhythmic effects, has obvious arrhythmogenic effects. The effect of prolongation of action potentials on dispersion of refractoriness in an animal model has been described earlier. However, more research on ventricular dispersion will have to be done in patients with non-sustained ventricular tachycardia, because some of them need a defibrillator. An electrophysiological test seems at present the most promising test for the decision to implant a defibrillator.

J. P. AMLIE
Rikshospitalet,
Oslo, Norway

References
More on intravenous Mg\textsuperscript{2+} and the unstable coronary artery

See page 1269 for the article to which this Editorial refers

Randomized trials of new treatments for unstable angina must surmount several practical difficulties. The clinical syndrome is variable in its evolution; case definition can be a problem at the time of presentation; and there is an ethical requirement to offer all usual treatment — typically including intravenous heparin, nitrate, aspirin, a beta-blocker and often a calcium antagonist. Against this complex pharmacological background it is a challenge to demonstrate incremental benefit from the treatment under test. In this issue, Redwood et al.\textsuperscript{1} describe a double-blind trial of a 24 h infusion of magnesium sulphate in patients with a diagnosis of unstable angina at admission. They report a significant reduction in ischaemic ECG changes and in creatine kinase-MB release in Mg\textsuperscript{2+}-treated patients compared to the placebo group. Unsurprisingly in this small study, clinical outcome was similar in the two groups at one month, by which time half the patients had undergone a revascularization procedure.

It is necessary to look to laboratory models to gain insight into how Mg\textsuperscript{2+} might act on the pathophysiology of acute coronary syndromes. Valuable new work has emerged following the controversy surrounding the efficacy of Mg\textsuperscript{2+} salts in acute myocardial infarction. Three components must be considered: coronary spasm, the behaviour of platelets on disrupted atheromatous plaques, and the effect of intermittent ischaemia on myocardial viability. For each, the possible time-dependence and concentration dependence of any Mg\textsuperscript{2+} effect must be considered.

Mg\textsuperscript{2+} is a potent relaxant of human coronary arteries in vivo and in vitro. However, it is unclear whether any additional coronary vasodilatation would occur at the concentrations achieved in the trial in the presence of a nitrate. In man, vasodilatation by Mg\textsuperscript{2+} is typically a transient response to a rapid increase in plasma Mg\textsuperscript{2+}. Of potentially greater importance is the recent evidence that elevation of plasma Mg\textsuperscript{2+} profoundly inhibits platelet thrombus formation (and distal embolization) at a site of arterial endothelial disruption\textsuperscript{3}. A qualitative description of the same phenomenon was published by Adams and Mitchell nearly 20 years ago. This effect of Mg\textsuperscript{2+} elevation is limited to a narrow time-window, being attenuated if delayed until thrombus formation had become established\textsuperscript{2}. The same group has demonstrated in vitro that Mg\textsuperscript{2+} acts synergistically with aspirin to inhibit the platelet aggregation response to collagen\textsuperscript{12}. A highly significant enhancement of the platelet inhibition by aspirin was observed at 2 mM Mg\textsuperscript{2+}.

A number of experimental studies have demonstrated a protective effect of infused Mg\textsuperscript{2+} on myocardial ischaemia–reperfusion injury. The importance of the timing of Mg\textsuperscript{2+} administration has been shown in two recent studies which sought to replicate the conditions of coronary occlusion and reperfusion in vivo. In a dog model, Mg\textsuperscript{2+} was started at 15 or 45 min of coronary occlusion or after 15 min of reperfusion. Infarct size in relation to area at risk was significantly reduced by more than 60% in the two groups in which Mg\textsuperscript{2+} was started during coronary occlusion but not in the group starting Mg\textsuperscript{2+} after 15 min of reperfusion\textsuperscript{41}. A similar time window of myocardial protection in relation to reperfusion has also been reported in a swine coronary occlusion model\textsuperscript{42}.

Downloaded from https://academic.oup.com/eurheartj/article-abstract/18/8/1200/437037 by guest on 16 December 2018