The Significance and Management of Ventricular Arrhythmias

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The medical literature of twenty years ago shows a remarkable dearth of papers about the ventricular arrhythmias. There were a few reports on their clinical and electrocardiographic aspects, but scarcely anything about their natural history, diagnosis or therapy. Presumably because of this lack of interest, instrument manufacturers and drug companies were developing little new in this field.

In 1959 a development took place which triggered an intense and widespread interest in ventricular arrhythmias and it has persisted ever since. In that year, closed chest cardiopulmonary resuscitation became a reality[1]. Because of the importance of ventricular fibrillation as a cause of death in myocardial infarction, it became apparent that the potential of this technique was considerable. However, the fact that ventricular fibrillation complicating ischaemic heart disease is mainly an out-of-hospital phenomenon has continued to challenge those undertaking research in this field. Stimulated both by the successes and by the failures of clinicians, cardiac electrophysiologists and biochemists have made important advances in our understanding of the mechanisms of the ventricular arrhythmias in different contexts. New techniques of clinical study, including continuous electrocardiographic monitoring and programmed intracardiac stimulation, have been developed and pharmacologists and drug companies have introduced a large number of new anti-arrhythmic agents with different modes of action.

It is now clear that the ventricular arrhythmias, and particularly ventricular fibrillation, are common causes of disability and the commonest immediate cause of death. On the other hand, studies in apparently normal individuals have demonstrated that ventricular arrhythmias which, in other circumstances, might be considered of ill omen are in fact benign and of no prognostic consequence. This has brought to the fore a point of the greatest importance, namely that the significance, and therefore the management, of a ventricular arrhythmia depends upon its context.

Aetiological Varieties of Ventricular Arrhythmias

Numerous disease processes may be responsible for ventricular arrhythmias. They may occur in the otherwise normal person or they may complicate both electrical and mechanical disorders of the heart.

Normal Individuals

It is important to recognise that ventricular ectopic beats and, indeed, ventricular tachycardia may occur in individuals whose hearts in every other respect are normal. Ambulatory monitoring has demonstrated the frequency of ventricular arrhythmias in the normal population, particularly those in middle age[2], and there is ample evidence that, in the absence of any other signs of heart disease, these are benign. Nevertheless, the finding of a ventricular arrhythmia poses the physician with a difficult problem. Although, statistically, the individual whose first cardiac abnormality is a ventricular arrhythmia is unlikely to succumb because of it, such arrhythmias are sometimes the first manifestation of ischaemic heart disease or cardiomyopathy. Therefore, when frequent ventricular ectopic beats and, more particularly, when complex forms of arrhythmia such as multiform beats or the R-on-T phenomenon are seen in the apparently normal individual, further investigations are called for. These should include exercise testing and echocardiography and may require, if the patient's occupation depends on the demonstration of freedom from significant coronary disease, coronary arteriography.

Even though benign, ventricular arrhythmias in the normal individual may produce symptoms and therefore may suggest the need for drug treatment. This should be avoided if possible, but if not it may be wiser to try a sedative rather than an anti-arrhythmic agent. If an anti-arrhythmic agent is to be used, a beta-adrenergic blocking drug should probably be tried first.

Primary Rhythm and Conduction Disorders

Ventricular arrhythmias not uncommonly complicate other disorders of electrophysiological function.

Ventricular fibrillation is a rare but important complication of aberrant conduction. It is most likely to develop when a very rapid sequence of impulses reaches the ventricles via the aberrant pathway in the presence of atrial fibrillation. This is particularly apt to occur if

digitalis is used, and can best be prevented by the use of amiodarone[3], although other drugs such as quinidine, procainamide and disopyramide have been found useful in individual cases. Occasionally, surgical division of the accessory pathway may be necessary[4].

A group of disorders of particular interest are those associated with a prolonged QT. A feature of prolonged QT syndromes, irrespective of their genesis, is a liability to ventricular tachycardia of the torsade de pointes type[5]. The second feature is that there may well be an association with sympathetic imbalance with relative overactivity of the left stellate ganglion. It has been clearly shown that left stellate ganglionectomy may restore the QT to normal and prevent the recurrence of ventricular arrhythmia[5].

In the Jervell and Lange-Nielsen syndrome, QT prolongation is associated with congenital deafness, syncopal attacks and sudden death; it is frequently heritable. A similar syndrome, the Romano-Ward syndrome, in which deafness is not a feature, is inherited as an autosomal dominant. It is probable that both syndromes are more common than is recognised. The attacks of syncope may be provoked by exercise or anxiety, but may occur with no warning. A number of cases appear to have been successfully treated by beta-adrenergic blockade, but other therapy has included diphenylhydantoin, mexiletine and tegretol. Increasing experiences suggest that left stellate ganglionectomy may have an important role in the management of these cases.

Prolonged QT with the induction of arrhythmias is a feature of a number of anti-arrhythmic drugs, notably quinidine and disopyramide, but also the anti-anginal drug prenylamine, and tricyclic antidepressants. The interesting drug amiodarone, which differs from most other drugs in causing homogeneous QT prolongation in the different cardiac tissues, is usually effective in the suppression of ventricular arrhythmias, although in rare cases it may provoke them. Electrolyte disturbances, such as hypokalaemia, hypocalcaemia and hypomagnesaemia, may also cause ventricular arrhythmias and correction of the underlying disorder is curative. A prolonged QT may also be encountered in association with hypothermia, cerebrovascular disease, neck surgery and ischaemic heart disease. Although beta-blocking drugs have been used particularly in association with the prolonged QT syndrome, Krikler[6] reported the beneficial effects of small doses of isoprenaline, although others have found this to be arrhythmogenic.

It is important to recognise that QT prolongation may not be present at rest, but may occur on exercise and that ventricular tachycardia may occur only in response to this[6]. Although formerly thought to be rare, exercise-induced ventricular arrhythmias are by no means uncommon. They are sometimes responsible for angina pectoris or syncope on exertion. A particularly fascinating form has been described in detail by Coumel[7]. In this variety, exercise or the infusion of catecholamines results in a sinus tachycardia, which merges into a supraventricular tachycardia and then into ventricular tachycardia, and terminates in ventricular fibrillation. The patient then becomes unconscious and the sequence of arrhythmias goes into reverse. The condition is commonest in children and few, if any, patients have survived beyond the age of twenty years. Diagnosis can be established by exercise ECG or by catecholamine infusion. The most effective treatment appears to be amiodarone combined with a beta-adrenergic blocking drug.

Ventricular arrhythmias are a feature of many cases with atrioventricular block and of some cases with sinus bradycardia and the sick sinus syndrome. It has been recognised for a long time that the Adams-Stokes attack in patients with atrioventricular block may be due not to ventricular asystole, as one would presume, but to the occurrence of ventricular tachycardia or fibrillation. This is particularly likely to be provoked by the use of drugs such as quinidine. Such attacks can usually be completely suppressed by pacemaking.

Ventricular Arrhythmias Secondary to Disorders of Myocardial Structure and Function

Ventricular arrhythmias are particularly associated with ischaemic heart disease. In most other disorders of the heart, ventricular arrhythmias tend to be correlated with the severity of the ventricular damage. Thus, in valvular heart disease, ventricular arrhythmias become increasingly common as myocardial failure develops. Usually, in rheumatic mitral valve disease, they do not have a serious prognosis unless induced by digitalis and associated with potassium depletion. On the other hand, in both aortic regurgitation and stenosis, ventricular arrhythmias are common, may be responsible for palpitation, angina and syncope, and are probably responsible for many sudden deaths. While valvular surgery in such cases may limit the adverse effects of the ventricular arrhythmias, these arrhythmias often continue subsequently and require anti-arrhythmic treatment with such drugs as mexiletine and disopyramide.

Non-rheumatic mitral valve disease may also be associated with ventricular arrhythmias, particularly mitral valve prolapse[8]. Although the majority of ventricular arrhythmias encountered in this condition are benign, severe arrhythmias can occur with repetitive ventricular fibrillation and the risk of sudden death. Treatment with any of the oral anti-arrhythmic drugs such as quinidine, procainamide, mexiletine and disopyramide may be effective, but in some cases it has proved necessary to carry out mitral valve replacement[6].

Ventricular tachycardia may complicate myocarditis rarely, and cardiomyopathies more commonly. We have encountered a case in association with varicella[9] and occasional cases have been reported in association with the other common infections. Ventricular arrhythmias also complicate the terminal stages of cardiomyopathy, but can be an early feature, particularly in the hypertrophic obstructive type. In the latter condition, they may be exceedingly difficult to control and do not seem to respond to beta-adrenergic blocking agents or to surgery. An interesting form of arrhythmia is that which complicates coronary arterial spasm. It is now well recognised

that in Prinzmetal variant angina, ST segment elevation (with or without chest pain) may immediately precede episodes of ventricular tachycardia or ventricular fibrillation, which can be responsible for syncope and even death. It is important to appreciate that beta-adrenergic blocking drugs can aggravate spasm[10], whereas nitrates, and the calcium blocking drugs verapamil and nifedipine can prevent both the spasm and the arrhythmia.

Ventricular Arrhythmias in Ischaemic Heart Disease

It is in ischaemic heart disease that ventricular arrhythmias are responsible for the greatest problems and have excited the most interest.

It has long been suspected that ventricular fibrillation is the major cause of sudden death in the hospital and in the pre-hospital phase, and experience in the coronary care unit and from mobile coronary care units has substantiated this. Observations in the animal laboratory and clinical findings suggest that this single arrhythmia has many different mechanisms. Thus, animal experiments have suggested that ventricular fibrillation occurring soon after the onset of infarction is due to re-entry within the myocardium. When this arrhythmia occurs at a later phase, it is probably related to increased automaticity in ischaemic but not necrotic Purkinje fibres. Finally, when the acute event has subsided, ventricular arrhythmias may be due to re-entry around the border zone of a ventricular aneurysm or ischaemic segment. It is not yet clear what parallels exist between these animal models and the arrhythmia in humans. However, it is apparent that we should regard ventricular fibrillation occurring in different clinical contexts as having different aetiologies, different managements and different prognoses.

Thus, it has been shown, particularly by the fire squads in Seattle and Miami[11], that ventricular fibrillation occurring outside hospital is usually unassociated with acute myocardial infarction but occurs in individuals with advanced coronary artery disease and varying degrees of left ventricular dysfunction. Although, in most cases, victims of this type of ventricular fibrillation respond well to defibrillation, they are liable to recurrence of ventricular fibrillation in the succeeding weeks or months, as a consequence of which their long-term prognosis is not good; it is not clear whether the use of anti-arrhythmic drugs or coronary artery surgery in these patients prolongs their survival.

When ventricular fibrillation supervenes within the first few hours of myocardial infarction it frequently develops in those who otherwise seem to be doing well. It often occurs in the absence of cardiac failure or shock, and because of this has been labelled 'primary'. It was cases of this kind that acted as the greatest stimulus to the developing of coronary care units because it was apparent that patients with 'hearts too good to die' were succumbing in general wards. Based on observations in the early 1960s, Lown, in 1967[12], proposed the concept of 'warning arrhythmias', suggesting that certain forms of arrhythmia, particularly ventricular beats that were frequent, multi-focal or very early, were predictors of ventricular fibrillation. He considered that if these arrhythmias could be identified and lignocaine therapy given, ventricular fibrillation should not occur. Subsequently, many physicians found that, in spite of applying these principles, ventricular fibrillation continued to be seen. One possible explanation of this was inadequate monitoring and, indeed, as has been shown by comparing computerised monitoring with nurse monitoring, many of the 'warning arrhythmias' are missed by nurses in a conventional coronary care unit[13]. However, it has also been suggested that 'warning' arrhythmias are, in fact, as common in those patients who do not proceed to primary ventricular fibrillation as they are in those who do[14, 15]. Scrutiny of these studies suggests, however, that they do not satisfactorily disprove the hypothesis. For one thing, the patients who developed ventricular fibrillation were observed for only one or two hours whereas those who failed to develop this arrhythmia were monitored for 48 hours. Secondly, in at least one of the studies, anti-arrhythmic therapy was given to patients with ventricular arrhythmia, thus distorting the natural history. Thirdly, they did not consider the importance of changes in frequency or severity.

We felt that the subject required a complete re-evaluation because conventional coronary care, as widely practised, demands immense human resources or expensive computer apparatus. Our studies are not yet complete, but it has become apparent that there is no relationship between such ventricular arrhythmias as ventricular tachycardia, frequent ventricular ectopic beats and pairs of ventricular ectopic beats and subsequent primary ventricular fibrillation[16]. Indeed, these forms of ventricular arrhythmia become increasingly common over the first 12 hours but are not particularly found in the initial one or two hours when ventricular fibrillation is most prone to occur. By contrast, the R-on-T phenomenon, i.e. the early ectopic beat, is a characteristic feature of this period and in our experience is related to ventricular fibrillation in some 25 per cent of cases. Although this is a finding of interest in terms of the genesis of ventricular fibrillation, it is of little practical importance, as the detection of R-on-T ectopic beats by nurses or even by computer is difficult and, furthermore, only a minority of cases of ventricular fibrillation are preceded by such beats. Thus, from the point of view of prophylaxis of primary ventricular fibrillation, conventional electrocardiographic monitoring is of little value, and only two forms of approach seem reasonable. One of these is to monitor the patient for ventricular fibrillation only and institute resuscitatory measures immediately this occurs. Certain centres have reported satisfactory results from this policy, and we have also had this experience. On the other hand, others have argued that it is undesirable to allow ventricular fibrillation to occur and prophylactic therapy with a drug such as lignocaine is preferable. Although there is evidence to suggest that this form of therapy is effective[17], the risks of toxicity are not negligible if it is given in an adequate dose and the regimes recommended

are difficult to implement outside an intensive care unit. There is certainly a need to develop new methods for the prevention of ventricular fibrillation that can be applied in an intensive care unit and also in a general ward or outside hospital. So far, no form of prophylactic therapy has been proved to be effective in these environments.

While we no longer believe in the importance of identifying and treating the 'warning' arrhythmias it is necessary, of course, to correct haemodynamically serious episodes of ventricular tachycardia. These usually respond to lignocaine; if they do not, synchronised DC shock should be administered. Recurrences can be prevented by intravenous lignocaine, or by oral mexiletine, disopyramide or procainamide. Occasionally, overdrive pacing is necessary.

Ventricular fibrillation is a frequent terminal event in those with severe cardiac failure and shock, 'secondary ventricular fibrillation'. In most of these cases, death is likely to ensue whether or not the patient develops the arrhythmia. However, there is a 25 per cent immediate resuscitation rate in such cases, although the long-term prognosis is poor. It is still not clear whether certain forms of ventricular arrhythmia are predictive of ventricular fibrillation in these patients. It may well be that the use of prophylactic anti-arrhythmic therapy would be of value in these patients but this has not been established.

Ventricular fibrillation is also prone to occur during the convalescent phase of myocardial infarction, a week or more after the onset of the acute event ('late ventricular fibrillation'). In many cases, the patient, after an initial stormy passage, makes a good recovery only to die suddenly in the general ward or shortly after he has gone home. Deaths in these circumstances are particularly tragic because if such patients are kept under close supervision, the chances of resuscitation and the long-term prognosis are both reasonably good[18]. As it is now fashionable to discharge patients from hospital some seven days after their admission for acute myocardial infarction, it is important that we should be able to identify those patients at greatest risk of developing 'late ventricular fibrillation' so that these may be retained in hospital. Several reports have detailed the features that may be predictive of this phenomenon[18]. These include acute pulmonary oedema during the early phase, the presence of other signs of cardiac failure such as a third heart sound and cardiomegaly, as well as the relatively prolonged persistence of ST segment elevation, of tachycardia and of conduction defects such as left and right bundle branch block. We believe that it is appropriate to keep patients with these forms of abnormality in hospital for two to three weeks and, if necessary, to employ telemetric monitoring. As yet, there have been no studies to show that anti-arrhythmic therapy for such patients is beneficial.

It has been known for many years that the risk of sudden death after myocardial infarction diminishes progressively over the first six months following the acute attack, and then remains at a relatively low level. Many studies have been concerned with the prognostic significance of ventricular arrhythmias after infarction, and several reports have shown a relationship between arrhythmias, whether demonstrated on the routine ECG, on exercise ECG or on tape monitoring, and subsequent sudden death[19-22]. There is little doubt about the association between left ventricular dysfunction and death[22]. It may well be that ventricular arrhythmias have little direct connection with terminal ventricular fibrillation but are an index of severe left ventricular damage. In other words, the ventricular arrhythmias have relatively little significance in the absence of left ventricular dysfunction, but probably add a small risk in those whose left ventricular performance is poor. Attempts so far to use anti-arrhythmic drugs to prevent death in patients following myocardial infarction seem to have been relatively ineffective. Quinidine, procainamide, diphenylhydantoin, aprindine and mexiletine have all been tried in this context and, although the incidence of ventricular arrhythmias is clearly diminished, no statistically significant effect upon mortality has been demonstrated. This may partly be due to the fact that all the trials have been on a rather small scale but may also suggest that high risk patients will die of left ventricular dysfunction by some other mechanism if ventricular fibrillation is prevented. Alternative approaches include the use of beta-adrenergic blocking drugs and platelet active agents. The well-known studies with alprenolol[23] and practolol[24] have suggested that beta-blockade is a valuable prophylactic measure following myocardial infarction. However, there are some reservations about their design, and a recent study with propranolol has failed to show a beneficial effect of this drug[25]. This may have been due to an inadequate dose or the lack of an action such as intrinsic sympathomimetic activity which might contribute to its prophylactic effect.

Encouraging studies with aspirin[26] and sulphinpyrazone[27] suggest the use of platelet active agents may be helpful but, again, design problems leave a question mark about their value.

Finally, there is a troublesome sub-group of ischaemic heart disease patients who have repetitive ventricular tachycardia, often associated with a ventricular aneurysm. Anti-arrhythmic drugs such as procainamide, mexiletine and disopyramide, are frequently ineffective. In some cases aneurysmectomy and other surgical procedures may be of value[28].

Summary

Ventricular arrhythmias are the result of a variety of mechanisms that can occur in many different contexts. Although it would be, in principle, desirable to identify and treat the mechanism, therapy at present is best chosen for the particular context in which the rhythm disturbance develops. It seems probable that no one drug will ever be 'the best' and that the physician must be prepared to be familiar with many different drugs and be aware of the potential benefits of electrical therapy and surgery.

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