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Pathophysiological mechanisms of ventricular tachyarrhythmias

G. BREITHARDT, M. BORGGREFE, A. MARTINEZ-RUBIO AND T. BUDDE

Medical Hospital of the Westfälische Wilhelms-University of Münster, Department of Cardiology and Angiology, Münster, Federal Republic of Germany

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The pathophysiological background for ventricular tachyarrhythmias based on experimental and clinical evidence is presented. Sudden cardiac death may occur as the first manifestation of coronary artery disease without antecedent complaints or it may occur in patients with a previous myocardial infarction. In the latter situation, a circumscribed area of cardiac tissue may be responsible for the genesis and maintenance of a ventricular tachyarrhythmia which may be called the 'arrhythmogenic substrate'. This zone of electrically abnormal ventricular myocardium is usually located at the border of a previous myocardial infarction, and is characterized by islands of relatively viable muscle alternating with areas of necrosis and, later, fibrosis. The consequent fragmentation of the propagating electromotive forces leads to the development of high-frequency components that can be recorded directly or non-invasively using signal-averaging techniques. These signals have been called ventricular late potentials. The 'arrhythmogenic substrate' may be present permanently or may rise acutely and be present only transiently in the case of extensive ischaemia or acute myocardial infarction. In the setting of a chronic 'arrhythmogenic substrate', this electrically abnormal tissue may be triggered by spontaneously occurring ventricular ectopic beats or salvoes or by programmed ventricular stimulation, as well as by transient episodes of ischaemic causing spontaneous arrhythmias. These trigger factors modify the 'arrhythmogenic substrate' in such a way that ventricular tachyarrhythmias are sustained.

It is apparent that sudden cardiac death is due to a wide spectrum of pathophysiological mechanisms which may be interrelated. There is obviously no single parameter that helps the clinician to predict the propensity for sudden cardiac death in the individual patient.

Introduction

The purpose of this paper is to present the view of the clinician on the pathophysiological background for ventricular tachyarrhythmias based on experimental and clinical evidence. It will not be possible to cover the vast amount of recent data from experimental and clinical studies. Instead, an attempt will be made to discuss those factors and mechanisms that may be considered important from the clinical point of view and that may have an impact on clinical decision-making.

Observations in patients during long-term ECG recording at the time of out-of-hospital sudden cardiac death have shown that the great majority of these events is due to some type of ventricular tachyarrhythmia, mostly monomorphic ventricular tachycardia degenerating into ventricular fibrillation (Fig. 1)[1,2]. In a survey of the literature, Bayes de Luna *et al.* reported 61 patients who died from ventricular fibrillation during ambulatory long-term ECG recording[1]. In 28% of cases, ventricular fibrillation was the initial rhythm, whereas in 69%, ventricular fibrillation had been initiated by monomorphic ventricular tachycardia. In the remaining 3%, ventricular flutter degenerated into ventricular fibrillation[1]. These initiating ventricular tachycardias frequently had a rate below 300 beats min^{-1}[2]. The mechanisms leading to ventricular tachyarrhythmias have been studied in animal models and in man[3]. These studies identify a multitude of possible mechanisms that may underlie the occurrence of ventricular tachyarrhythmias and thus sudden cardiac death (Table 1). The most important factors

Address for correspondence: Prof Dr med. Günter Breithardt, Medizinische Klinik und Poliklinik, Innere Medizin C (Kardiologie, Angiologie), Westfälische Wilhelms-Universität, Albert-Schweitzer-Strasse 33, D-4400 Münster, Germany (F.R.)

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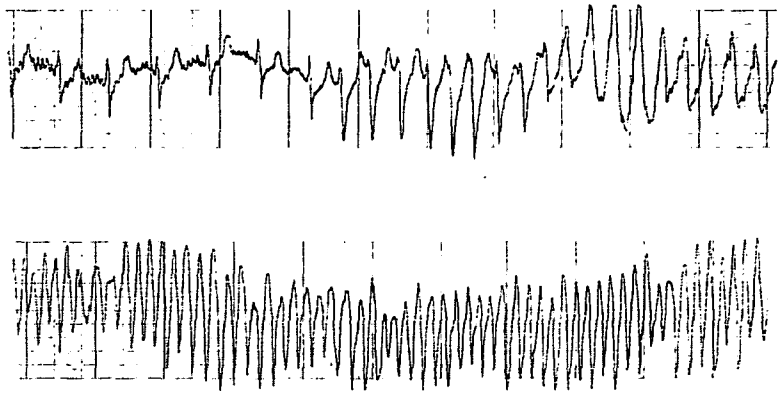

Figure 1 Occurrence of sudden cardiac death outside hospital in a patient with known coronary artery disease who was on 24 h long-term ECG recording for evaluation of ventricular ectopic beats at the time of death.

Table 1 Pathophysiological mechanisms of sudden cardiac death

*chronic electrophysiological abnormalities
*transient ischaemia
— acute coronary occlusion without/with a preceding myocardial infarction
— coronary spasm
— unstable coronary artery plaques leading to embolization into the peripheral coronary system
— exercise-induced ischaemia
*emotional responses

that govern prognosis after myocardial infarction are the frequency and type of spontaneous ventricular arrhythmias, the degree of left ventricular dysfunction, the occurrence of ischaemia, and the influence of the central nervous system.

Sudden cardiac death may occur as the first manifestation of coronary artery disease without antecedent complaints. In other instances, a patient may die suddenly after a previous myocardial infarction which has left some regional abnormalities of the electrophysiological properties of the heart constituting the basis for the occurrence of ventricular tachyarrhythmias. It is obvious that any diagnostic or preventive measure can only be instituted early enough in patients with a previous manifestation of cardiac disease. Therefore, this differentiation is of major importance for planning strategies to prevent sudden cardiac death.

The arrhythmogenic substrate

In many manifestations of clinically important ventricular tachycardias, a circumscribed area of cardiac tissue may be responsible for the genesis and maintenance of the tachyarrhythmia. In the context of this review, this area will be called the 'arrhythmogenic substrate' (Fig. 2). Though this term is not well defined, its use has some conceptual advantages as it emphasizes the regional character of both the morphological and the electrophysiological aspects.

Experimental and clinical studies have provided evidence that myocardial infarction may leave such an 'arrhythmogenic substrate', a zone of electrically abnormal ventricular myocardium that may have a propensity to ventricular tachycardia (Fig. 2). This tissue is usually located at the border zone of a previous myocardial infarction, and is characterized by islands of relatively viable muscle alternating with areas of necrosis and, later, fibrosis. Such tissue may result in fragmentation of the propagating electromotive forces with the consequent development of high-frequency components that can be recorded directly from these areas[4–8] and non invasively using signal-averaging techniques[9–20]. These signals have been called ventricular late potentials[16] (Figs 3, 4). The individual components of fragmented electrograms most probably

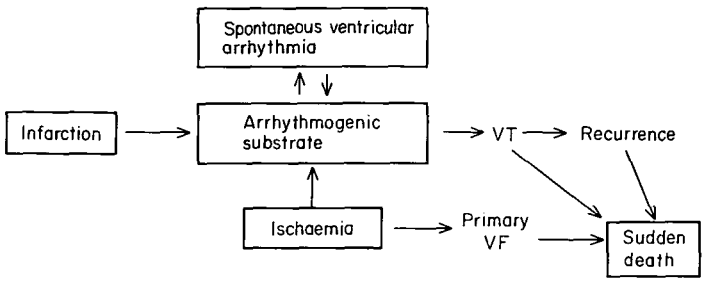

Figure 2 Interaction between various factors leading to sustained ventricular tachycardia and sudden death after a previous myocardial infarction that may have left behind an arrhythmogenic substrate.

represent asynchronous electrical activity in each of the separate bundles of surviving muscle under the electrode. The intrinsic asymmetry of cardiac activation due to fibre orientation (anisotropy) may be accentuated by infarction and may predispose to re-entry[5,6]. The slow activation might result from conduction over circuitous pathways, caused by the separation and distortion of the myocardial fibre bundles. The low amplitude of the electrograms from these regions probably results from the paucity of surviving muscle fibres under the electrode due to the large amount of connective tissue, and not from depression of the action potentials. Therefore, the anatomic substrate for re-entry seems to be present in regions where fragmented electrograms can be recorded which, thus, indicate slow inhomogenous conduction.

The recent study by Pagé *et al.*[21] in a canine model of myocardial infarction has raised discussion about the relationship between regional late activation detected by direct recordings or by recording on the body surface and the occurrence of sustained ventricular tachycardia. One conflicting finding in this paper[21] was that late potentials were not observed in most unipolar recordings made from the same sites at which biopolar recordings revealed fractionated potentials. Bipolar electrograms appeared to be less specific than unipolar electrograms in detecting the myocardium critical for the maintenance of ventricular tachycardia. In an accompanying editorial, Ideker *et al.*[22] highlighted the importance of their findings for the discussion on the mechanisms leading to ventricular late potentials on the body surface. Based on previous studies that have shown that late fractionated potentials recorded directly from the myocardium are not specific in identifying the site of origin of the arrhythmia[23], Ideker *et al.*[22] presented three still hypothetical explanations for the lack of specificity of late fractionated potentials. The first explanation was that late fractionated potentials are present both in the region of myocardium from which ventricular tachycardia originates as well as in other peri-infarction regions, and that late fractionated cardiac potentials in both regions give rise to late high-frequency potentials on the body surface. This would put late potentials into the position of a non-specific phenomenon not always directly related to the presence of an 'arrhythmogenic substrate'. Thus, body surface late potentials and ventricular tachycardia are separate effects, the common cause being a large myocardial infarction. The second explanation is that late fractionated potentials recorded from the myocardium may give rise to the late high-frequency potentials recorded from the body surface, but that the tissue exhibiting the late fractionated potentials does not give rise to the arrhythmia. The third explanation is that the arrhythmogenic region gives rise to late high-frequency signals from the body surface, but does not usually give rise to late fractionated potentials in direct cardiac recordings.

Electrical recordings from areas of previous myocardial infarction have demonstrated that, if present, the fractionated low-amplitude activity may extend beyond normal ventricular activation into the ST-segment of the surface ECG. With conventional methods of ECG recording, these signals cannot normally be registered on the body surface. Berbari *et al.*[9] in the experimental animal and Fontaine *et al.*[16] in man were the first to report that late potentials (Figs 3, 4) could be recorded from the body surface by the use of high-gain amplification, appropriate filtering, and computer-averaging techniques[11].

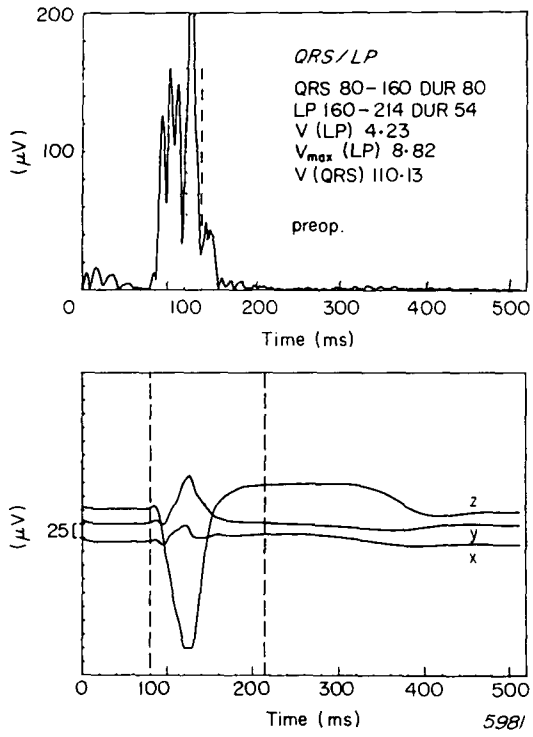

Figure 3 Signal-averaged and filtered recording of leads x, y, z, (vector magnitude) in a patient with ventricular tachycardia. QRS-duration in the highly amplified recording was 134 ms preoperatively. The programme automatically identified the end of the total QRS-complex at 214 ms on the x-axis. The amplitude in the terminal 40 ms was low (V(40) = 3·57 μV which was automatically measured by the programme. Additionally, the onset of low-amplitude activity was automatically identified at 160 ms on the horizontal axis. The programme also measured the mean voltage of the late potential (V(LP) = 4·23 μV), the maximal voltage of the late potential (V_{max}(LP) = 8·82 μV), and the mean voltage of the true QRS-complex (V(QRS) = 110·13 μV).

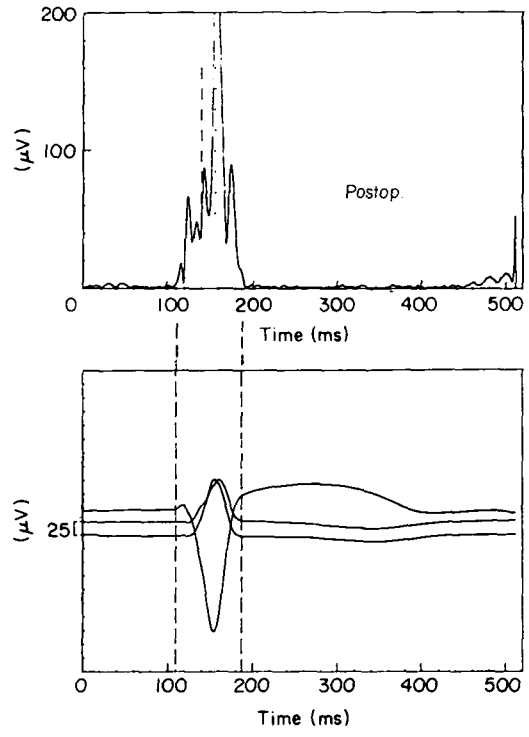

Figure 4 The same patient as in Fig. 3 studied after map-guided antitachycardia surgery. There was no longer a low-amplitude tail at the end of the QRS-complex; ventricular tachycardia was no longer inducible. This indicates the close association between late potentials and the propensity to ventricular tachycardia.

Acute vs chronic arrhythmogenic tissue

In chronic postmyocardial infarction, the 'arrhythmogenic substrate' is usually considered to be permanently present in the form of myocardium infiltrated by fibrosis after a previous myocardial infarction (as described above). However, a zone with arrhythmogenic properties may also rise acutely and be present only transiently. The classical example of an acutely developing arrhythmogenic tissue is acute myocardial infarction; a condition frequently accompanied by ventricular fibrillation. The changes that occur in this situation are often transient in nature and may subside as soon as the tissue is completely necrotic.

Ischaemia may also occur in the presence of a chronic 'arrhythmogenic substrate'. The importance of this combination is suggested by the high incidence of recurrent ventricular fibrillation and sudden cardiac death in survivors of out-of-hospital cardiac arrest, where ischaemic events in the presence of pre-existing healed myocardial infarction obviously enhance the risk for the occurrence of fatal arrhythmias. This is analogous to experimental studies that have shown that the incidence of spontaneous ventricular tachycardia and fibrillation is higher when acute ischaemia is superimposed on previous myocardial infarction than with acute ischaemia alone[24,25]. Patterson and co-workers[24] elegantly showed that ventricular fibrillation could result from ischaemia at a site remote from previous myocardial infarction. Induction of stenosis of the left anterior descending coronary artery caused ventricular fibrillation in 29 of 40 dogs if there was a previous myocardial infarction in an area distant from that stenosed coronary artery, but only in 2 o

10 dogs with a similar stenosis but without a previous infarct ($P < 0.004$). The authors hypothesized that a critical mass of myocardial infarction is required for initiation and maintenance of ventricular tachycardia. Other studies have shown that cat hearts with acute infarction superimposed on healed myocardial infarction have a greater incidence of spontaneous and induced ventricular arrhythmias than do hearts with acute infarction alone[26]. The cellular electrophysiologic changes that occur during transient acute ischaemia superimposed on a healed myocardial infarction were studied in isolated coronary-perfused cat left ventricles 2–4 months after ligation of multiple distal branches of the left anterior descending and circumflex coronary arteries[27]. Transmembrane action potentials were recorded from the endocardial cells in normal and in infarcted zones. There were no significant differences in measured action potential variables and refractory periods between cells in the normal and infarcted zones before acute ischaemia. However, when global ischaemia was induced by discontinuation of coronary perfusion, resting potential, action potential amplitude and action potential duration were reduced, and the refractory period was shortened progressively in cells of the normal zone. In cells in the infarcted zone, however, the action potential changes were less prominent, and the refractory period was unchanged. These changes resulted in significant differences in resting membrane potential, action potential amplitude, action potential duration, and refractory period between cells in the normal and infarcted zones at 10 min of ischaemia. Spontaneous rapid ventricular activity was observed during the last 20–30 min of ischaemia in four of eight preparations with healed myocardial infarction, whereas no spontaneous rapid ventricular activity was recorded in any of six normal heart preparations. These data of Kimura *et al.*[27] suggest that superimposition of acute ischaemia on healed myocardial infarction produces electrophysiologic inhomogeneities that may enhance arrhythmogenesis. It remains unclear from this study why ischaemia-induced electrophysiologic changes were less remarkable in cells of the infarcted zone.

Besides more extended ischaemia or acute myocardial infarction, ischaemia may be confined to a small area of the myocardium that may be too small to sustain a re-entrant tachycardia. However, it may be the site of origin for some type of abnormal automaticity that could act as a trigger factor modifying a chronic arrhythmogenic tissue after a previous myocardial infarction in such a way that it becomes able to sustain a tachyarrhythmia (Fig. 2). The potential role of this mechanism will be discussed below.

Role of the size of myocardial infarction

It has been well established that cardiac mortality is largely determined by the size of a previous myocardial infarction[28–30]. One might expect that any impairment in left ventricular contraction (i.e. a reduction in left ventricular ejection fraction) should lead to the development of heart failure, and, thus, should be the factor that determines prognosis. However, there is sufficient evidence that left ventricular dysfunction is more strictly correlated with the occurrence of sudden and, thus, possibly arrhythmic death. This suggests that the greater the impairment of left ventricular function, the greater the chance for arrhythmias to occur. The greater chance of arrhythmias with larger infarcts is probably due to the increased chance for an 'arrhythmogenic substrate' to be created. This is supported by several studies that have shown that ventricular late potentials (considered in this context as an indicator of an 'arrhythmogenic substrate') are more frequent in patients with extensive left ventricular dysfunction[13], and that fragmented electrograms are recorded more frequently in the circumference of the border zone of an aneurysm in patients with ventricular tachycardia than in patients without[31]. In addition, ventricular tachycardia can be induced more frequently in patients with more extensive left ventricular dysfunction[12,14,32,33]. Long-term follow-up of patients with left ventricular aneurysms have shown their mode of death to be more from arrhythmic causes than from heart failure[29,34].

Factors modifying the arrhythmogenic substrate

Without any further modifying factors (triggers), an 'arrhythmogenic substrate' may lead to ventricular tachycardia only if conduction delay is sufficiently long to extend beyond the end of the refractory period of the encompassing normal tissue. Such might cause a permanent propensity to ventricular tachycardia. Normally, regional slow conduction is not sufficient to develop ventricular tachycardia. Instead, some additional factor is usually necessary to initiate a re-entrant type of ventricular tachycardia by triggering the arrhythmogenic substrate. Once initiated, re-entrant tachycardia may perpetuate within the re-entrant circuit

if the conditions remain appropriate. Initiation of ventricular tachycardia, however, can be achieved only if the prerequisites for the occurrence of re-entry (unidirectional block, regional slow activation, re-excitation of the previously blocked tissue) exist within the arrhythmogenic substrate. Factors that interact with the arrhythmogenic substrate include spontaneous ventricular arrhythmias and regional or more extended ischaemia.

The most commonly held view is that single premature ventricular beats, ventricular couplets or short runs of ventricular tachycardia (salvoes) may act as initiating factors causing re-entry (thus acting as a trigger). These arrhythmias may originate from outside the region of subsequent re-entry. Above all, frequent and repetitive ventricular arrhythmias are indicators of the risk of subsequently developing ventricular tachyarrhythmias after myocardial infarction[30]. In addition, artificially induced premature beats using programmed stimulation[3,12,14,33,35–37] or changes in the activation properties within the potential re-entrant circuit due to changes in basic heart rate[8,24] may cause re-entrant excitation. All these events may obviously be modulated by changes in autonomic nervous innervation[38,39]. Conversely, if an 'arrhythmogenic substrate' is not present, the same spontaneous ventricular arrhythmias are not able to initiate re-entry. This explains why these ventricular arrhythmias are benign in otherwise healthy hearts[40].

Despite the obvious association between spontaneous ventricular arrhythmias and the occurrence of ventricular tachyarrhythmias and sudden cardiac death, data from prospective studies in patients after myocardial infarction have also shown the limited value of these findings during long-term ECG recording for predicting prognosis[41,42]. Depending on the criteria used to define an abnormal finding, sensitivity, specificity and the predictive value of these arrhythmias for sudden death (<1 h) vary[42]. In the Beta-blocker Heart Attack Trial (BHAT)[42], 1640 patients were included in the placebo group giving the possibility of analysing their natural history. When an abnormal finding during long-term ECG recordings was defined as ≥ 10 ventricular extrasystoles h^{-1}, or ventricular pairs or runs (≥ 3 consecutive beats), 418 patients would have fallen into the category of 'abnormality'. 33 of these 418 patients died suddenly (predictive value 8%). However, another 43 patients also died suddenly though they had a 'normal' long-term ECG recording. Thus, 43 of 76 patients (57%) dying suddenly had a low grade of ventricular arrhythmias. In this setting, the chance of dying suddenly was markedly less (43 of 1222 patients, 3·5% vs 8% in those with an 'abnormal' finding). An increased frequency of spontaneous ventricular arrhythmias, therefore, heralds an increased propensity to sustained ventricular tachyarrhythmias which, according to the pathophysiological concepts presented above, act as the trigger factor for any arrhythmogenic substrate which may be present. Nevertheless, even in the absence of frequent ventricular extrasystoles, tachycardias may occur if only a single episode of a critical sequence of ventricular ectopic beats supervenes. A typical situation is seen in patients with a history of sustained ventricular tachycardia or aborted sudden death; $>50\%$ have only rare spontaneous ectopic beats during their attacks despite a persistent propensity to tachycardias.

Ischaemia may cause acute (transient) changes in the electrophysiological properties of the arrhythmogenic substrate, either affecting it directly (thereby slowing conduction velocity and modifying refractory period) or indirectly via ischaemia-induced spontaneous repetitive ventricular activity acting as a trigger factor. The potential role of the latter mechanism for the occurrence of sudden cardiac death might be suggested by some recent pathological studies[43,44]. Davies *et al.*[43] were able to show that in patients who died suddenly within 6 h of the onset of symptoms, 50% had either isolated multifocal microscopic necrosis or regional coagulative necrosis. This was frequently caused by unstable plaques in the proximal coronary arteries due to rupture with or without thrombus deposition. Part of this thrombotic material might have been washed downwards into the coronary system.

Similar conclusions might be derived from a study by Falk[44] who reported the significance of platelet microemboli in sudden cardiac death occurring within 24 h. Further support for the role of intramyocardial platelet aggregates in survivors of cardiac arrest was recently presented by Lo *et al.*[45] Ruptured atherosclerotic plaques manifested angiographically, were more prevalent in patients without inducible monomorphic ventricular tachycardia (11 of 22, or 50%) than in those with it (5 of 27, or 19%; $P<0{\cdot}05$). A similar higher incidence of ruptured plaques was found in patients without akinetic or dyskinetic segments (8 of 14, or 57%) than in those with them (8 of 34, or 24%; $P<0{\cdot}06$). Thus, ruptured plaques were more prevalent in patients without a demonstrable anatomic and/

or electrophysiologic substrate for re-entrant ventricular tachycardia.

Another factor that may cause transient episodes of regional ischaemia and serve as a trigger factor, may be the occurrence of coronary arterial spasm. Bertrand *et al.*[46] reported that in 20% of patients with recent transmural myocardial infarction coronary spasm could be provided after intravenous injection of 0·4 mg methergine compared with only 6·2% in patients studied later after myocardial infarction.

The relatively small areas of necrosis as found in the studies by Davies[43] and Falk[44] are themselves not sufficient to cause ventricular fibrillation. However, by acting as a trigger factor to locally induce spontaneous ventricular activity, they might provoke ventricular tachyarrhythmias at sites distant from the ischaemia. This latter mechanism, though still hypothetical, would explain why these patients died suddenly showing only small areas of necrosis and without evidence of extended myocardial infarction. This may be the link between anatomic and physiologic disturbances in sudden cardiac death[47]. Another apparent difference between the patient with the chronic electrophysiologic substrate and the one with an acute ischaemic syndrome due to a ruptured plaque is the difference in time between onset of symptoms and death. In the latter situation, it is conceivable that focal necrosis needs some time to develop and expand during which the necessary conditions for triggering a ventricular tachyarrhythmia are met.

Thus, on the basis of the data presented above, one might speculate that a previous myocardial infarction provides the 'arrhythmogenic substrate' which is then triggered by ischaemia-induced ventricular arrhythmias occurring at a site distant from this infarction. This would be another explanation for the observation by Patterson *et al.*[24] that transient ischaemia caused ventricular fibrillation only if there was a previous myocardial infarction. Though these hypothetical links between disturbances in coronary circulation due to regional occlusions and sudden death are attractive, they are not as yet corroborated by data from clinical intervention studies.

In the recent preliminary report from the aspirin component of the ongoing Physicians Health Study[49] there was no significant difference in the prevalence of sudden cardiac death (JCD code 798) in those on placebo compared with aspirin. In contrast, data from the registry of the Coronary Artery Surgery Study (CASS)[48] suggest that recurrent ischaemia may play a role in sudden cardiac death. Freedom from sudden death (< 1 h) in high-risk patients (i.e. with three-vessel disease and left ventricular dysfunction) was observed in 69% of medically treated patients, but in 91% of surgically treated patients ($P < 0{\cdot}0001$). This may imply that prevention of recurrent ischaemia by adequate revascularization may be the underlying mechanism responsible for the greater protection from sudden death in these patients. With regard to the contradictory findings of these studies, more information is needed before a definite role for ischaemia in the mechanisms of sudden death can be established.

If the area of ischaemic myocardium is sufficiently large, ventricular fibrillation in the absence of previous myocardial infarction may occur and cause sudden cardiac death. The true incidence of this mechanism is unknown. This mechanism would apply to persons who die suddenly without an antecedent myocardial infarction ('primary' sudden death). Long-term ECG recording is rarely performed, if at all, in these asymptomatic patients. Therefore, no information from patients studied out-of-hospital is available. However, as this situation resembles the very early stage of acute myocardial infarction, it can be assumed that in most of these cases, sudden cardiac death is initiated by ventricular fibrillation. This is obviously in contrast to the mechanism of sudden cardiac death in patients with previous myocardial infarction in whom the initiating event is usually a sustained monomorphic ventricular tachycardia[1,2].

Clinical course

If the first episode of sustained ventricular tachycardia is very fast and leads to severe haemodynamic compromise, it may degenerate into ventricular fibrillation causing sudden cardiac death (Fig. 2). This course of events is suggested by a retrospective analysis of long-term ECG tapes that were taken at the time of sudden cardiac death in out-of-hospital patients (Fig. 1). It was rare to have immediate ventricular fibrillation as the initial tachyarrhythmia. Instead, most patients who died from ventricular tachyarrhythmias, initially exhibited sustained monomorphic ventricular tachycardia, usually at a rate below 270 to 300 beats min^{-1}[1,2].

The degeneration of sustained monomorphic ventricular tachycardia into ventricular fibrillation may be due to tachycardia-induced ischaemia. This

may be aggravated by tachycardia-induced hypotension, and by changes in reflex-induced innervation of the myocardium. Another possibility might be that the myocardium is from the onset more susceptible to degeneration into ventricular fibrillation due to a more extensive and diffuse scarring. Data from Stevenson *et al.*[50] have shown differences in the clinical characteristics of patients with previous ventricular fibrillation ('aborted' sudden death) vs patients with episodes of sustained ventricular tachycardia. 36% of patients with sudden death but no patient with ventricular tachycardia had two separate areas of infarction ($P<0{\cdot}05$). Patients with previously documented sustained ventricular tachycardia had a longer cycle length of induced tachycardia (319 ± 69 ms) than did patients with aborted sudden death (248 ± 31 ms) ($P<0{\cdot}05$). The induced arrhythmia caused syncope during the electrophysiological study in one of 19 patients with documented sustained ventricular tachycardia compared with 6 of 15 patients with aborted sudden death ($P<0{\cdot}01$). In contrast, there were no differences with regard to age, the time interval from myocardial infarction to ventricular tachycardia or sudden death, ejection fraction (0·31% vs 0·29%), and the number of patients with a major area of contracting myocardium supplied by an artery with a $\geqslant 50\%$ or $\geqslant 70\%$ stenosis (84% vs 64% and 68% vs 41%).

If the patient survives the first episode of ventricular tachycardia (occurring outside the acute phase of myocardial infarction), there is a long-term risk of recurrence in a high percentage of cases[51]. Patients who have survived a great number of episodes of ventricular tachycardia obviously are self-selected survivors but they nevertheless are at risk of developing late ventricular fibrillation.

Patients who present with syncope occurring for the first time after a myocardial infarction represent a specific subset who are at an increased risk of sudden death[52,53]. In this situation, the underlying mechanism of syncope and of sudden death seems to be a ventricular tachyarrhythmia which differs, however, with regard to the duration of the attack. The majority of these patients have an arrhythmogenic substrate for the occurrence of ventricular tachyarrhythmias as is apparent from the high prevalence of ventricular late potentials[53].

Conclusions

It is apparent that sudden cardiac death represents a great spectrum of pathophysiological mechanisms which may be interrelated. No single investigative method will be sufficient to elucidate this complex background of mechanisms. This may explain that there is no single parameter that helps the clinician to predict the propensity to sudden cardiac death in the individual patient.

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References

[1] Bayes de Luna A, Torner P, Guindo J, Soler M, Oca F. Holter ECG study of ambulatory sudden death, review of 158 published cases. New Trends Arrhythm 1985; I: 293–7.

[2] Olshausen K, Pop T, Treese N, Meyer J. Sudden death during Holter monitoring. Eur Heart J 1985; 6: (abstr suppl 1): 45.

[3] Breithardt G, Seipel L, Loogen F. Der akute Herztod. Bedeutung elektrophysiologischer Stimulationsverfahren. Verh Dtsch Ges Hertz- Kreislafforschg 1980; 46: 38–64.

[4] Flowers NC, Horan LG, Thomas JR, Tolleson WJ. The anatomic basis for high frequency components in the electrocardiogram. Circulation 1969; 39: 531–9.

[5] Gardner PI, Ursell PC, Fenoglio JJ, Wit AL. Electrophysiologic and anatomic basis for fractionated electrograms recorded from healed myocardial infarcts. Circulation 1985; 72: 596–611.

[6] Richards DA, Blake GJ, Spear JF, Moore EN. Electrophysiologic substrate for ventricular tachycardia: correlation of properties in vivo and in vitro. Circulation 1984; 69: 369–81.

[7] Daniel T, Boineau J, Sabiston D. Comparison of human ventricular activation with canine model in chronic myocardial infarction. Circulation 1971; 44: 74–89.

[8] El-Sherif N, Scherlag BJ, Lazzara R, Hope RR. Reentrant ventricular arrhythmias in the later myocardial infarction period. I. Conduction characteristics in the infarction zone. Circulation 1977; 55: 686–702.

[9] Berbari EJ, Scherlag BJ, Hope RR, Lazzara R. Recording from the body surface of arrhythmogenic ventricular activity during the ST segment. Am J Cardiol 1978; 41: 697.

[10] Breithardt G, Becker R, Seipel L, Abendroth RR, Ostermeyer J. Non-invasive detection of late potentials in man: a new marker for ventricular tachycardia. Eur Heart J 1981; 2: 1–11.

[11] Breithardt G, Borggefe M. Pathophysiological mechanisms and clinical significance of ventricular late potentials. Eur Heart J 1986; 7: 364–85.

[12] Breithardt G, Borggrefe M, Haerten K. Role of programmed ventricular stimulation and noninvasive recording of ventricular late potential for the identification of patients at risk of ventricular tachyarrhythmias after acute myocardial infarction. In: Zipes DP, Jalife J,

Eds. Cardiac electrophysiology and arrhythmias. Grune and Stratton, 1985; 553–61.

[13] Breithardt G, Borggrefe M, Karbenn U, Abendroth RR, Yeh HL, Seipel L. Prevalence of late potentials in patients with and without ventricular tachycardia: correlation to angiographic findings. Am J Cardiol 1982; 49: 1932–7.

[14] Breithardt G, Borggrefe M, Quantius B, Karbenn U, Seipel L. Ventricular vulnerability assessed by programmed ventricular stimulation in patients with and without late potentials. Circulation 1983; 68: 275–81.

[15] Denniss AR, Cody DV, Fenton SM *et al.* Significance of delayed activation potentials in survivors of myocardial infarction. J Am Coll Cardiol 1983; 1: 582 (Abstr).

[16] Fontaine G, Frank R, Gallais-Hamonno F, Allali I, Phan-Thuc H, Grosgogeat Y. Electrocardiographie des potentials tardifs du syndrome de post-exitation. Arch Mal Coeur 1978; 71: 854.

[17] Kacet S, Libersa C, Caron J *et al.* The prognostic value of averaged late potentials in patients suffering from coronary artery disease. (Personal communication).

[18] Kanovsky MS, Simson MB, Falcone RA, Dresden C, Josephson ME. The late potential is an indepedent marker for ventricular tachycardia. J Am Coll Cardiol 1983; 1: 582.

[19] Kuchar D, Thorburn C, Sammel N. Natural history and clinical significance of late potentials after myocardial infarction. Circulation 1985; 72: III-477.

[20] Simson MB. Use of signals in the terminal QRS complex to identify patients with ventricular tachycardia after myocardial infarction. Circulation 1981; 64: 235–42.

[21] Pagé PL, Cardinal R, Savard P, Shenasa M. Sinus rhythm mapping in a canine model of ventricular tachycardia. Pace 1988; 11: 632–44.

[22] Ideker RE, Tang ASL, Daubest JP. On the trail of ventricular tachycardia or the adventure of the unspeckled bent. Pace 1988; 11: 650–5.

[23] Cassidy DM, Vassallo JA, Buxton AE, Doherty JU, Marchlinski FE, Josephson ME. The value of catheter mapping during sinus rhythm to localize site of origin of ventricular tachycardia. Circulation 1984; 69: 1103–10.

[24] Patterson E, Gibson JK, Lucchesi BR. Electrophysiologic actions of lidocaine in a canine model of chronic myocardial ischemic damage. Arrhythmogenic actions of lidocaine. J Cardiol Pharmacol 1982; 4: 925–34.

[25] Garan H, McComb JM, Ruskin JN. Spontaneous and electrically induced ventricular arrhythmias during acute ischemia superimposed on two-week-old canine myocardial infarction. J Am Coll Cardiol 1988; 11: 603–11.

[26] Myerburg RJ, Epstein K, Gaide MS *et al.* Electrophysiologic consequences of experimental acute ischemia superimposed on healed myocardial infarction in cats. Am J Cardiol 1982; 49: 323–30.

[27] Kimura S, Basset AL, Cameron JS, Huikuri H, Kozlovskis PL, Myerburg RJ. Cellular electrophysiological changes during ischemia in isolated, coronary-perfused cat ventricle with healed myocardial infarction. Circulation 1988; 78: 401–6.

[28] Grande P, Pedersen A. Myocardial infarct size: Correlation with cardiac arrhythmias and sudden death. Eur Heart J 1984; 5: 622.

[29] Jehle J, Heerdt M, Spiller P, Loogen F. Verlaufsbeobachtungen bei Patienten mit Aneurysma des linken Ventrikels nach konservativer und chirurgischer Therapie. Z Kardiol 1982; 71: 566.

[30] Moss AJ. Clinical significance of ventricular arrhythmias in patients with and without coronary artery disease. Progr Cardiovasc Dis 1980; 23: 33.

[31] Wiener I, Mindlich B, Pitchon R *et al.* Epicardial activation in patients with coronary artery disease: effects of regional contraction abnormalities. Circulation 1982; 65: 154–60.

[32] Hamer A, Vohra J, Hunt J, Sloman G. Prediction of sudden death by electrophysiologic studies in high risk patients surviving acute myocardial infarction. Am J Cardiol 1982; 50: 223–9.

[33] Richards DA, Cody DV, Denniss AR, Russell PA, Young AA, Uther JB. Ventricular electrical unstability: a predictor of death after myocardial infarction. Am J Cardiol 1983; 51: 75–80.

[34] Sager PT, Perlmutter RA, Rosenfeld LE, McPherson CA, Wackers FJT, Batsford WP. Electrophysiologic effects of thrombolytic therapy in patients with a transmural anterior myocardial infarction complicated by left ventricular aneurysm formation. J Am Coll Cardiol 1988; 12: 19–24.

[35] Breithardt G, Seipel L, Meyer T, Abendroth R. Prognostic significance of repetitive ventricular responses during programmed ventricular stimulation. Am J Cardiol 1982; 49: 693–8.

[36] Han J. Ventricular vulnerability during acute coronary occlusion. Am J Cardiol 1969; 24: 857.

[37] Wellens HJJ, Durrer DR, Lie KI. Observations on mechanisms of ventricular tachycardia in man. Circulation 1976; 54: 237–44.

[38] Lombardi F. Acute myocardial ischemia, neural reflexes and ventricular arrhythmias. Eur Heart J 1986; 7 (Suppl A): 91–7.

[39] Tavazzi L, Zotti AM, Rondanelli R. The role of psychologic stress in the genesis of lethal arrhythmias in patients with coronary artery disease. Eur Heart J 1986; 7(Suppl A): 99–106.

[40] Kennedy HL, Whitlock JA, Sprague MK, Kennedy LJ, Buckingham TA, Goldberg RJ. Long-term follow-up of asymptomatic healthy subjects with frequent and complex ventricular ectopy. N Engl J Med 1985; 312: 193–7.

[41] Cats VM, Lie KL, van Capelle FJL, Durrer D. Limitations of 24 hour ambulatory electrocardiographic recording in predicting coronary events after acute myocardial infarction. Am J Cardiol 1979; 44: 1257.

[42] Kostis JB, Byington R, Friedman LM, Goldstein S, Furberg C, for the BHAT Study Group. Prognostic significance of ventricular ectopic activity in survivors of acute myocardial infarction. J Am Coll Cardiol 1987; 10: 231–42.

[43] Davies, MJ, Thomas AC, Knapman PA, Hangartner JR. Intramyocardial platelet aggregation in patients with unstable angina pectoris suffering sudden ischemic cardiac death. Circulation 1986; 73: 418–27.

[44] Falk E. Unstable angina with fatal outcome: dynamic coronary thrombosis leading to infarction and/or sudden death. Autopsy evidence of recurrent mural thrombosis with peripheral embolization culminating in total vascular occlusion. Circulation 1985; 71: 699–708.

[45] Lo YS, Cutler JE, Blake K, Wright AM, Kron J, Swerdlow ChD. Angiographic coronary morphology in survivors of cardiac arrest. Am Heart J 1988; 115: 781–5.

[46] Bertrand ME, Lablanche JM, Tilmant PY *et al.* Frequency of provoked coronary arterial spasm in 1089 consecutive patients undergoing coronary arteriography. Circulation 1982; 65: 1299–306.

[47] Gorlin R, Fuster V, Ambrose JA. Anatomic-physiologic links between acute coronary syndromes. Circulation 1986; 74: 6–8.

[48] Holmes JDR, Davis KB, Mock MB *et al.* The effect of medical and surgical treatment on subsequent sudden cardiac death in patients with coronary artery disease: a report from the Coronary Artery Surgery Study. Circulation 1986; 73: 1254–63.

[49] Steering Committee of the Physicians Health Study Research Group. Preliminary report: Findings from the aspirin component of the ongoing Physicians' Health Study. N Engl J Med 1988; 318: 262–6.

[50] Stevenson WG, Brugada P, Waldecker B, Zehender M, Wellens HJJ. Clinical angiographic and electrophysiologic findings in patients with aborted sudden death as compared with patients with sustained ventricular tachycardia after myocardial infarction. Circulation 1985; 71: 1146–52.

[51] Breithardt G, Borggrefe M, Podczeck A. Has the clinical presentation of ventricular tachycardia changed? In: Non-pharmacological therapy of tachyarrhythmias. Breithardt G, Borggrefe M and Zipes DP, Eds. New York: Futura 1987: 51–64.

[52] Borggrefe M, Breithardt G, Seipel L. Syncope after myocardial infarction. Electrophysiologic findings. Circulation 1983; 68 (Suppl III): 55.

[53] Borggrefe, Breithardt G, Karbenn U. Clinical value of late potentials in patients with syncope of unknown origin. Eur Heart J 1985; 6 (Suppl 1): 18 (Abstr).