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ABSTRACT

Many patients who survive an acute myocardial infarction (AMI) remain at risk of sudden cardiac death despite optimal medical treatment. AMI survivors are currently risk assessed and selected for implantable cardioverter defibrillator (ICD) insertion mainly on the basis of their left ventricular ejection fraction. Several other cardiovascular tests are available that can detect the myocardial substrate abnormalities and help refine risk. These investigations include ECG-based tests (signal averaged ECG and T-wave alternans), Holter-based recordings (heart rate variability and heart rate turbulence) and imaging techniques (cardiac magnetic resonance). Recent evidence also points towards a potential role for other indices on the 12-lead ECG and genetic profiling in risk prediction. This study reviews the current evidence for the use of these tests in AMI survivors and addresses their pros and cons in guiding the selection of ICD recipients.

INTRODUCTION

A significant number of patients who survive an acute myocardial infarction (AMI) continue to die suddenly after hospital discharge, despite appropriate coronary revascularisation and optimal medical therapy.[1] Multiple clinical trials completed over the past decade have demonstrated the effectiveness of the implantable cardioverter defibrillator (ICD) in reducing overall mortality in patients at high risk for sudden death.[2–4] Patients enrolled in these studies were mainly chosen on the basis of reduced left ventricular ejection fraction (LVEF). As a consequence, current international guidelines for prophylactic ICD insertion are also predominantly based on LVEF. However, it is becoming increasingly apparent that additional variables other than reduced LVEF may influence the risk of sudden cardiac death and that LVEF alone is insufficient in determining which patients are most likely to benefit from prophylactic ICD insertion.[5] Indeed, the majority of sudden deaths occur in patients with LVEF >30%,[6] highlighting need for improved methods to risk stratify patients.

In order to predict which patients are most likely to die suddenly after an AMI, one first needs to understand the pathophysiological mechanisms that cause sudden cardiac death. Autopsy studies reveal that approximately two-thirds of sudden death victims have coronary atherosclerosis with a recent plaque rupture or erosion resulting in acute coronary thrombosis.[7] The remaining third often have evidence of prior myocardial infarction, but no acute coronary thrombosis. These patients are likely to have died from an acute arrhythmic event, most often ventricular tachycardia (VT) or ventricular fibrillation (VF). An important but largely unresolved question is what are the precipitating/predisposing factors that cause an AMI survivor, who may remain stable for months or even years following the initial ischaemic event, to become electrically unstable and develop malignant arrhythmias? Figure 1 shows some of the factors that may lead to electrical instability and sudden cardiac death in patients following an AMI. Although acute ischaemia may be the initiating trigger for VT or VF at any time in patients with coronary artery disease, a number of other mechanisms may also cause cardiac arrest. These include the generation of re-entrant circuits as a result of fibrosis on the border of an infarct zone, triggered activity in scar tissue, worsening heart failure and metabolic/electrolyte disturbances. In addition, certain genetic polymorphisms may predispose individuals to a greater chance of developing ventricular arrhythmias in the presence of an initiating insult.[7]

In principle, any test that can identify the substrate or predisposing factors responsible for sudden cardiac death in patients post AMI, and reliably distinguish those individuals who are likely to develop malignant arrhythmias from those who are less likely, will have a valuable role to play in guiding which patients should be offered a prophylactic ICD. Several invasive and non-invasive tests have been evaluated over the past few decades for this purpose. These tests, mainly based on traditional measurements, such as conventional electrocardiography (12-lead ECG and signal averaged ECG), Holter monitoring and programmed electrophysiological stimulation, have largely been limited by their low positive predictive values. Recent advances in Holter-based and ECG-based technology and myocardial imaging have allowed for the assessment of newer parameters with promising results. This study reviews the current evidence for the use of these tests and their pros and cons in predicting the risk of sudden arrhythmic death among AMI survivors.

THE 12-LEAD ECG

A number of parameters on the conventional 12-lead ECG have been demonstrated to give important prognostic information in patients following an AMI. These include the presence of bundle branch block, QRS duration, left ventricular hypertrophy and QT dispersion.[8 9] However, many of these parameters are likely to represent more advanced degrees of ventricular dysfunction following an AMI, which itself is a cause for

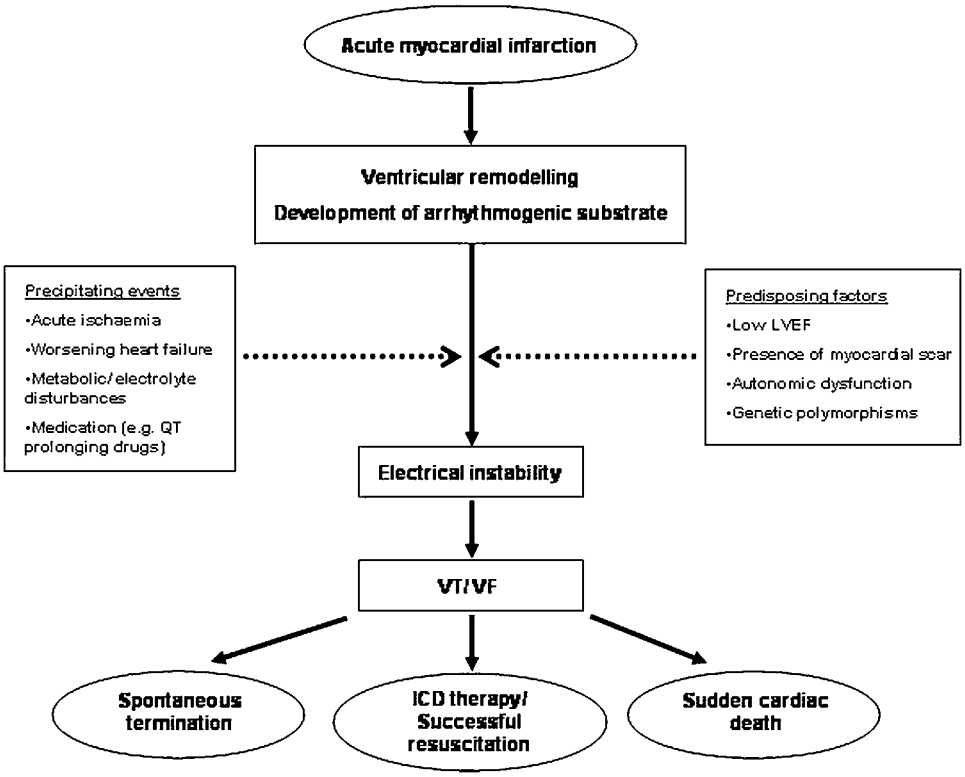

Figure 1 Events leading to sudden cardiac death in patients after an acute myocardial infarction. Adverse ventricular remodelling leads to the development of the arrhythmogenic substrate, usually in the form of myocardial scar. Patients may remain stable for months or even years after the initial event, before a precipitating event leads to electrical instability. The presence of certain predisposing factors may increase the likelihood of the precipitating event triggering ventricular tachycardia or ventricular fibrillation (VT/VF). If VT or VF occurs, three possible outcomes may result: spontaneous termination of the arrhythmia, implantable cardioverter defibrillator (ICD) therapy/successful resuscitation or sudden cardiac death. LVEF, left ventricular ejection fraction.

increased mortality, rather than a specific increase in risk for VT/VF. For example, the MUSTT (Multicentre UnSustained Tachycardia Trial) investigators found that left bundle branch block and non-specific intraventricular conduction delay (IVCD) were associated with increased total mortality risk, although there was no significant link between bundle branch block and inducible monomorphic VT.[10] In the PainFree RX II trial, QRS duration did not predict the delivery of appropriate therapies for VT/VF in 431 patients with coronary artery disease who received an ICD for either primary or secondary prevention.[11] In addition, parameters such as QT dispersion vary widely between individuals and there is considerable overlap in QT dispersion values between healthy subjects and cardiac patients, as well as between cardiac patients with and without ventricular arrhythmias. As such, the use of individual ECG parameters in deciding which patients post AMI should receive an ICD is limited.

The presence of a fragmented QRS complex (fQRS) on the routine 12-lead ECG has recently been described as a marker of abnormal ventricular depolarisation and demonstrated to be a predictor of mortality and sudden cardiac death.[12] Fragmented QRS complexes include various RSR′ patterns, with or without QRS duration <120 ms, and probably represent conduction delay caused by myocardial scar in patients with ischaemic heart disease. fQRS is a simple, inexpensive and easily accessible ECG sign that may be of value in determining the risk for sudden cardiac death and guiding prophylactic ICD insertion in AMI survivors. However, a greater understanding of the significance of this non-specific finding and future prospective, multicentre data is required before it can routinely be adopted into clinical practice.

The presence of early repolarisation of the QRS complex, previously regarded as a benign and a normal variant,[13] is now recognised to have prognostic significance in some individuals and may have a potential role to play in the risk prediction of ventricular arrhythmias. Early repolarisation, defined as elevation of the QRS-ST junction (J point) by 0.1 mV in at least two leads (other than V1 to V3), has been demonstrated to occur in patients with idiopathic VF.[14] Haissaguerre *et al* recently analysed the ECGs of 206 subjects from 22 centres that had been resuscitated after cardiac arrest due to idiopathic VF and found that the prevalence of early repolarisation was more frequent than in matched controls.[15] Furthermore, during a mean follow-up of 61±50 months, the incidence of recurrent VF (as recorded on defibrillator monitoring) was higher in subjects with repolarisation abnormalities than in those without. In another recent study, Tikkanen *et al* assessed the prevalence and prognostic significance of early repolarisation in 10 864 middle-aged subjects (age 44±8 years) and found that the presence of an early repolarisation pattern in the inferior leads was associated with an increased risk of death from cardiac causes during a mean follow-up of 30±11 years.[16] Whether early repolarisation is a useful ECG parameter to predict arrhythmic risk in AMI survivors remains to be determined, although its simplicity and ease of measurement make it an attractive parameter for further investigation.

SIGNAL-AVERAGED ELECTROCARDIOGRAPHY

The signal-averaged ECG (SAECG) compares and averages consecutive QRS complexes (usually around 300) to produce a filtered QRS complex that provides information on the presence of ventricular late potentials (VLPs). VLPs represent slowed conduction through a diseased myocardium, which may serve as a substrate for subsequent ventricular arrhythmias, and have been documented in 25–50% of patients soon after an AMI.[17] An example of a normal and abnormal SAECG, with cut-off values, is shown in figure 2. The prognostic value of SAECG in predicting mortality among AMI survivors has been examined in multiple studies over the past few decades.[17 18] The sensitivity of SAECG to predict arrhythmic events has been very variable from these studies, ranging from 15% to 75%, with follow-up of between 6 and 24 months. The main value of SAECG appears to

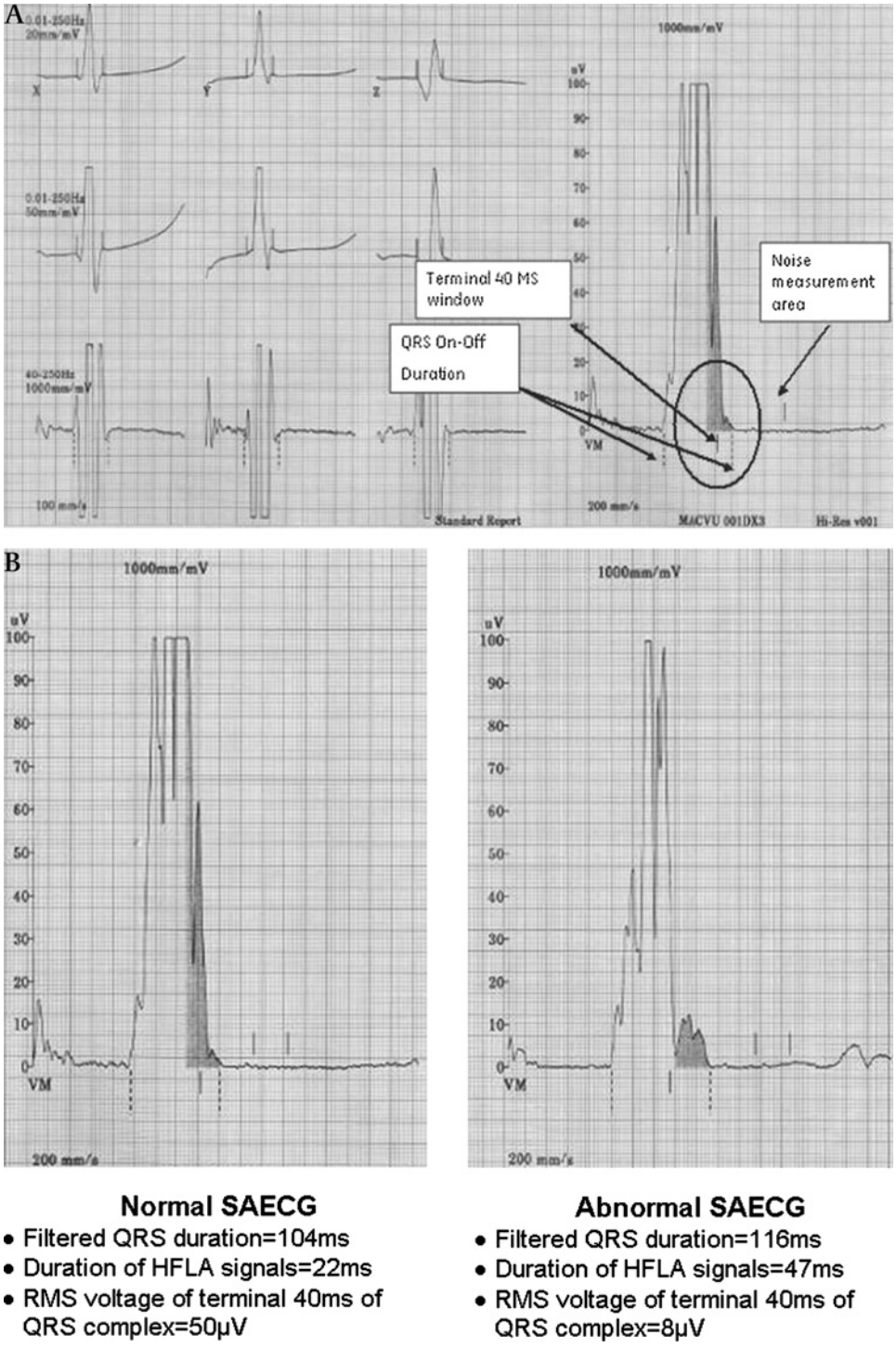

Figure 2 Sample signal averaged ECG (SAECG) traces. A. Measurements taken from SAECG obtained from averaging 253 beats. B. Examples of a normal and abnormal SAECG. A SAECG is considered to be abnormal when at least two of the following three parameters are present: duration of filtered QRS complex >114 ms, duration of high-frequency low-amplitude (HFLA) potentials of the terminal portion of the filtered QRS complex >38 ms and root mean square (RMS) of the terminal 40 ms of the filtered QRS complex <20 μV. Note the increased duration of the HFLA potentials and reduced RMS voltage of the terminal 40 ms of the QRS complex in the abnormal case.

be its use in identifying low-risk patients in view of its high negative predictive value (over 90%). However, its positive predictive accuracy is much lower, thus decreasing its usefulness as a single variable to identify high-risk patients.[17] Other limitations of SAECG are that it is better at predicting VT than VF and normal standards in the presence of bundle branch block or ventricular pacing have not been established. As a result, patients with conduction system abnormalities or paced-rhythms have been excluded from most major studies looking at SAECG.

The Coronary Artery Bypass Graft (CABG) Patch Trial was an important negative study in which SAECG appears to have been unhelpful in identifying a high-risk group of patients.[19] In this study, 900 patients with LVEF <36% and abnormalities on SAECG were randomly assigned to receive a prophylactic ICD at the time of coronary artery bypass surgery or to a control group. The investigators found no significant difference in survival between the two groups during an average follow-up of 32±16 months. One explanation for this negative finding is that patients recruited in this study (on the basis of LVEF and SAECG abnormalities) were at lower risk of ventricular arrhythmias compared with those recruited in earlier primary prevention studies, such as MADIT (Multicenter Automatic Defibrillator Implantation Trial),[2] in which subjects had similar degrees of LV

dysfunction (≤35%) and ventricular arrhythmias at electrophysiological testing or documented asymptomatic non-sustained VT.

With the increasing use of primary percutaneous coronary intervention (PCI) in the treatment of AMI, the prognostic value of the SAECG has become less clear. Bauer *et al*, performed SAECGs in 968 patients following AMI, 91% of whom underwent PCI, and found that the presence of VLPs was not significantly associated with cardiac death or a serious arrhythmic event during a median follow-up of 34 months.[20] Ikeda *et al* also found that VLPs had no significant prognostic role in predicting the primary outcome of death or resuscitated cardiac arrest when measured in 627 patients post AMI (82% underwent PCI), although the follow-up was short (3–6 months) in this study.[21]

The value of the SAECG in arrhythmic risk prediction among AMI survivors may be increased when it is used in combination with other tests to further refine risk in patients already deemed to be at higher risk, such as those with decreased LVEF. Gomes *et al* demonstrated that the combination of an abnormal SAECG and LVEF<30% in 1268 patients with coronary artery disease and non-sustained VT identified a particularly high-risk subset of patients, which represented 21% of the total population.[22] In this group, 36% and 44% succumbed to arrhythmic and cardiac death respectively.

HOLTER ANALYSIS

Detection of ventricular arrhythmias

Early studies on the use of ambulatory ECG-recordings (24-h Holter monitoring) in risk stratification of patients post AMI reported that the detection of ventricular arrhythmias, most often non-sustained VT or frequent premature ventricular complexes (PVCs), was predictive of serious arrhythmic events and death.[23 24] A more recent study conducted in the modern era of interventional cardiology demonstrated that non-sustained VT remained an independent predictor of sudden cardiac death in 2130 patients following AMI after adjustment for age, diabetes and LVEF, and was especially useful in patients with LVEF>35%.[25] In this study, 86% of patients presenting with ST-elevation AMI underwent primary angioplasty, whereas the remaining 14% were treated with thrombolysis. Unfortunately, the sole use of conventional 24-h Holter monitoring for the prediction of ventricular arrhythmias is significantly limited by its low sensitivity and specificity. Recent advances in Holter-based technology have made it possible for additional parameters to be obtained from ambulatory ECG-recordings, which appear to be useful in identifying the high-risk patient post AMI. These parameters, such as heart rate variability and heart rate turbulence, represent changes in cardiac autonomic tone that occur following AMI. There is strong evidence linking changes in the autonomic nervous system with sudden cardiac death – increased sympathetic activity favours the development of cardiac arrhythmias, whereas increased vagal tone appears to be protective.[26–30]

Heart rate variability

Heart rate variability (HRV) can be assessed by estimating the SD of all normal cardiac cycles (RR intervals) during Holter monitoring. HRV decreases early after AMI and begins to increase towards normal within 6–12 weeks.[29] Early reports suggested that decreased HRV is associated with increased ventricular arrhythmias and mortality.[28 30] In the Multicenter Postinfarction Study (MPS) involving 808 patients, a strong correlation was found between reduced HRV and total mortality following AMI.[27] However, HRV is also influenced by other variables such as age, gender and certain medication (eg, thrombolysis, antiarrhythmic drugs, β-blockers and ACE inhibitors).[8] In addition, many of the early studies on HRV changes post AMI were performed before the routine use of primary angioplasty, thereby casting doubt on the applicability of the results to modern-day practice. Increasing evidence suggests that HRV and autonomic cardiac function are better preserved in patients treated with primary angioplasty compared with thrombolysis or conservative management.[31 32] These considerations, and the fact that HRV cannot be evaluated in patients with atrial fibrillation or frequent arrhythmias, have limited its use as a sole determinant of increased risk in the post AMI patient.

HRV does not appear to fare as well as other makers of autonomic dysfunction when directly compared. In the Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) study, involving 1284 patients with a recent (<28 days) myocardial infarction, baroreceptor sensitivity (calculated from measuring the rate-pressure response to intravenous phenylephrine) was a better predictor of mortality, particularly in patients with LVEF<35%.[30] More recent studies using additional software have suggested that other markers of autonomic dysfunction, such as deceleration capacity, may be stronger predictors of mortality following AMI than HRV.[33]

Heart rate turbulence

Heart rate turbulence (HRT) is a recently described marker of baroreceptor sensitivity measured from Holter analysis that appears to have a useful role to play in risk prediction. It is a measure of fluctuations in sinus rhythm (SR) cycle length following a single PVC. In normal and low-risk patients, there is a characteristic acceleration followed by a subsequent deceleration in SR cycle length after a PVC; this pattern is not present in high-risk patients. Figure 3 shows a sample screenshot of HRT measurements. Several large-scale prospective studies performed in the modern era of interventional cardiology have provided strong evidence that HRT is a powerful independent predictor of risk following AMI.[25 34 35] The REFINE study (Noninvasive Risk Assessment Early After a Myocardial Infarction) investigators performed a number of autonomic function tests, including measurements of HRT, in 322 patients with LVEF <50% post AMI and demonstrated that these tests could reliably identify those at high risk of serious cardiac events.[34] Interestingly, they found that the time at which the tests were performed post AMI was important – performing the tests at 10–14 weeks, but not 2–4 weeks, post MI was predictive of mortality and sudden cardiac death. Another recent prospective study, the ISAR-Risk study (Improved Stratification of Autonomic Regulation for risk prediction in post-infarction patients with preserved left ventricular function), involving 2343 survivors of AMI found that the combination of HRT and deceleration capacity could be used together to identify a high-risk group equivalent in size and mortality to patients with LVEF<30%.[35] In these two studies, 81% and 92%, respectively, of patients underwent PCI (the number who received primary angioplasty was not reported). Therefore, the results of these studies are likely to be relevant to current practice. In contrast, in a retrospective analysis of 884 patients enrolled in the MADIT II study, HRT parameters were not found to be predictive of outcome, after adjustment for confounding covariates.[36] However, HRT parameters in this study were obtained from 10 min ECG recordings, which may have limited the ability to derive accurate HRT data. It should also be noted that the MADIT II patients comprise a different group of post-AMI patients (ie, prior AMI with impaired LVEF)

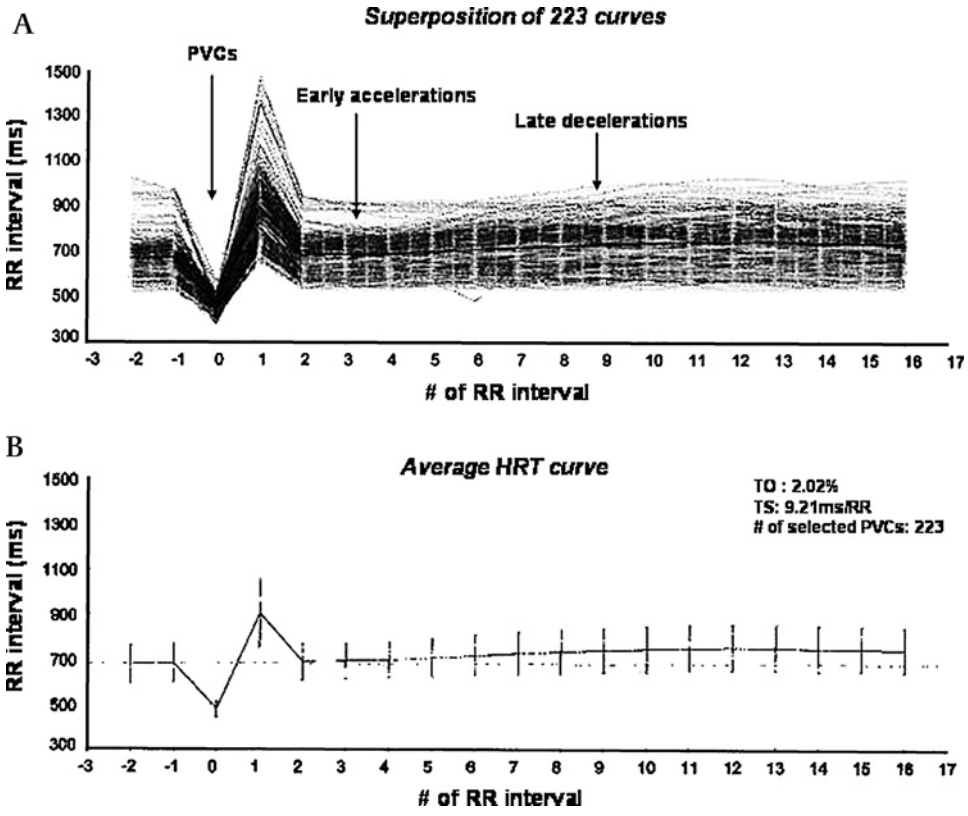

Figure 3 Screen shot of heart rate turbulence (HRT) measurements. A. HRT curves produced for each of the 223 premature ventricular complexes (PVCs) obtained from this 24-h Holter recording. The areas of early acceleration and late deceleration are annotated. B. Average HRT trace obtained from mean of all the individual HRT curves. HRT is quantified by two parameters: turbulence onset (TO) and turbulence slope (TS). TO (expressed as a percentage) is calculated as the difference between mean of the two sinus RR intervals immediately after and before the PVC divided by the mean of the two sinus RR intervals immediately before the PVC. TS is calculated as the maximum positive regression slope assessed over any five consecutive sinus RR intervals within the first 15 sinus rhythm RR intervals after the PVC (expressed in ms per RR interval).

compared with patients in the REFINE and ISAR-Risk studies, who were recruited shortly after their AMI.

T-WAVE ALTERNANS

Electrical alternans of the T-wave (ie, alternating amplitude from beat to beat) on the ECG is thought to be due to dispersion of repolarisation and has been demonstrated to be associated with life-threatening ventricular arrhythmias.[21 37 38] Recent advances in technology have allowed for the assessment of T-wave alternans during exercise (microvolt T-wave alternans, MTWA) using fast Fourier transform spectral analysis or during ambulatory Holter-based recordings (modified moving average analysis). Rosenbaum *et al* first showed that MTWA detected during atrial pacing (over a range 95–150 beats/min) was an independent predictor of inducible sustained VT.[39] Since then, MTWA has been demonstrated by other investigators to be a powerful predictor of life-threatening arrhythmias and sudden cardiac death in patients post AMI, both with and without depressed LV function.[21 37 38] MTWA appears to be a better risk predictor when compared with SAECG[40] and may be even more powerful when combined with LVEF and invasive electrophysiological testing.[41] In the recent prospective multicentre MASTER (Microvolt T Wave Alternans Testing for Risk Stratification of Post- Myocardial Infarction Patients) Trial, Chow *et al* found that MTWA testing in 575 patients with ischaemic heart disease and LVEF<30% who already qualified for an ICD did not predict subsequent ventricular arrhythmic events, although MTWA non-negative patients (ie, positive and indeterminate MTWA results) had significantly higher mortality compared with MTWA negative patients.[42] The value of MTWA in risk stratification may actually be in deciding which patients are least likely to benefit from ICD insertion, as suggested by the ABCD (Alternans Before Cardioverter Defibillator) trial.[43] This prospective, multicentre study was the first to use MTWA to guide prophylactic ICD insertion. The investigators demonstrated that MTWA achieved 1-year positive and negative predictive values of 9% and 95%, respectively, and that its use in risk stratification was comparable to invasive electrophysiological study at 1 year and complementary when applied in combination. It should be noted that patients investigated in both the MASTER and ABCD trials had a history of ischaemic heart disease and poor LVEF, and were not recruited immediately post AMI. Only 52% and 47% of patients, respectively, had prior coronary angioplasty, whereas the percentage of those who underwent primary angioplasty was not reported. The applicability and use of MTWA in the risk stratification of patients soon after AMI, particularly those who undergo primary angioplasty, requires further attention.

INVASIVE ELECTROPHYSIOLOGICAL TESTING

The idea of performing programmed ventricular stimulation or electrophysiological (EP) testing in AMI survivors is to investigate the ability of the diseased myocardium to sustain re-entrant ventricular arrhythmias, which can degenerate into VF and cause sudden death. Early studies on the use of EP testing to risk stratify patients post AMI reported conflicting data, with nearly half of all studies finding that the inducibility of sustained VT was unhelpful in predicting later mortality or arrhythmic events.[6] The apparent confusion in the literature is probably related to differences in patient population, stimulation protocols and time intervals between AMI and EP testing. For example, Bourke *et al* performed EP testing in 502 patients 11±4 days after AMI using a protocol containing four extrastimuli from the right ventricular apex only and demonstrated that the induction of sustained monomorphic VT with a cycle length >230 ms was an indicator of electrical instability and a poorer prognosis.[44] In contrast, Roy *et al* performed EP testing in 150 survivors of AMI 12±2 days following the acute event

using a protocol consisting of up to three extrastimuli from the right ventricular apex and right ventricular outflow tract. During a mean follow-up of 10±5 months, they found no significant difference in outcome between patients with and without inducible ventricular arrhythmias during EP testing.[45]

In a more recent study in the modern era of interventional cardiology, Chong *et al* demonstrated that the rate of inducible VT at EP testing did not depend on whether patients were treated with primary angioplasty or thrombolysis.[46] Thus, results from the early studies of EP testing among AMI survivors may still be valid today. However, one should also take into account that the routine use of β-blockers in most of the early studies was suboptimal. For example, the MUSTT investigators demonstrated that the induction of ventricular arrhythmias at EP testing in patients with coronary artery disease and left ventricular dysfunction (LVEF<40%) identified a group at higher risk group for sudden death that may benefit from antiarrhythmic medication or ICD implantation.[47] However, only 35% of non-inducible and 51% of inducible patients received a β-blocker at discharge. With current pharmacological management of patients with heart failure and reduced LVEF, it is likely that the rates of sudden cardiac death would be lower today in both groups.

In addition to the invasive nature of EP testing and need for specialist equipment and personnel, another limitation to its routine use in risk prediction includes the wide range of reported sensitivities (between 28% and 80%).[6] Nonetheless, based predominantly on data from the MADIT and MUSTT studies, EP testing is recommended in some of the current guidelines on the selection of candidates with ischaemic heart disease and reduced LVEF for prophylactic ICD insertion. The future role of this invasive test in risk prediction may lie in its combined use with other non-invasive tests, such as MTWA and HRV, to further refine the selection of potential ICD recipients.[28 41 43 48] The assessment of more novel parameters at EP testing, aimed at defining the arrhythmogenic substrate in more detail, may also prove useful. For example, Saumarez *et al* demonstrated that analysis of paced ventricular electrogram fractionation at EP testing in patients with hypertrophic cardiomyopathy identified areas of delayed conduction through fibrotic/diseased myocardium, which provided a more accurate prediction of the risk of sudden cardiac death than that provided by non-invasive techniques.[49]

ROLE OF CARDIAC MAGNETIC RESONANCE

In recent years the use of cardiac magnetic resonance (CMR) in assessing myocardial scar burden among AMI survivors and predicting mortality and arrhythmic events has been explored. Yan *et al* were the first to demonstrate that quantification of the peri-infarct zone by contrast-enhanced CMR is an independent predictor of mortality following AMI.[50] A number of other investigators have since demonstrated that tissue heterogeneity in the peri-infarct zone, as detected by contrast-enhanced CMR, is likely to signify a pro-arrhythmic substrate and is one of the strongest predictors of ventricular arrhythmias and appropriate ICD therapies.[51 52] These pioneering studies have opened up the field to additional imaging-based methods for arrhythmic risk stratification of AMI-survivors and pave the way for larger, prospective, multicentre studies using these techniques.

USE OF GENETIC PROFILING IN RISK PREDICTION

It has been known for some time from large-scale epidemiological studies that there appears to be a hereditary component to the risk of sudden cardiac death and the development of VF during AMI.[53–56] In recent years, the genetic basis for this has begun to become unravelled with several investigators demonstrating an association between certain genetic mutations/polymorphisms and the risk of sudden cardiac death. Population-based cohort analyses and case–control studies have provided evidence for a link between sudden cardiac death and a number of common single nucleotide polymorphisms, such as those associated with nitric oxide synthase 1 adapter protein,[57] the β2-adrenergic receptor,[58] the transforming growth factor signalling pathway (TGFBR2 polymorphism)[59] and chromosome 9p21 polymorphisms (which have previously been associated with an increased risk of AMI).[60] In addition, it is conceivable that genetic mutations or polymorphisms in genes coding for ion channel proteins may increase the susceptibility of individuals with AMI to VF and thereby increase the risk of sudden cardiac death. Targeted genetic testing of patients with unexplained cardiac arrest and structurally normal hearts revealed mutations in cardiac ion channels in approximately 50% of subjects.[61] However, attempts so far at demonstrating such an association in AMI patients have proved unsuccessful.[62] This may partly be related to the complexity of the association between a genetic abnormality and the development of ventricular arrhythmias in patients with AMI, confounded by the potential of other polymorphisms to modify the clinical expression of a mutation.[63] Nonetheless, the use of genetic profiling among AMI survivors to help refine arrhythmic risk remains a very attractive and real possibility for the future.

CONCLUSIONS

A wide variety of factors affect the prognosis of AMI survivors. Assessment of the degree of left ventricular dysfunction, with or without invasive EP testing, remains the key investigation in determining which patients should be offered an ICD, as reflected in current international guidelines. Although not yet incorporated into current guidelines, a number of non-invasive tests can provide additional information that may prove useful to clinicians in deciding which patients are at greatest risk of developing malignant ventricular arrhythmias following AMI. Many studies to date have provided evidence in support of a role for each of these tests individually or in combination in the risk stratification of AMI survivors. The pros and cons of each of these investigations are summarised in table 1. As no single test possesses adequate sensitivity or specificity for predicting sudden cardiac death, the most promising way forward is probably in the use of specific algorithms which incorporate a number of cardiovascular investigations and risk prediction parameters.[6] Such algorithms would need to be prospectively validated before being accepted into clinical practice.

In addition to the obvious clinical benefit of improving the selection of suitable candidates for ICD insertion, the use of additional tests/algorithms for risk prediction may also have important health-economic implications. Several investigators have demonstrated that the prophylactic use of ICDs becomes increasingly more cost-effective the longer the patient survives following implantation and that the number of life-years gained from one ICD increases non-linearly with time.[64–66] In the MADIT II trial, the number needed to treat (NNT) with an ICD to save one life was calculated to be unacceptably large (133 patients) at 1 year, but became more attractive at 2 years (NNT=17) and even better at the end of 3 years (NNT=8).[4] Such health-economic evaluations need to be re-assessed if additional risk prediction tests/algorithms are used to select potential ICD recipients.

Table 1 Summary of the advantages and disadvantages/ limitations of the current methods available for arrhythmic risk prediction in patients post AMI

Risk stratification method	Advantages	Disadvantages/limitations	Comments
Echocardiography	► Available in almost all hospitals ► Routinely performed in patients post AMI ► Provides additional information (eg, valvular function) ► Cut-off values for ICD insertion stated in guidelines	► LVEF is an indicator of increased mortality, rather than SCD, therefore there are limitations to its use in guiding ICD insertion ► Majority of patients who die suddenly have LVEF>40% ► LVEF may improve with time (with medication or revascularisation)	► Assessment of LVEF remains essential in risk stratification, in line with current guidelines ► Can be used to initially select on which patients to perform further risk stratification
12-lead ECG	► Cheap, quick and easy to perform ► Can be obtained serially at each follow-up visit to reassess risk ► Large databases can be generated and analysed retrospectively/prospectively	► Many abnormal parameters are markers of increased mortality, rather than specifically SCD ► Low positive predictive and negative predictive accuracies ► Subject to interobserver variability (unless automated software is used) ► Considerable overlap in some parameters between healthy subjects and patients	► Remains a standard investigation in patients with CAD ► Low positive and negative predictive accuracies for SCD limit its use in risk stratification
Signal averaged ECG	► Easy and quick to perform ► High negative predictive accuracy ► Can be used in patients with AF	► Low positive predictive accuracy ► Numerous negative studies, especially in current era of interventional cardiology ► Better at predicting risk of VT than VF ► Normal standards for patients with bundle branch block or paced rhythm have not been established	► Improved risk stratification when used in combination with other tests ► Probably more useful in identifying low-risk patients
Standard 24 h Holter	► Provides information on other arrhythmias post AMI (eg, AF, heart block) ► Standard test, easy to perform ► Can be used in patients in AF or paced rhythms	► Low sensitivity and specificity	► Most promising use is in combination with other parameters (eg, HRV and HRT) obtained from Holter recordings
Heart rate variability	► Can be automatically recorded with standard Holter (using additional software) ► Short (2—30 mins) and longer (24 h) measurements are possible	► Cannot be reliably assessed in patients with AF or frequent PVCs ► Influenced by a number of factors (eg, age, gender medication) ► May be affected by functional state of sinus node ► Short-term measurements in risk prediction have not been well tested ► No consensus on which parameters of HRV or method of assessment is best	► A consensus opinion on which parameters of HRV to record and which method of assessing HRV is required
Heart rate turbulence	► Value in risk prediction supported by several recent large-scale prospective studies ► Provides prognostic information in patients with normal and impaired LVEF	► Optimal time post AMI to perform the test has not been established ► Can only be performed in patients in SR with a significant number of PVCs	► A promising test for risk prediction that can be used with other Holter-based measurements ► More information is required on when is the optimal time to perform the test
T wave alternans	► Easy to perform in post AMI patient ► Can use existing equipment or modification of equipment ► High negative predictive accuracy	► Can only be used in patients in SR ► Clean' ECG trace required (difficult to obtain during exercise) ► Indeterminate result if target heart rate not achieved during exercise ► Low positive predictive accuracy	► Useful in risk stratifying patients with impaired and preserved LVEF ► Useful role in determining which patients are unlikely to benefit from ICD insertion ► Improved risk stratification when used in combination with other tests
Invasive electrophysiological study	► Can be performed in patients with atrial arrhythmias and paced rhythm ► Easily measured end point	► Invasive ► Relatively costly ► Requires specialised equipment and trained staff to perform ► Varying protocol between different electrophysiologists ► Conflicting data on its value in the literature	► In view of the invasive nature of the test, its most likely future role will be in combination with other non-invasive tests to help refine risk in high-risk patients
Cardiac magnetic resonance	► Provides additional anatomical information (eg, accurate assessment of LV function)	► Relatively more costly than other non-invasive tests ► Requires hospital to have a MRI scanner ► Relatively longer to analyse results ► Cannot be performed in patients with ICDs	► Good potential for use in this field ► Only imaging technique to date to provide information on arrhythmic risk ► Larger, prospective studies are required

AF, atrial fibrillation; AMI, acute myocardial infarction; CAD, coronary artery disease; ICD, implantable cardioverter defibrillator; HRT, heart rate turbulence; HRV, heart rate variability; LVEF, left ventricular ejection fraction; PVC, premature ventricular complex; SCD, sudden cardiac death; SR, sinus rhythm; VT/VF, ventricular tachycardia/fibrillation.

A number of unanswered questions remain, such as when is the best time to perform the tests, how often should the tests be repeated and which criteria should be taken to signify an abnormal result. Furthermore, with the increasing use of primary angioplasty in the treatment of acute ST-elevation myocardial infarction, more survivors are likely to have preserved LV function and improved prognosis.[67] Consequently, the applicability of current guidelines for prophylactic ICD

insertion (based predominantly on impaired LVEF) to modern-day cardiological practice has been called into question.[68] Future prospective, multicentre studies are required to correlate use of these tests or specific algorithms involving a combination of tests with outcome before they can be universally adopted and their use reflected in guidelines. With improvements in technology and more patients surviving AMI, it is likely to be only a matter of time before additional cardiovascular investigations are routinely used in predicting which patients post AMI are at greatest risk of sudden cardiac death.

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