Heart rhythm at the time of death documented by an implantable loop recorder

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Aims
The aims of this study were to describe arrhythmias documented with an implantable loop recorder (ILR) in post-acute myocardial infarction (AMI) patients with left ventricular dysfunction at the time of death and to establish the correlation to mode of death.

Methods and results
Post-mortem ILR device interrogations were analysed from patients dying in the CARISMA study. Mode of death was classified by a modified CAST classification. Twenty-six patients died with an implanted ILR. Of these, 16 had an electrocardiogram recorded at the time of death. Ventricular tachycardia (VT)/ventricular fibrillation (VF) was terminal rhythm in eight patients and bradyarrhythmias were observed in another eight patients. Of the deaths with peri-mortem recordings, seven were classified as sudden cardiac death (SCD). In six of these, VF was documented at the time of death. Six monitored deaths were classified as non-SCD (NSCD) of which only two had recordings of VT/VF, whereas four had bradyarrhythmias. All peri-mortem recordings in non-cardiac death (NCD) were bradyarrhythmia.

Conclusion
Long-term monitoring in a population of post-AMI patients with left ventricular ejection fraction ≤40% showed that VT/VF and bradyarrhythmia each accounted for half of the recorded events at the time of death. The ILR confirmed that ventricular tachyarrhythmias are associated primarily with SCD, whereas bradyarrhythmias and electromechanical dissociation seems dominant in NSCD and NCD.

The study was registered at ClinicalTrials.gov: NCT00145119.

Keywords
Arrhythmia • Myocardial infarction • Implantable loop recorder • CARISMA

Introduction
Survivors of an acute myocardial infarction (AMI) with subsequent left ventricular dysfunction have a high mortality rate. The extent of myocardial damage and reduction of cardiac function are correlated to the risk of death.1–3 Approximately 10–15% die within 1 year of the AMI and about half of the deaths classified as cardiac are sudden.4–6 However, the fraction of patients who die suddenly due to malignant arrhythmias and the classification of the terminal arrhythmias have been debated.7,8 Differentiating the exact mode of death has been limited by technical shortcomings in documenting the heart rhythm immediately before death. Continuous long-term electrocardiographic (ECG) surveillance has not been feasible in out-of-hospital patients. In-hospital- and short-term out-of-hospital surveillance studies utilizing telemetry and Holter monitoring show that 80% of peri-mortem heart rhythms are ventricular tachyarrhythmias, whereas 20% are bradyarrhythmias in sudden cardiac death (SCD).9–12 Post-mortem implantable cardioverter defibrillator (ICD) interrogations also indicate that the majority of SCDs in patients with ischaemic heart disease and reduced left ventricular function are caused by ventricular tachyarrhythmia.13–17 A typical event sequence is described for the
terminal ventricular tachyarrhythmias in SCD. Ventricular tachycardia, sometimes preceded by sinus tachycardia, deteriorates into VF and ultimately into asystole. This course of events was confirmed in ambulatory monitoring studies.

Recently, the investigators of the Cardiac Arrhythmias and Risk Stratification after Myocardial infArction (CARISMA) study reported the results of 2 years of continuous arrhythmia monitoring in post-AMI patients using an implantable loop recorder (ILR). The objectives were to assess the 2-year incidence of arrhythmias after an AMI and estimate the predictive value of several non-invasive and invasive tests regarding ICD preventable ventricular tachycardia (VT)/ventricular fibrillation (VF). Holter-derived measures of heart rate variability were found to be significant predictors of VT/VF. The incidence of AV block was found to be high and associated with an increased mortality rate. In this study, the electrical activity of the heart at the time of death was documented in patients dying with an ILR.

The purpose of the present study was to determine which arrhythmias were observed at the time of death in different categories of mode of death. We analysed post-mortem ILR interrogations from the patients who died in the CARISMA study. Also, we investigated the occurrence of rhythms preceding VF.

Methods

Patients

This substudy included all patients that died with an implanted ILR in the CARISMA study. Briefly, the CARISMA study included 312 patients with an AMI and a subsequent left ventricular ejection fraction (LVEF) <40% estimated by 2D echocardiography. An ILR (Medtronic Reveal Plus) was implanted 5–21 days after the AMI in 297 of these patients for continuous arrhythmia monitoring. The patients underwent a vast series of risk stratification tests (12-lead ECG, 24 h Holter monitoring, signal-averaged ECG, echocardiography, T-wave alternans, exercise test, and an invasive electrophysiological study). Clinical follow-up visits were scheduled quarterly for up to 2 years after the AMI.

The study was conducted in accordance with the declaration of Helsinki and supplements hereof. All appropriate Ethics Review Boards approved the study. Patients gave informed consent prior to inclusion.

Implantable loop recorder

The ILR recorded one bipolar lead and was programmed to automatically record at pre-determined triggering events. Asystole was detected as R-R interval >5 s, bradycardia as >4 beats with a frequency <30 min⁻¹ and tachycardia as >16 beats with a frequency >125 min⁻¹. Electrocardiogram of automatic recordings contained 1 min before and after the triggering event. The ILR was able to store 13 automatic events and also allowed storage of one manually activated recording. Manual recordings were of 14 min length and offered the opportunity to link the recording to patient symptoms at the time of recording. The total device storage capacity was 42 min of ECG. Explanation and interrogation was performed post-mortem in patients who died during follow-up. Interrogation was performed using a standard programmer (Medtronic 9790).

Mode of death

A modified CAST classification was applied to establish the mode of death. Sudden cardiac death was defined as unexpected death within 1 h of onset of symptoms or unexpected and unwitnessed death within 24 h after the deceased was last seen alive. Deaths were classified as non-SCD (NSCD) if the cause of death was cardiac but did not meet SCD criteria. Death was presumed cardiac if there were no specific evidence of non-cardiac death (NCD). Cardiac death was presumed arrhythmic unless specific evidence suggested otherwise. Resuscitated cardiac arrest was not considered death. An endpoint committee reviewed the clinical information preceding the death in each case and defined the mode of death.

Arrhythmias

The terminal cardiac rhythm was categorized as VT, VF, or bradyarrhythmia. If death occurred at a time where ECG showed any other rhythm, this was interpreted as signal noise or non-classifiable agonal rhythm.

Time of death

The time of death stated on the death certificate corresponding to the time of clinical death was employed whenever available. Otherwise, information about the clinical events surrounding the time of death of the patient was retrieved from the medical record and compared with the time of the ECG suspected to contain the terminal event. Electrocardiogram recorded within 1 h of the derived time of death was accepted as connected to the death. If exact time of death could not be established from the above, the ILR recordings were used to determine a likely time of death, e.g. when a patient died at night at home and the ECG showed an event of VF during the night.

Statistics

Analysis of variance between patients in the three subgroups of mode of death was performed using ANOVA and Fisher’s exact test for continuous and categorical variables, respectively. P-values of <0.05 were considered significant. Statistical analyses were done using SAS 9.1.3 (SAS Institute, Cary, NC, USA). The authors had full access to all study data and performed the necessary analysis independent of the sponsor.

Results

The characteristics of patients dying with an ILR are shown in Table 1. Significant variance was found in subgroup analysis by mode of death regarding clinical heart failure prior to inclusion (P = 0.02), NYHA class at discharge (P = 0.02), and medication status at the last follow-up visit including beta-blockers (P < 0.05), diuretics (P = 0.005), and statins (P = 0.04). The proportion of patients with AMI prior to inclusion was also markedly higher in the NSCD group than in patients of other modes of death.

During an average follow-up of 1.9 ± 0.5 years, 36 of the 297 ILR patients died. The ILR was explanted before the time of death in 10 patients due to coronary artery bypass grafting (n = 1), battery end-of-life (n = 1), or implantation of either ICD (n = 6) or pacemaker (PM) (n = 2). The remaining 26 patients died with an implanted ILR (Table 2). Electrocardiogram was recorded in 16 (62%) of these patients within 1 h of the time of death. The time of death was derived from terminal event ECG in three cases. Seven patients had no reliable recordings at the time of death due to memory overwriting (n = 3), PM (n = 1), time-stamping malfunction (n = 1), and unknown...
reasons \((n = 2)\). In three instances, the device was not interrogated post-mortem.

Ventricular fibrillation was observed in six SCDs and one NSCD (Figure 1). Initiation of VF was visible in five instances. Ventricular tachycardia did not precede VF in any of these. Monomorphic VT was detected as terminal rhythm in one patient dying of NSCD. Bradyarrhythmias were detected in one SCD, four NSCDs, and three NCDs (Figure 2). In two of the patients dying of NSCD, the peri-mortem recordings were of PM rhythm \((60 \text{ bpm})\). Underlying bradyarrhythmia and electromechanical dissociation was assumed in these cases.

Of the 26 deaths with an implanted ILR, 19 were cardiac; 9 were sudden and 10 were non-sudden. Electrocardiogram was available at the time of death in 68% of the patients dying of cardiac causes. Seven patients died from non-cardiac causes; septic shock \((n = 4)\), advanced lung cancer \((n = 1)\), severe pneumonia \((n = 1)\), and abdominal bleeding \((n = 1)\). Recordings were present in 43% of the NCDs.

No significant differences were found in the ILR device settings of sensibility and gain in patients dying without terminal event recordings compared with the overall CARISMA population.

Analysis of the circadian variation at the time of death showed that half of the patients dying with an ILR died at nighttime \((0–8 \text{ a.m.})\). There were no differences in mode of death in regard to time of death.

**Discussion**

To determine which arrhythmias were observed at the time of death in different categories of mode of death, we analysed

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### Table 1 Characteristics of patients dying with an implanted ILR

|                     | Total, \(n = 26\) | SCD, \(n = 9\) | NSCD, \(n = 10\) | NCD, \(n = 7\) |
|---------------------|-------------------|---------------|-----------------|---------------|
| **Demographics**    |                   |               |                 |               |
| Age (years)         | 70 ± 11           | 69 ± 11       | 69 ± 14         | 73 ± 7        |
| Gender \(\%\)       | 69                | 89            | 70              | 43            |
| BMI (kg/m\(^2\))    | 27.0 ± 6.7        | 27.5 ± 4.0    | 30.3 ± 9.8      | 22.4 ± 3.2    |
| Smoking \(\%\)      | 85                | 100           | 80              | 71            |
| **Medical history** |                   |               |                 |               |
| Hypertension \(\%\) | 42                | 33            | 40              | 57            |
| Diabetes \(\%\)     | 31                | 33            | 40              | 14            |
| Hypercholesterolaemia \(\%\) | 42   | 22            | 70              | 29            |
| Renal disease \(\%\) | 12            | 11            | 20              | 0             |
| Prior MI \(\%\)     | 50                | 33            | 80              | 29            |
| Clinical heart failure \(\%\) \(^1\) | 27           | 11            | 50              | 14            |
| NYHA class >1 \(\%\) \(^1\) | 88           | 100           | 100             | 57            |
| LVEF \(\%\)         | 31 ± 5            | 31 ± 6        | 31 ± 6          | 32 ± 4        |
| **Medication at last follow-up** |               |               |                 |               |
| Beta-blocker \(\%\) \(^1\) | 81         | 89            | 90              | 57            |
| Calcium channel antagonists \(\%\) | 12     | 0             | 20              | 14            |
| ACE-I/AT-II antagonists \(\%\) | 77         | 89            | 80              | 57            |
| Diuretics \(\%\) \(^1\) | 81          | 89            | 100             | 43            |
| Digoxin \(\%\)      | 19                | 11            | 30              | 14            |
| Statins \(\%\) \(^1\) | 62          | 56            | 80              | 43            |
| Clopidogrel \(\%\)  | 38                | 44            | 40              | 29            |
| Amiodarone \(\%\)   | 4                 | 0             | 0               | 14            |

\(^1\) Two-sided \(P\)-value < 0.05.

### Table 2 Heart rhythm recorded within 1 h of death

| Mode of death | Ventricular fibrillation | Ventricular tachycardia | Bradyarrhythmia | No rhythm | No interrogation | Total |
|---------------|--------------------------|-------------------------|-----------------|-----------|-----------------|-------|
| SCD           | 6                        | –                       | 1               | 1         | 1               | 9     |
| NSCD          | 1                        | 1                       | 4               | 3         | 1               | 10    |
| NCD           | –                        | –                       | 3               | 3         | 1               | 7     |
| Total         | 7                        | 1                       | 8               | 7         | 3               | 26    |
post-mortem ILR interrogations from the CARISMA study. The major finding from these analyses was that the majority of sudden deaths occurring in post-AMI patients with left ventricular dysfunction are in fact due to VF. Previous studies assessing the terminal rhythm at the time of sudden death have been based on selected patient populations. Primarily, these included hospitalized patients with indications for Holter recording or telemetry and patients with an implanted ICD in whom the device was not able to prevent sudden death.\(^9\)\(^{21}\) In contrast, the ILR recordings in patients dying of SCD in the CARISMA study represent peri-mortem arrhythmia occurrences in patients without pre-existing symptoms of arrhythmia or indications for ICD by contemporary guidelines (which changed over the course of the study since MADIT II came out in 2002 and the study was conducted from 2001 to 2006). Since the electrograms (EGM) of the terminal events were blinded to the endpoint committee classifying the mode of death, this observation shows that SCD defined by common clinical criteria is indeed a result of ventricular tachyarrhythmia in the majority of patients dying suddenly after AMI. This challenges conclusions from ICD studies suggesting that
SCD defined by common methods is not frequently caused by ventricular tachyarrhythmia. This controversial result may be due to differences in patient characteristics. Also, the present population represents post-AMI patients without a previously documented life-threatening arrhythmia, whereas the ICD study patients usually have a history of malignant arrhythmic events and the ICD may have rescued them from an arrhythmic death before their fatal event. The current data support the notion that SCD among post-AMI patients may well serve as a surrogate for ventricular tachyarrhythmia in clinical observational studies.

Bradyarrhythmia was terminal rhythm in only one patient in whom death was defined as sudden. The ILR is currently mostly acknowledged for its ability to detect bradyarrhythmias and the proportion of ILR documented bradyarrhythmic sudden deaths are in agreement with the results of previous studies.

We also investigated the occurrence of rhythms preceding VF. In contrast to the observations of Bayes de Luna et al. from Holter recordings at the time of sudden death, VT did not precede VF in any of the cases with sudden death in the present study. The events were preceded by sinus rhythm or sinus tachycardia with
ventricular premature beats in all EGMs with visible onset of VF. This is also in contrast to experience from ICD recipients in whom fast VTs treated by anti-tachycardia pacing are relatively common.\(^25,26\) Again, the discrepant results most likely originate from differences in the population characteristics.

The terminal rhythm was ventricular tachyarrhythmia only in two cases defined as NSCD or NCD, again suggesting to a relatively high specificity that ventricular tachyarrhythmia is primarily associated to SCD. Of the NSCDs, 40% were due to progressive heart failure and 50% were caused by terminal heart failure within hours to days following a re-AMI. The data reported here are in agreement with previous studies showing that the terminal rhythm is often bradyarrhythmia leading to asystole among patients with advanced heart failure.\(^27\)

The comparison of patient characteristics in this substudy revealed a few significant differences in administered medications at the time of the last follow-up visit. Patients dying of cardiac causes received beta-blockers and diuretics significantly more often than those dying of non-cardiac causes. This is most likely explained by the difference in NYHA class at discharge, the prevalence of prior AMI, and the significantly higher frequency of pre-existing congestive heart failure among patients dying from cardiac causes. Hypercholesterolaemia was found to be more frequent in patients dying of NSCD and this probably accounts for the difference in treatment with statins. We cannot exclude an effect of these differences in medication on the mode of death and the peri-mortem arrhythmias recorded. However, the present study does not have the power of numbers to make any such inferences.

The differences observed in the proportion of AMI and clinical heart failure prior to inclusion are likely to have affected arrhythmia substrates. Macro-re-entrant VT can potentially evolve encircling areas of scared myocardium after AMI. However, since the NSCD patients had the highest frequency of these characteristics, this study indicates that if the prior AMI and heart failure had not been present areas of scared myocardium after AMI. However, since the NSCD patients had the highest frequency of these characteristics, this study indicates that if the prior AMI and heart failure had not caused fatal arrhythmia before the time of inclusion, then bradyarrhythmias were the most probable arrhythmia at the time of death.

Limitations

Sample size

The sample size of the present study limited the number of deaths with ILR recordings. Also, the ILR was explanted in 57 patients receiving an ICD for primary (n = 45) or secondary (n = 12) prophylaxis. Appropriate therapy (ATP/shock) for fast ventricular tachyarrhythmias was delivered at least once in 11 patients by their device. These patients might otherwise have died monitored by their ILR. The low number of ILR-monitored deaths precludes further elaboration on the precision of existing classifications of mode of death.

The sample size also means that the statistical analyses are fragile and must be interpreted with caution.

Technical limitations

Implantable loop recorder memory capacity was a limitation of terminal event recording in three cases. Manual handling of the deceased generated numerous signal noise recordings up to 4 days post-mortem. These artefact recordings may have overwritten recordings from the time of death.

This sensitivity makes it essential to explant the device as soon as possible post-mortem in future studies. One missing recording was possibly lost because of PM activity post-mortem preventing the device from triggering EGM storage. This renders the ILR unsuitable for bradyarrhythmia surveillance when other therapeutic devices are implanted.

General technical device limitations have already been discussed elsewhere.\(^28\) Briefly, the ILR recordings are limited to arrhythmias within the frequency spectrum of the algorithms, most likely underestimating the occurrence. Furthermore, ST-segment deviation analyses are not reliable from ILR EGM.

Conclusion

From long-term monitoring in a population of post-AMI patients with LVEF ≤ 40% using an insertable loop recorder, we found that VT/VF and bradyarrhythmia each accounted for 50% of recorded events at the time of death. The ILR confirmed that ventricular tachyarrhythmias are associated primarily with SCD, whereas bradyarrhythmia and electromechanical dissociation seems dominant in NSCD and NCD. Peri-mortem arrhythmias were recorded in almost twice as many deaths classified as cardiac as in deaths classified as non-cardiac.

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