QRS duration: a simple marker for predicting cardiac mortality in ICD patients with heart failure

L Bode-Schnurbus, D Böcker, M Block, R Gradaus, A Heinecke, G Breithardt, M Borggrefe

Background: Patients resuscitated from ventricular tachyarrhythmias benefit from implantable cardioverter-defibrillators (ICDs) as opposed to medical treatment. Patients with increased QRS duration receiving an ICD in the presence of heart failure are at greatest risk of cardiac death and benefit most from ICD therapy.

Objective: To determine whether an increased QRS duration predicts cardiac mortality in ICD recipients.

Design: Consecutive patients with heart failure in New York Heart Association functional class III were grouped according to QRS duration (< 150 ms, n = 139, group 1; > 150 ms, n = 26, group 2) and followed up for (mean (SD)) 23 (20) months.

Patients: 165 patients were studied (80% men, 20% women); 73% had coronary artery disease and 18% had dilated cardiomyopathy. Their mean age was 62 (10) years and mean ejection fraction (EF) was 33 (14)%. They presented either with ventricular tachycardia (VT) or ventricular fibrillation (VF).

Main outcome measures: Overall and cardiac mortality; recurrence rates of VT, fast VT, or VF.

Results: Mean left ventricular EF did not differ between group 1 (33 (13)%) and group 2 (31 (15)%). Forty patients died (34 cardiac deaths). There was no difference in survival between patients with EF > 35% and ≤ 35%. Cardiac mortality was significantly higher in group 2 than in group 1 (31.3% at 12 months and 46.6% at 24 months, v 9.5% at 12 months and 18.2% at 24 months, respectively; p = 0.04). The recurrence rate of VT was similar in both groups.

Conclusions: Within subgroups at highest risk of cardiac death, QRS duration—a simple non-invasive index—predicts outcome in ICD recipients in the presence of heart failure.

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Conclusions: Within subgroups at highest risk of cardiac death, QRS duration—a simple non-invasive index—predicts outcome in ICD recipients in the presence of heart failure.
From this database, 165 patients were identified who were in NYHA functional class III at the time of implantation. These patients formed the basis for further analysis. In all but two patients, a transvenous lead system was successfully implanted, in part in combination with a subcutaneous patch or an array electrode to achieve a sufficient defibrillation threshold. All implanted devices had the capability of either storing intracardiac electrograms. All patients had antitachycardia pacing capabilities in combination with cardioversion/defibrillation treatment features. Shock therapy was programmed to be non-committed.

Follow up
The follow up period of all patients started at the time of implantation, and patients were seen regularly on an outpatient basis at 2–3 month intervals. At each visit, the device was functionally tested (sensing, pacing impedance, and threshold) and interrogated for treated episodes. Primary end points were perioperative mortality (defined as death within one hour of the onset of symptoms or unwitnessed death in a formerly stable patient). Recurrence of VT or death within one hour of the onset of symptoms or unwitnessed death in a formerly stable patient). Recurrence of VT or syncope. All these patients gave written informed consent before device implantation.

Statistical analysis
QRS duration was measured in a 12 lead ECG taken at the time of implantation, using leads V3–V6. A mean of at least three complexes was used for further analysis. Univariate analyses were undertaken to detect differences between subgroups. Kaplan-Meier analysis was done using the end points all cause death, cardiac death, sudden death, VT recurrence at any rate, and recurrence of fast VT (> 240 beats/min), to generate survival tables for each subgroup including the Breslow test. Patients were divided into two groups according to QRS duration. A cut off point of 150 ms was chosen, as it has recently been suggested that this identifies patients with heart failure who benefit from a biventricular pacing system.

RESULTS
Baseline characteristics of study groups
In all, 165 patients in NYHA functional class III received a transvenous endocardial ICD system. In 61 patients this was combined with a subcutaneous array or a finger electrode. Only two patients underwent thoracotomy for implantation of an epicardial lead system. There were 132 men (80%) and 33 women, mean (SD) age, 62 (10) years (table 1). The mean ejection fraction (EF) as assessed by left ventricular angio-gramy was 33 (14)%). A history of cardiac arrest was present in 63% of patients; 73% had coronary artery disease and 18% had dilated cardiomyopathy. At the time of implantation, 139 patients (85%) had a QRS duration of < 150 ms, while 26 (16%) had a QRS duration of > 150 ms or more. There were no significant differences in the clinical characteristics of these two groups. In addition, there were no differences in the use of either class III antiarrhythmic drugs or β blockers.

The following devices were used: Guidant/CPL, either P2 or P3 in 28 patients; PRx in 14; PRx2/3 in 38; Mini in 13; Mini II in four; Medtronic 7216A and 7217B in 20; 7218 in seven; 7219 in 30; Jewel plus in five; Ventritex V-100 in two; Contour in two; Biotronik Phylax 06 in one; and Telecronic Guardian ATP2/3 in one.

Postoperative period
Five patients died within the first 30 days after implantation. In one patient with congenital heart disease and multiple previous surgical procedures, perforation of the subclavian vein led to haemothorax which, in conjunction with advanced liver...
disease, caused the patient’s death five days after implanta-
tion. Two patients died because of heart failure on day 3 and
day 24 after implantation. Another patient died because of
resistant incessant VT and heart failure on day 6 after implan-
tation. One further patient died from pulmonary embolism 12
days after implantation of an epicardial lead system. The mean
ejection fraction in the patients who died perioperatively was
36 (8)%.

Long term outcome
During a follow up of 23 (20) months, 40 deaths occurred,
most within the first two years (fig 1). Thirty four of these
were classified as cardiac, 11 of which were sudden. The inci-
dence of cardiac death was 9.6% and 15.1% at 12 and 24
months, respectively. The sudden death incidence (not shown)
was 2.4% and 6.3% at 12 and 24 months. Death from any other
cause occurred in 2.0% after 12 and 24 months. The overall
mortality was 14% and 23% at 12 and 24 months. VT recurred
in 59% and 70% within 12 and 24 months. Fast VT (≥ 240
beats/min), which would presumably have been lethal
without termination by the device, occurred in 22% and 28%
within 12 and 24 months.

Ejection fraction and mortality and recurrences of VT or
fast VT
The survival rates at 12 and 24 months did not differ in
patients with EF > 35% compared with those with EF < 35%
(fig 2). Cardiac mortality, sudden death rates, or recurrence
rates of any ventricular tachyarrhythmia were similar in the
two groups (table 2). The risk ratio for cardiac mortality using
a cut off of 35% was 1.235 (95% confidence interval (CI) 0.609
to 2.504). The recurrence of fast VT (≥ 240 beats/min) was
similar in the group with EF < 35% and > 35% (77% v
68% at
24 months, NS).

QRS duration and mortality
At the end of follow up, overall mortality from any cause was
similar in patients with a QRS duration of < 150 ms (group
1, 52.4%) and in those with a QRS duration of ≥ 150 ms (group
2, 46.6%), as evaluated by Kaplan-Meier analysis (p = 0.13).
However, cardiac mortality was significantly higher in patients
with an increased QRS duration (group 2). Kaplan-Meier
analysis showed that cardiac mortality in group 1 at 12 and 24
months was 9.5% and 18.2%, respectively, compared with
31.3% and 46.6% in group 2 (increased QRS duration)
(p = 0.04) (fig 3). Thus in patients with heart failure,
increased cardiac mortality was associated with a widened
QRS (risk ratio 2.178, 95% CI 0.946 to 5.055). This effect
appeared to have prognostic importance, especially in the long
term. The difference in mortality between the two groups
increased in the second year of follow up (fig 3).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Survival according to ejection fraction</th>
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<td>Survival/event-free interval</td>
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<td>Overall mortality</td>
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<tr>
<td>Cardiac death</td>
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<tr>
<td>Sudden death</td>
<td>97.8%</td>
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<tr>
<td>VT</td>
<td>58.9%</td>
</tr>
<tr>
<td>Fast VT</td>
<td>85.0%</td>
</tr>
</tbody>
</table>

Actuarial survival rates and intervals free of recurrence of ventricular tachycardia in relation to ejection fraction (cut-off value 35%). There were no significant differences between subgroups.

EF, ejection fraction; fast VT, ventricular tachycardia of ≥240 beats/min; VT, ventricular tachycardia.
with dilated cardiomyopathy. mortality with an adjusted hazard ratio of 1.84 (95% CI 1.22 to 2.76; p = 0.0035). Xiao and colleagues studied 58 patients with dilated cardiomyopathy. Patients with a QRS duration of ≥ 160 ms (n = 10) had a mortality of 80%, compared with 13% in the remaining patients. In an early study of 33 patients with congestive cardiomyopathy, there was a tendency for the QRS duration to increase during the course of the disease. 11 Senni and colleagues reported the clinical characteristics and natural history in 216 patients with their first diagnosis of heart failure in a single US county in 1991 12; 88% were older than 65 years and 54% were in NYHA grade III or IV. Fifty patients (23%) had either left bundle branch block or an intraventricular conduction delay which was predictive of a left ventricular ejection fraction of less than 50%. Overall survival was 86% at three months, 76% at one year, and 35% at five years.

In the present study in patients with NYHA grade III heart failure and documented VT or VF, the prevalence of conduction abnormalities was 16% (26 of 165 patients). Stellbrink and colleagues retrospectively analysed data from 384 patients for NYHA class, QRS duration, and incidence of atrial fibrillation at the time of ICD implantation. 13 Patients with advanced congestive heart failure were older and had an increased QRS duration; 33% of patients with NYHA grade III heart failure had a QRS duration of ≥ 120 ms, and 37% (48 of 129 patients) had a QRS width of ≥ 150 ms—somewhat higher than the 16% in the present study.

Possible clinical consequences of ventricular asynchrony include abnormal interventricular septal wall motion, a reduction in the peak rate of rise of left ventricular pressure, reduced diastolic filling times, and prolonged duration of mitral regurgitation. 14 Within the subgroup of patients with a depressed left ventricular ejection fraction (≤ 35%), the presence of an increased QRS duration was associated with a greater cardiac mortality. Several studies that have included signal averaging methods have shown that an increased QRS duration of the filtered QRS complex identifies postmyocardial infarction patients at risk of arrhythmic death. 20-23 In addition, the GUSTO-I investigators analysed the initial ECG at the time of acute infarction to predict all-cause mortality. 24 An increased QRS duration in the presence of acute anterior infarction was predictive of mortality (odds ratio 1.55). In the cardiac arrhythmia suppression trial (CAST), Josephson and colleagues recently analysed multiple variables to predict mortality of patients with poor left ventricular function. Along with previous coronary bypass grafting, basic heart rate, and diastolic blood pressure, QRS duration was a strong and simple predictor of mortality. The prognostic value of QRS width—a simple, non-invasive, and reliable index in ICD recipients—has not yet been analysed. Thus, independently of NYHA functional status and impairment of left ventricular function, QRS width is a marker of increased cardiac mortality in ICD recipients. This has not been reported previously, despite assessments of the effects of variables predicting outcome in ICD recipients.

Sheldon and colleagues recently undertook a retrospective analysis of the Canadian implantable defibrillator study (CIDS) to predict those patients who might benefit most from an ICD. 25 In the group at highest risk, there was a 50% relative reduction of mortality in patients fitted with ICDs. Patients who were most likely to benefit from an ICD could be identified by a simple risk score (two or more of the following risk factors): age ≥ 70 years, left ventricular ejection fraction ≤ 55%, and NYHA class III or IV. Thirteen of 15 deaths prevented by the ICD occurred in patients with two or more risk factors. The implications of these findings regarding clinical selection of patients for ICD and the cost-effectiveness of using expensive ICD therapy primarily in the group of patients at highest risk are self evident. The findings from the CIDS group are in agreement with a recent paper by Domanowski and colleagues from the AVID investigators. 26 The AVID data indicate that patients with a relatively well preserved ejection fraction (≥ 35%) do not have better survival when treated with the ICD than with antiarrhythmic drugs. However, in patients with a lower ejection fraction, the ICD was associated with improved survival. Relatively improved survival occurred in patients with an ejection fraction in the range of 20–34%, as well as in those with a value of less than 20%, although in the latter group this difference was non-significant.
In MADIT (multicenter automatic defibrillator implantation trial), Moss reported an increased benefit of the ICD over conventional medical treatment in the subgroup of patients with an EF ≤ 26%, as opposed to those with a value between 26–35%. The eligibility criteria for MADIT were an ejection fraction of ≤ 35% and non-sustained VT on Holter monitoring (primary prevention study). It should be mentioned that in MADIT, as in our study, there was a disparity in β blocker use between the subgroups. Böcker and colleagues also showed a substantial benefit of ICD treatment in patients with more advanced heart failure, using hypothetical event calculations based on recurrence of potentially lethal VT/VF (fast VT ≥ 240 beats/min). Thus patients with moderate to severe left ventricular dysfunction obtained the greatest benefit from ICD treatment.

Although mortality generally increases with increasing NYHA functional class, the proportion of deaths that are sudden declines from 50–80% in class II to 30% in class IV. The sicker patients are more likely to die from progressive heart failure than from suddenly fatal bradycardiac rhythms or electro-mechanical dissociation. As the various mechanisms of death have different frequencies depending on the severity of the heart failure, the prediction of arrhythmic deaths in such patients is difficult. In the present study, an increased QRS duration identified patients with increased cardiac mortality in the presence of depressed left ventricular function. This finding has implications for the selection of patients who will benefit from an ICD over time; for stratifying those patients eligible for heart transplantation at the time of implantation if no further contraindications exist; and for implementation of biventricular pacing devices combined with ICD treatment in patients with heart failure.

Recent preliminary acute and short term studies employing pacing (either biventricular or left ventricular) have shown a significant clinical improvement in patients with heart failure. Although the long term outcome of pacing therapy in heart failure is presently being assessed in prospective controlled studies, the data from our analysis indicate that the influence of biventricular pacing on mortality is probably best studied in patients with heart failure and documented VT or VF, as the overall event rates in patients with an increased QRS duration are high. Thus relatively small numbers of patients would need to be included in a prospective trial to gain a better understanding of the role of biventricular pacing in improving the prognosis in patients with heart failure.

**Limitations**

The total number of patients available for analysis was small in the light of recently published large prospective defibrillator trials. However, even with these limited numbers of patients, statistically meaningful outcome data could be provided. Only 17% of the patients included in the analysis had dilated cardiomyopathy and the majority of cases (73%) had coronary artery disease. As yet, we do not know whether these data are applicable to patients with dilated cardiomyopathy.

Dynamic changes of QRS duration over time were not analysed in the present study. The absence of serial measurements (progression of disease) limits the clinical applicability.

Medical treatment with β blockers (26%) and angiotensin converting enzyme inhibitors (73%) was being given at the time of ICD implantation. Although there were no significant differences in drug treatment on discharge within the two subgroups, the low β blocker use in this heart failure cohort may be a cause for concern.

**Conclusions**

Our study suggests that an increased QRS duration is a positive predictor of cardiac death in patients with NYHA functional class III heart failure and documented VT or VF. This simple, non-invasive, and easily measured index may help to determine the cost effectiveness of ICDs in the secondary prevention of sudden and cardiac death in patients with heart failure.

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Patients with β thalassaemia major are dependent upon regular blood transfusions, and consequently are subject to a large iron load. Accumulation of excess iron leads to heart failure. Iron chelation therapy can delay this process, but compliance is commonly poor. Severe cardiac failure in iron overloaded patients with β thalassaemia major has previously been reported as being invariably fatal.

A 21 year old man with β thalassaemia major was admitted with breathlessness. Examination revealed tachycardia, hypertension, and tachypnoea. He had a third heart sound, ankle oedema, raised venous pressure, smooth hepatomegaly, and dullness at the right base. Chest x ray showed cardiomegaly and a right pleural effusion. Ferritin was notably elevated (> 5000 µg/l). ECG showed sinus tachycardia. An echocardiogram (below left) showed severe left ventricular impairment (ejection fraction < 20%).

Despite diuretics the patient continued to decline. Inotrope and high dose desferrioxamine (70 mg/kg/day) intravenous infusions were initiated. He showed clinical improvement, inotropes were withdrawn after nine days, and he was eventually discharged home on oral frusemide (furosemide), spironolactone, ramipril, and chelation therapy (subcutaneous desferrioxamine and oral deferiprone).

Four months post-presentation he underwent cardiac T2* magnetic resonance imaging, which showed severe iron overload (cardiac T2* 9.1 ms; normal range 20–83 ms). After three months his cardiac T2* improved marginally (9.7 ms), and his ejection improved to within the normal range (57%, below right).

This case demonstrates that patients with severe cardiac failure caused by transfusional iron overload should receive full treatment including inotropic support since recovery is possible. High dose chelation therapy probably contributes to this improvement.

**Images in Cardiology**

β Thalassaemia major and severe left ventricular dysfunction

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