Impact of Viability, Ischemia, Scar Tissue, and Revascularization on Outcome After Aborted Sudden Death

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Background—Survivors of aborted sudden death attributable to ventricular arrhythmias in the presence of coronary artery disease are at risk for recurrences. The substrate underlying these arrhythmias is not clear, and therefore the relation between ischemia, viability, scar tissue (and revascularization), and the incidence of ventricular arrhythmias (and survival) was studied over up to 3 years.

Methods and Results—One hundred fifty-three survivors of sudden death underwent stress-rest perfusion imaging. Patients with ischemic/viable myocardium (n=73) were revascularized if possible. Final antiarrhythmic therapy was based on the outcome of electrophysiological testing or left ventricular ejection fraction (LVEF). Implantation of a defibrillator was performed in 112 (72%) patients. During 3-year follow-up, 15 cardiac deaths occurred and 42 (29%) patients had recurrent ventricular arrhythmias. Patients with events (death or recurrence) exhibited more often a severely depressed LVEF (≤30%), more extensive scar tissue, and less ischemic/viable myocardium on perfusion imaging and less frequently underwent revascularization. Multivariate analysis identified extensive scar tissue and LVEF ≤30% as the only predictors of death/recurrent ventricular arrhythmias.

Conclusions—In patients with aborted sudden death, extensive scar tissue and severely depressed LVEF are the only predictors of death or recurrent ventricular arrhythmias. These patients should be considered for implantation of a defibrillator. (Circulation. 2003;108:1954-1959.)

Key Words: ischemia • arrhythmia • death, sudden
apy included implantation of a defibrillator, catheter ablation of ventricular tachycardia (VT), or antiarrhythmic drugs. Patients with VT or ventricular fibrillation (VF) in the setting of an acute infarction (<48 hours) were excluded.

**SPECT Imaging**

**Data Acquisition**
The stress protocol included a symptom-limited treadmill exercise test. β-blocking agents and calcium channel antagonists were discontinued at least 24 hours before scintigraphy. Test end points were physical exhaustion, dyspnea, angina, significant decrease in blood pressure (>10 mm Hg), or achievement of maximum age-related heart rate. Blood pressure, heart rate, and electrocardiographic findings were monitored during the test. Technetium-99m tetrofosmin (500 MBq) was injected intravenously at peak exercise, which was continued for 1 minute after tracer injection. In patients unable to exercise (n=67), adenosine stress was used. On the second day, resting images were obtained (using 500 MBq technetium-99m tetrofosmin) after the patient’s daily dose of nitrates. The resting studies were acquired using ECG gating, allowing assessment of LVEF.15

Imaging was performed using a triple-head SPECT camera system (GCA 9300/HG, Toshiba Corp) equipped with low-energy general-purpose collimators. A 20% window was used around the 140-keV energy peak of technetium-99m tetrofosmin. A total of 90 projections (step and shoot mode, 35 seconds per projection, imaging time 23 minutes) were obtained over a 360-degree circular orbit. Data were stored in a 64×64, 16-bit matrix. The raw scintigraphic data were reconstructed by filtered back projection using a Butterworth filter (cutoff frequency at 0.17 cycles per pixel, of order 3.5). No attenuation correction was used.

**Data Analysis and Tissue Characterization**
Additional reconstruction yielded standard long- and short-axis projections perpendicular to the heart axis. Reconstructed slices were 8 mm in all projections. The short-axis slices were displayed in polar map format, adjusted for peak myocardial activity (100%). The myocardium was divided into 17 segments, as recently proposed.16 Segmental tracer activity was expressed as percentage of maximum. Perfusion defects on stress images were considered present when tracer activity was <75% of maximum. Significant fill-in (>10%) of perfusion defects was observed on the resting images, segments were classified as ischemic.17 Segments without fill-in were classified as viable when activity on the resting images was ≥50%.18 Ischemic and viable segments were combined and classified as jeopardized myocardium. Segments were classified as scar tissue when tracer activity on the resting images was <50%.18 Myocardial segments were subsequently allocated to the vascular territories according to recent guidelines.16

Patients were scored as having ischemic or viable tissue (jeopardized myocardium) or having scar tissue. Because nearly all patients exhibited some extent of scar tissue, patients were classified as having extensive scar tissue (>1 vascular territory) or small areas of scar tissue (≤1 vascular territories). LVEF was calculated from the gated SPECT images using commercially available automated software.13

**Long-Term Follow-Up**
Long-term follow-up was assessed by outpatient visits and chart review. Follow-up data were acquired up to a maximum of 3 years. Events included cardiac death (including sudden cardiac death and death attributable to ongoing heart failure) and recurrences of ventricular arrhythmias (documented cardiac arrest, VF/sustained VT). Moreover, in patients who underwent implantable cardioverter defibrillator (ICD) implantation, device discharges (based on VT/VF) were evaluated and included as recurrent ventricular arrhythmias. Only the first event was taken into account for statistical analysis.

**Statistical Analysis**
Continuous data are presented as median value and corresponding interquartile range (ie, 25th to 75th percentile of the distribution), and dichotomous data are presented as numbers and percentages. Differences between patient subgroups were evaluated by Wilcoxon tests, Kruskal-Wallis tests, and χ2 tests, as appropriate. The method of Kaplan-Meier was applied to describe and evaluate the incidence of the primary end point (cardiac death or recurrence) over time, and differences in event rate between patient subgroups were evaluated by log-rank tests. Univariable and multivariable Cox proportional hazards regression analyses were performed to evaluate the relation between age, gender, LVEF, prevalence of jeopardized or scar tissue, and treatment with coronary revascularization and the incidence of death or recurrence during long-term follow-up. All variables that were significant (P<0.05) in the univariable analysis were entered in the multivariable model. The multivariable model also included an interaction term between the prevalence of jeopardized myocardium and treatment with coronary revascularization. P<0.05 was considered significant.

**Results**

**Study Population**
A total of 156 survivors (132 men, mean age 63 ± 10 years) of nonfatal cardiac arrest were included in the study. The presenting arrhythmia was VF in 84 (54%) and VT in 72 (46%). Most (143, 92%) had a previous infarction (>2 months before study entrance). At presentation, 8 (5%) had creatine kinase-MB levels that were slightly elevated (maximum, 38 U/L), possibly indicating minimal myocardial damage.

Based on the inclusion criteria, all patients showed significant coronary artery disease on coronary angiography, and they had on average 2.0±0.8 stenosed coronary arteries. The mean LVEF was 40±19%, and 66 (42%) patients had a LVEF ≤30%.

All patients underwent stress-rest perfusion scintigraphy. Jeopardized myocardium was present in 73 (47%) patients, and subsequent revascularization was performed in 44 (60%) patients. Most revascularized patients (27, 61%) underwent coronary artery bypass grafting, whereas the remaining 17 (39%) underwent percutaneous transluminal coronary angioplasty. The decision for revascularization was based on the clinical data, combined with the presence of jeopardized myocardium; 29 (19%) patients with jeopardized myocardium did not undergo revascularization because of comorbidity or poor target vessel quality (not suited for coronary revascularization). Final therapy was based on the outcome of electrophysiologic testing or LVEF. Implantation of a defibrillator was performed in 112 (72%) patients. In addition, 21 (13%) patients underwent radiofrequency catheter ablation of VTs, and 81 (52%) patients received antiarrhythmic medication.

**Survival and Ventricular Arrhythmias**
During a median follow-up period of 26 months (25th to 75th percentile, 6 to 36 months), 15 (10%) patients died; cardiac death occurred in 11 (7%) patients. The cardiac deaths were sudden cardiac death in 1 patient and death attributable to (ongoing) heart failure in 10 (91%) patients.

The 3-year survival rate was 86%. Recurrences of ventricular arrhythmias occurred in 42 (27%) patients. Most of these recurrences (36, 86%) occurred in patients who underwent...
ICD implantation. A composite end point was reached in 50 patients (42 recurrences, 8 deaths; i.e., 7 patients died after a recurrence). Patients with recurrences had comparable QRS duration compared with patients without recurrences (112±84 versus 106±67 ms, NS).

Findings on SPECT

Segments
In the 156 patients, 2652 segments were analyzed. Of these, 748 exhibited a defect on the stress perfusion images. Ischemia was observed in 174 (23%) segments. Of the remaining 574 segments with a fixed defect, 217 (29%) showed ≥50% tracer uptake and were classified as viable, whereas 357 (48%) had <50% tracer uptake and were classified as scar tissue.

Patients
Of the 156 patients, 111 (71%) exhibited extensive scar tissue, and 73 (47%) had jeopardized myocardium.

Predictors of Death or Recurrences
Baseline characteristics of patients with and without events (death or recurrences) are shown in the Table. Patients with events had a significantly lower LVEF, more frequently had scar tissue, less frequently had jeopardized myocardium, and less frequently underwent revascularization. Univariable analysis identified these last 4 characteristics as predictors of events (Figures 1 through 4). The event curves of patients with and without revascularization are shown in Figure 1. A significantly higher event rate was observed in patients who did not undergo revascularization (53% versus 15%, P<0.05).

As displayed in Figure 2, the event rate was 54% in the patients with extensive scar tissue compared with 16% (P<0.05) in patients without or with small areas of scar tissue (≤1 vascular territory). Patients with jeopardized myocardium had a significantly lower event rate compared with patients without jeopardized myocardium (30% versus 55%, P<0.05, Figure 3). Finally, patients with severely depressed LVEF (≤30%) had a significantly higher event rate compared with patients with LVEF >30% (59% versus 33%, P<0.05).

Thus, revascularization and the presence of jeopardized myocardium were beneficial on univariable analysis, whereas extensive scar tissue and LVEF ≤30% were harmful (Figure 5A, □). The finding that jeopardized myocardium was beneficial was unexpected. However, patients with jeopardized myocardium underwent revascularization when possible. When the patients with jeopardized myocardium only were analyzed according to the treatment, it seemed that the event rate was significantly higher in patients with jeopardized myocardium who did not undergo revascularization (38%) compared with the patients with jeopardized myocardium who underwent revascularization (14%, P<0.05).

Multivariable analysis identified LVEF ≤30% (hazard ratio, 2.0; 95% CI, 1.1 to 3.5; P=0.02) and the presence of extensive scar tissue (hazard ratio, 2.4; 95% CI, 1.0 to 5.9; P=0.05) as the only 2 independent predictors of events (Figure 5, left, □).

The survival analysis was repeated when only arrhythmic death (and recurrences) were used as the combined end point (and heart failure deaths were excluded); the results of the univariable and multivariable analysis were similar (Figure 5, right) and confirmed that, on multivariable analysis, LVEF ≤30% (hazard ratio, 2.4; 95% CI, 1.2 to 4.4; P<0.09) and the presence of extensive scar tissue (hazard ratio, 4.2; 95% CI, 1.3 to 14; P=0.02) were the only 2 independent predictors of events.

Baseline Characteristics of Patients With and Without Events

<table>
<thead>
<tr>
<th></th>
<th>Alive and No Recurrence</th>
<th>Death or Recurrence</th>
<th>Arrhythmic Death or Recurrence</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>106</td>
<td>50</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Age, median, y (IQR)</td>
<td>64 (55–71)</td>
<td>67 (61–70)</td>
<td>66 (60–70)</td>
<td>0.28</td>
</tr>
<tr>
<td>Male gender, %</td>
<td>85</td>
<td>84</td>
<td>81</td>
<td>0.88</td>
</tr>
<tr>
<td>LVEF, median (IQR)</td>
<td>35% (25–55)</td>
<td>30% (25–45)</td>
<td>30% (25–45)</td>
<td>0.020</td>
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<tr>
<td>Revascularization, %</td>
<td>35.9</td>
<td>12.0</td>
<td>12.0</td>
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<tr>
<td>Extensive scar, %</td>
<td>63.2</td>
<td>88.0</td>
<td>93.0</td>
<td>0.001</td>
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<tr>
<td>Jeopardized myocardium, %</td>
<td>52.8</td>
<td>34.0</td>
<td>31.0</td>
<td>0.028</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range.

The P values concern the comparison between variables in columns 1 and 2.

Figure 1. Three-year event curves according to revascularization treatment. Patients who underwent revascularization (n=44) had a significantly lower event rate compared with patients who were treated medically (n=112).
Discussion
The present study evaluated, in survivors of out-of-hospital cardiac arrest, the interaction between ischemia, viability, scar tissue, and revascularization on the one hand and survival and recurrences of ventricular arrhythmias on the other hand. The results indicated that, in a multivariable model, extensive scar tissue and LVEF ≤30% were the only predictors of events.

Events
Most (91%) cardiac deaths were attributable to heart failure, whereas only 1 sudden cardiac death occurred. However, because 86% of the recurrences occurred in patients who underwent ICD implantation, the likelihood of sudden cardiac death would have been high when patients would not have received an ICD. Previous studies focusing on ischemia, viability, scar tissue, and long-term survival were not capable of distinguishing between these modes of deaths, but because of the presence of the ICD, the present study is the first to provide information on mode of death in these patients. This is probably also the explanation for the relatively low death rate in the present study compared with earlier studies. The main question is whether these recurrences were caused by jeopardized myocardium or scar tissue.

Ischemia, Viability, and Scar Tissue Versus Treatment and Prognosis
The beneficial effect of revascularization of ischemic myocardium has been demonstrated in large studies. Indeed, revascularization of ischemic myocardium resulted in superior survival, as evidenced by the results from the CASS and European Coronary Surgery Study Group. More recently, focus has shifted toward the importance of viable myocardium.

Figure 2. Three-year event curves according to the presence or absence of extensive scar tissue on SPECT. Patients without extensive scar tissue (n=45) had a significantly lower event rate compared with patients with extensive scar tissue (n=111).

Figure 3. Three-year event curves according to the presence and absence of jeopardized myocardium on SPECT. Patients with jeopardized myocardium (n=73) had a significantly lower event rate compared with the patients without jeopardized myocardium (n=83).

Figure 4. Three-year event curves according to the LVEF; patients with severely depressed LVEF (≤30%, n=66) had a significantly higher event rate compared with patients with LVEF >30% (n=90).

Figure 5. Left, Results of univariable (●) and multivariable (□) analyses to identify predictors of events (cardiac [heart failure and arrhythmic] death, recurrences). In the univariate model, extensive scar tissue, jeopardized myocardium, revascularization, and LVEF were predictive, whereas in the multivariate model, only LVEF and the presence of extensive scar tissue remained predictive. Right, Results of univariable (●) and multivariable (□) analyses to identify predictors of events (arrhythmic death, recurrences). In the univariate model, extensive scar tissue, jeopardized myocardium, revascularization, and LVEF were predictive, whereas in the multivariate model, only LVEF and the presence of extensive scar tissue remained predictive.
Various studies have shown that revascularization of dysfunctional but viable myocardium resulted in improvement of contractile function. However, not all patients with viable myocardium exhibited improvement in function after revascularization. Still, patients with viable myocardium who underwent revascularization had an excellent survival. In contrast, an extremely high event rate was observed in patients with viable myocardium who were treated medically. Pooling of the available studies revealed an annual death rate of 16% among patients with substantial viable tissue who did not undergo revascularization. Based on these observations, additional benefits of revascularization of viable myocardium were considered. In particular, the prevention of ventricular arrhythmias was considered an explanation for the beneficial effect of revascularization of viable myocardium. This issue has not been studied previously and was addressed in the present study. Patients with ischemia or viable myocardium were grouped and referred to as having jeopardized myocardium. To our surprise, patients with jeopardized myocardium had a lower event rate compared with patients without jeopardized myocardium. However, when treatment was considered, it seemed that patients with jeopardized myocardium who underwent revascularization had a low event rate (13%) whereas patients with jeopardized myocardium who were treated medically had a significantly higher event rate (38%). These findings confirm the suggestion that revascularization of jeopardized myocardium is needed to avoid events. It has been suggested previously that jeopardized myocardium may provide an unstable substrate and that revascularization may result in electrical stability.

Of interest, the presence of extensive scar tissue was another strong predictor of events. Moreover, severely depressed LVEF was also a predictor of events. These 2 parameters are both reflecting the severity of (infarct) damage of the LV. Previous studies have already indicated that scar tissue and depressed LVEF were important predictors of events. Macheouriet al performed a long-term follow-up study (33±10 months) in 1926 patients and clearly showed the relation between the extent of defects on thallium-201 imaging and survival. The authors demonstrated that the probability of cardiovascular mortality was 0.24% in patients without perfusion defects, 6% in patients with perfusion defects extending to 3 segments, and 17% in patients with defects extending to ≥4 segments (67% of the LV). Recent data by Hachamovitch et al also demonstrated an increasing event rate that paralleled the increasing abnormalities on perfusion imaging. In addition, Shariri et al have recently emphasized again the strong prognostic value of LVEF (in that study derived from gated SPECT data).

Another finding in the present study was that on multivariable analysis, only LVEF and extensive scar tissue remained predictive. These findings suggest that for long-term risk stratification, viability or ischemia may not be that important. However, in the present study, revascularization and the presence of jeopardized myocardium were interrelated, which makes definitive conclusions difficult. Additional, randomized (to treatment) trials are needed to draw definitive conclusions concerning this issue.

Limitations

Several limitations of the present study need to be addressed. First, although the data were collected in a prospective manner, randomization to treatment (revascularization versus medical therapy) is lacking and future studies (eg, the STICH Trial) may provide additional insight in these complex issues. Second, viability and ischemia were grouped as jeopardized myocardium. However, from a pathophysiologic point of view it may be difficult to separate these entities exactly, because it is likely that ischemia and viability are parts of a continuum of damage in ischemic heart disease. Moreover, from a scintigraphic point of view, it may be difficult to separate these issues exactly, because many segments contain viable myocytes that also suffer from ischemia (segments with tracer uptake ≥50% and reversible defects). In addition, 5% of patients presented with minimally elevated creatine kinase-MB levels at the index event. It cannot be ruled out that some viable myocardium progressed to scar tissue and that, at the time of the SPECT study, only scar tissue could be detected. This may have influenced the results in the present study. Finally, assessment of viability with technetium-99m tetrofosmin may slightly underestimate the presence of viable tissue, as demonstrated in direct comparisons with positron emission tomography and F18-fluorodeoxyglucose.

Clinical Implications and Conclusion

The findings in present study highlight the importance of scintigraphic evaluation of patients with aborted sudden death and coronary artery disease. Gated SPECT imaging allows assessment of ischemia, viability, scar tissue, and LVEF. These aspects are important in the evaluation of these patients. In the presence of jeopardized myocardium, an attempt at revascularization should be made, because revascularization of jeopardized myocardium was associated with a low event rate. In addition, patients with extensive scar tissue and LVEF ≤30% are at high risk for recurrences, and ICD implantation may be preferred in these patients. ICD implantation will prevent sudden cardiac death, as illustrated in the present results. Finally, the next step in treatment of these patients will be focusing on treatment options for heart failure, because most (>90%) patients died of ongoing heart failure.

References


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