Implantable cardioverter defibrillator treatment : benefits and pitfalls in the currently indicated population

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Chapter 9

Cardiac Sympathetic Denervation Assessed with 123-Iodine Metaiodobenzylguanidine Imaging Predicts Ventricular Arrhythmias in Implantable Cardioverter-Defibrillator Patients

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Abstract

Objectives To evaluate whether 123-iodine metaiodobenzylguanidine (123-I MIBG) imaging predicts ventricular arrhythmias causing appropriate implantable cardioverter-defibrillator (ICD) therapy (primary endpoint) and the composite of appropriate ICD therapy or cardiac death (secondary endpoint).

Background Although cardiac sympathetic denervation is associated with ventricular arrhythmias, limited data are available on the predictive value of sympathetic nerve imaging with 123-I MIBG on the occurrence of arrhythmias.

Methods Before ICD implantation, patients underwent 123-I MIBG and myocardial perfusion imaging. Early and late 123-I MIBG (planar and SPECT) imaging was performed to assess cardiac innervation (heart-to-mediastinum ratio, cardiac washout rate and 123-I MIBG SPECT defect score). Stress-rest myocardial perfusion imaging was performed to assess myocardial infarction and perfusion abnormalities (perfusion defect scores). During follow-up, appropriate ICD therapy and cardiac death were documented.

Results One-hundred sixteen heart failure patients referred for ICD therapy were enrolled. During a mean follow-up of 23±15 months, appropriate ICD therapy (primary endpoint) was documented in 24 (21%) patients and appropriate ICD therapy or cardiac death (secondary endpoint) in 32 (28%) patients. Late 123-I MIBG SPECT defect score was an independent predictor for both endpoints. Patients with a large late 123-I MIBG SPECT defect (summed score >26) showed significantly more appropriate ICD therapy (52% vs. 5%, $p<0.01$) and appropriate ICD therapy or cardiac death (57% vs. 10%, $p<0.01$) than patients with a small defect (summed score ≤26) at 3-year follow-up.

Conclusions Cardiac sympathetic denervation predicts ventricular arrhythmias causing appropriate ICD therapy as well as the composite of appropriate ICD therapy or cardiac death.

Introduction

Sudden cardiac death (SCD) represents a leading cause of death in the developed world with an estimated annual incidence of 300.000 to 350.000 patients in the United States.[1] Implantable cardioverter-defibrillator (ICD) treatment is well established in patients at high risk for arrhythmic death. Initially, ICD treatment was indicated in survivors of sustained ventricular tachycardia or ventricular fibrillation and more recently, in a population at high risk, regardless of prior ventricular tachyarrhythmias.[2,3] Based on large randomized trials, current guidelines recommend ICD treatment based solely on a poor left ventricular (LV) systolic function with or without nonsustained ventricular tachycardia as a class I indication.[4]

Post-hoc analysis of the second Multicenter Automated Defibrillator Implantation Trial (MADIT II) population showed that only 35% of patients received appropriate ICD therapy after 3-year follow-up.[5] Additionally, the majority of arrhythmic deaths occurs in a population without ICD indication.[6] Although the benefits of ICD treatment have been demonstrated, the question has been raised whether improvements in patient selection can be made.

Dysfunction of the autonomic nervous system (which can be assessed with 123-iodine metaiodobenzylguanidine (123-I MIBG) imaging) is thought to play an important role in the development of ventricular tachyarrhythmias.[7,8] Observational studies have demonstrated that cardiac denervation (as evidenced by reduced 123-I MIBG uptake) is associated with the occurrence of ventricular tachyarrhythmias.[9,10] Moreover, it was recently shown that inducibility of ventricular tachyarrhythmias was related to regional cardiac sympathetic denervation as assessed with 123-I MIBG imaging.[10]

At present, limited data are available on the role of 123-I MIBG imaging for prediction of ventricular arrhythmias. Moreover, the value of 123-I MIBG imaging in identification of patients who may benefit from ICD treatment is unclear. Accordingly, this study evaluated the role of cardiac sympathetic nerve imaging with 123-I MIBG for the prediction of ventricular arrhythmias causing appropriate ICD therapy (primary endpoint) and the composite of appropriate ICD therapy or cardiac death (secondary endpoint).

Materials and methods

Patient population and protocol

The patient population consisted of consecutive advanced heart failure patients undergoing cardiac 123-I MIBG imaging for heart failure risk stratification. The patients were clinically referred for ICD implantation based on poor LV function with or without nonsustained ventricular tachycardia (primary prevention) or prior sustained ventricular tachycardia or ventricular fibrillation (secondary prevention).[4]

Prior to ICD implantation, 123-I MIBG imaging and gated myocardial perfusion single photon emission computed tomography (SPECT) imaging with 99m-technetium tetrofosmin (^{99m}Tc-tetrofosmin) were performed in all patients. 123-I MIBG imaging was clinically performed to assess cardiac sympathetic innervation for risk stratification of heart failure patients.[11] Stress-rest myocardial perfusion imaging was performed to assess myocardial infarction (location and extent) and perfusion abnormalities (ischemia).

During follow-up, ventricular arrhythmia with subsequent ICD therapy (appropriate ICD therapy) and cardiac mortality were documented. The occurrence of primary endpoints (appropriate ICD therapy) and secondary endpoints (the composite of appropriate ICD therapy or cardiac death) was assessed for all patients. Subsequently, the value of 123-I MIBG and myocardial perfusion imaging variables in the prediction of endpoints was studied.

123-I MIBG imaging

Patients were pretreated with 120 mg sodium iodide to block uptake of free iodine-123 by the thyroid gland. Sodium iodide was given orally one hour before intravenous administration of 185 MBq 123-I MIBG (General Electric Healthcare, UK). 123-I MIBG planar and SPECT imaging was performed in supine position. A 10-minute planar image was acquired from an anterior thoracic view (256 x 256 matrix) 10-15 minutes after tracer administration.

Thereafter, a SPECT study (step and shoot mode, 90 projections, imaging time 30 minutes) was performed using a dual-head camera system (GCA-7200, Toshiba Corp., Tokyo, Japan) equipped with low-energy, parallel-hole high-resolution collimators. A 128 x 128 matrix was used for SPECT studies and a 20% energy peak was centered around the 159-keV energy peak of 123-I MIBG. Planar and SPECT imaging were repeated after 3-4 hours after tracer administration.

Heart-to-mediastinum (H/M) ratio was calculated from planar imaging using manual drawn regions of interest (7 x 7 pixels), placed over the entire heart and upper mediastinum.[10]

123-I MIBG SPECT studies were processed with filtered back-projection and reconstructed into standard long- and short-axis, perpendicular to the heart axis.[12] Data analysis was performed by 2 blinded and independent observers. Three late SPECT studies were uninterpretable and excluded from evaluation of late 123-I MIBG SPECT imaging.

From planar images, the H/M ratio was computed by dividing the mean counts per pixel within the myocardium by the mean counts per pixel within the mediastinum. H/M ratio was computed for early and late planar imaging. Cardiac washout rate was calculated using the following formula: [(early H/M ratio) – (delayed H/M ratio)] / (early H/M ratio) x 100. No background correction was performed in this study.

From SPECT images, the 123-I MIBG SPECT defect score was calculated by assessment of patient's segmental 123-I MIBG tracer uptake score using the 17-segment model.[12]

Each myocardial segment was scored according to the following tracer uptake scale: 0 = normal tracer uptake, 1 = mildly reduced tracer uptake, 2 = moderately reduced tracer uptake, 3 = severely reduced tracer uptake, 4 = no tracer uptake. Subsequently, the 123-I MIBG SPECT defect score was calculated by summation of segmental tracer uptake scores. The 123-I MIBG SPECT defect score was calculated for early and delayed SPECT imaging.

Gated myocardial perfusion SPECT

Stress-rest gated myocardial perfusion SPECT imaging with ^{99m}Tc-tetrofosmin (500 MBq, MYOVIEW, General Electric Healthcare, United Kingdom) was performed as previously described.[13] Myocardial perfusion images were analyzed by 2 blinded observers.

The myocardium was divided into 17 segments and patient's segmental perfusion score was assessed using a similar tracer uptake scale as used for 123-I MIBG images.[12] The rest perfusion defect score was calculated by summation of segmental perfusion scores on resting myocardial perfusion imaging. Stress perfusion defect score was calculated by summation of segmental perfusion scores on stress myocardial perfusion imaging. Accordingly, both rest and stress perfusion defect scores could range from 0 to 68 (17 x 4) points. Subsequently, the summed perfusion difference score (indicating the extent of reversible myocardial perfusion defects) was calculated by subtracting the rest perfusion defect score from the stress perfusion defect score. Finally, the 123-I MIBG/perfusion mismatch score was calculated by subtracting the rest perfusion defect score from the late 123-I MIBG SPECT defect score.

ICD implantation

ICDs were implanted transvenously and without thoracotomy. Testing of sensing and pacing thresholds and defibrillation threshold testing was performed during implantation. In the study population, the following ICDs were used: Entrust, Marquis DR (Medtronic Inc., Minneapolis, Minnesota, United States); Endotak, Vitality 2 (Boston Scientific, Natick, Massachusetts, United States); Epic DR (St. Jude Medical, St. Paul, Minnesota, United States).

In case of patient eligibility for cardiac resynchronization therapy (CRT), a combined CRT-D device (InSync Sentry, Consulta, Medtronic Inc.; Atlas HF, St. Jude Medical; Contak, Contak Renewal, Boston Scientific; Lumax, Biotronik, Berlin, Germany) was implanted.[14]

Clinical follow-up and endpoints

Clinical follow-up was performed by evaluation of device interrogation printouts and patient medical record data every 3 to 6 months.

The primary endpoint was defined as the occurrence of appropriate ICD therapy. Appropriate ICD therapy was defined as anti-tachycardia pacing (ATP) or shock triggered by ventricular tachycardia or ventricular fibrillation. ICD discharges were evaluated at the

outpatient pacemaker clinic using ICD stored electrocardiographic data by 2 experienced electrophysiologists, blinded to other study data.

The secondary endpoint was a combined endpoint consisting of appropriate ICD therapy or cardiac death. Cardiac mortality included death caused by progressive heart failure or acute myocardial infarction.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation, and categorical data are expressed in numbers and percentages. Cox proportional hazards regression analysis was performed to evaluate which variables were associated with the primary or secondary endpoint. At first, univariable analysis of baseline characteristics was performed to determine significant predictors for both endpoints. All variables that were significantly associated with the primary or secondary endpoint at the $p<0.15$ level were included in a multivariable analysis. When early and late 123-I MIBG imaging variables showed strong interrelation (Pearson's correlation coefficient >0.8), early 123-I MIBG imaging variables were excluded from multivariable analysis. Only late 123-I MIBG imaging variables were included in the multivariable analysis as they are the most commonly used 123-I MIBG imaging parameters.[11] For each variable, a hazard ratio (HR) with a 95% confidence interval (CI) was calculated.

Cumulative event rates were assessed using the method of Kaplan-Meier and log rank test. Additionally, late 123-I MIBG SPECT defect score was subdivided using the median value (summed score of 26) as a cutoff. All analyses were two-sided and a p-value <0.05 was considered statistically significant. Statistical analyses were performed with SPSS software package, version 15.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Patient population

A total of 116 patients (80 men, mean age 65±9 yrs) were enrolled. Baseline characteristics of all patients are summarized in Table 1. One-hundred three (89%) patients received an ICD as primary prevention and 13 (11%) patients as secondary prevention for SCD. Eighty-six (74%) patients were diagnosed with ischemic cardiomyopathy and 30 (26%) patients with nonischemic cardiomyopathy. The mean NYHA functional class was 2.9±0.6 and the mean LV ejection fraction was 28±8%. A combined CRT-D device was implanted in 101 patients.

Table 1. Baseline characteristics of the study population (n = 116)

Characteristics	Values
Age (yrs)	65 ± 9
Male gender	80 (69)
CRT-D	101 (87)
ICD indication	
Primary prevention	103 (89)
Secondary prevention	13 (11)
Ischemic cardiomyopathy	86 (74)
NYHA functional class	2.9 ± 0.6
LVEF (%)	28 ± 8
Cardiovascular risk factors	
Diabetes	16 (14)
Hypertension	37 (32)
Hypercholesterolemia	30 (26)
Smoking	31 (27)
Family history of CAD	35 (30)
Medication use	
Beta-blocker	82 (71)
Amiodarone	22 (19)
ACE-I / ATII antagonist	98 (85)
Oral anticoagulant	76 (66)
Statin	79 (68)
Diuretic	102 (88)

Data are represented as mean ± standard deviation or as number (%).
ACE-I = angiotensin converting enzyme - inhibitor; AT = angiotensin; CAD = coronary artery disease; CRT-D = cardiac resynchronization therapy - defibrillator; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

123-I MIBG and myocardial perfusion imaging

Baseline variables of 123-I MIBG and myocardial perfusion imaging are shown in Table 2. Mean values of early and late H/M ratio were 1.58±0.18 and 1.47±0.18. Accordingly, the mean value of cardiac washout rate was 6.80±6.37. Furthermore, the early 123-I MIBG SPECT defect score had a mean value of 21.6±10.1 and the late 123-I MIBG SPECT defect score had a mean value of 26.8±10.0.

The mean rest perfusion defect score was 16.8±10.3, whereas the mean stress perfusion defect score was 18.3±10.6. Accordingly, the mean summed perfusion difference score was 1.7±3.6.

The mean 123-I MIBG/perfusion mismatch score was 9.9±12.3, indicating larger 123-I MIBG defects as compared to perfusion defects (26.8±10.0 vs. 16.8±10.3, $p<0.01$). Figure 1 shows an example of normal resting myocardial perfusion with a defect on late 123-I MIBG SPECT imaging in a patient who received appropriate ICD therapy after 18 months of follow-up.

Table 2. Baseline variables of 123-I MIBG and myocardial perfusion imaging

123-I MIBG imaging	
Early planar H/M ratio	1.58 ± 0.18
Late planar H/M ratio	1.47 ± 0.18
Cardiac washout rate (%)	6.80 ± 6.37
Early 123-I MIBG SPECT defect score	21.6 ± 10.1
Late 123-I MIBG SPECT defect score	26.8 ± 10.0
Myocardial perfusion imaging	
Rest perfusion defect score	16.8 ± 10.3
Stress perfusion defect score	18.3 ± 10.6
Summed perfusion difference score	1.7 ± 3.6
123-I MIBG/perfusion mismatch score	9.9 ± 12.3

Data are represented as mean ± standard deviation. H/M ratio = heart-to-mediastinum ratio; 123-I MIBG = 123-iodine metaiodobenzylguanidine; SPECT = single photon emission computed tomography.

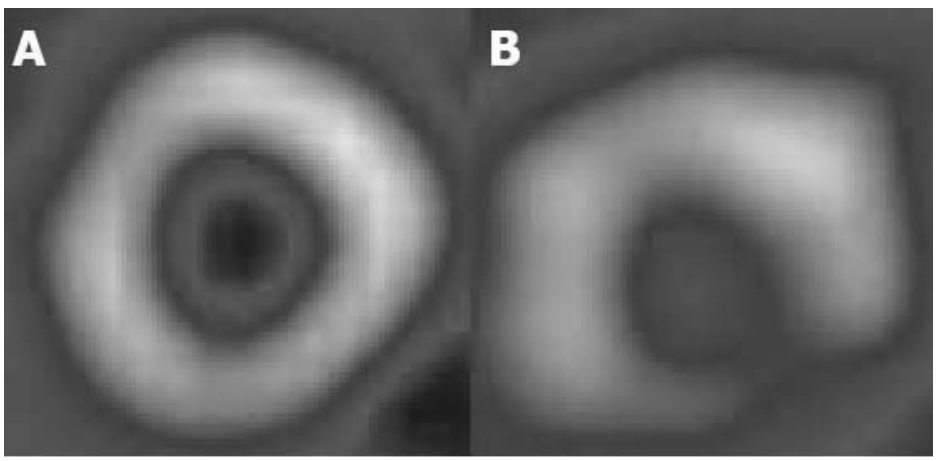


Figure 1. Example of resting myocardial perfusion (panel A) and late 123-I MIBG (panel B) imaging in an ICD patient. In this patient, showing normal myocardial perfusion and abnormal 123-I MIBG imaging, an appropriate ICD therapy (ATP) was documented after 18 months of follow-up.

Primary endpoint: appropriate ICD therapy

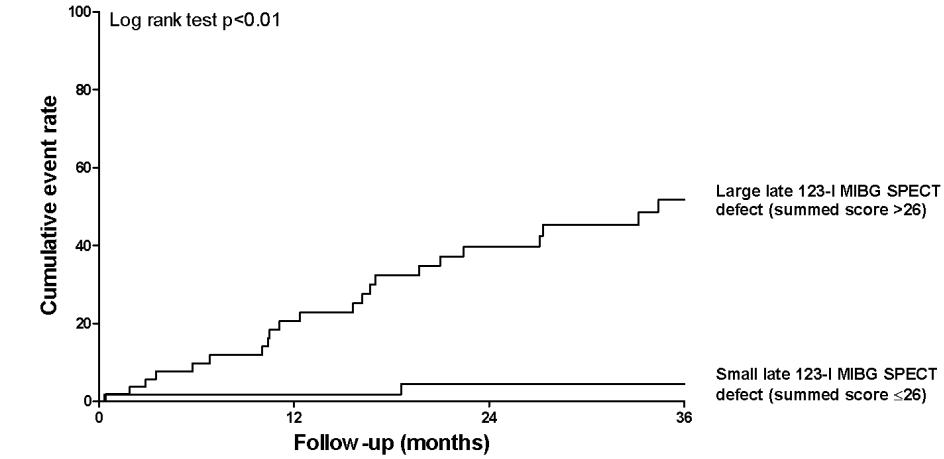
During 23±15 months follow-up, 86 episodes of ventricular tachycardia or ventricular fibrillation were terminated by appropriate ICD therapy in 24 (21%) patients. Appropriate ICD therapy consisted of 44 episodes of ATP in 16 (14%) patients and 42 ICD shocks in 15 (13%) patients.

Univariable analyses demonstrated that ICD indication (secondary vs. primary prevention), ischemic cardiomyopathy, early 123-I MIBG SPECT defect score, late 123-I MIBG SPECT defect score, summed perfusion difference score, and the 123-I MIBG/perfusion mismatch score were significantly associated with appropriate ICD therapy (Table 3). The

Table 3. Univariable and multivariable analyses of baseline variables for appropriate ICD therapy (primary endpoint)

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (yrs)	1.02 (0.98 - 1.08)	0.4		
Male gender	1.52 (0.57 - 4.06)	0.4		
CRT-D	1.15 (0.34 - 3.86)	0.8		
ICD indication (secondary vs. primary prevention)	4.55 (1.95 - 10.65)	< 0.01*	3.85 (1.43 - 10.37)	<0.01**
Ischemic cardiomyopathy	3.16 (0.94 - 10.60)	0.06*	2.10 (0.58 - 7.64)	0.3
NYHA functional class	1.10 (0.54 - 2.24)	0.8		
LVEF (%)	1.02 (0.97 - 1.07)	0.5		
Cardiovascular risk factors				
Diabetes	0.60 (0.14 - 2.54)	0.5		
Hypertension	1.13 (0.48 - 2.65)	0.8		
Hypercholesterolemia	1.08 (0.43 - 2.73)	0.9		
Smoking	1.39 (0.61 -3.19)	0.4		
Positive family history of CAD	0.87 (0.36 - 2.09)	0.7		
Medication use				
Beta-blockade	1.03 (0.43 - 2.47)	1.0		
Amiodarone	1.64 (0.65 - 4.12)	0.3		
ACE-I / ATII antagonist	1.23 (0.37 - 4.14)	0.7		
Oral anticoagulant	0.61 (0.27 - 1.37)	0.2		
Statin	1.45 (0.57 - 3.65)	0.4		
Diuretic	1.13 (0.27 - 4.83)	0.9		
123-I MIBG imaging				
Early H/M ratio	0.35 (0.04 - 3.30)	0.4		
Late H/M ratio	0.27 (0.03 - 2.32)	0.2		
Cardiac washout rate (%)	1.02 (0.95 - 1.09)	0.6		
Early 123-I MIBG SPECT defect score	1.07 (1.03 - 1.12)	<0.01*		
Late 123-I MIBG SPECT defect score	1.14 (1.08 - 1.20)	<0.01*	1.13 (1.05 - 1.21)	<0.01**
Myocardial perfusion imaging				
Rest perfusion defect score	1.02 (0.98 - 1.06)	0.4		
Stress perfusion defect score	1.03 (0.99 - 1.07)	0.2		
Summed perfusion difference score	1.08 (0.98 - 1.20)	0.14*	0.93 (0.83 - 1.05)	0.3
123-I MIBG/perfusion mismatch score	1.06 (1.02 - 1.09)	<0.01*	1.01 (0.97 - 1.06)	0.5

* Significant association with appropriate ICD therapy at a level of $p<0.15$ in univariate analysis. **Significant association with appropriate ICD therapy in multivariate analysis. ACE-I = angiotensin converting enzyme - inhibitor; AT = angiotensin; CAD = coronary artery disease; CRT-D = cardiac resynchronization therapy - defibrillator; H/M ratio = heart-to-mediastinum ratio; 123-I MIBG = 123-iodine metaiodobenzylguanidine; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SPECT = single photon emission computed tomography.



Patients at risk

>26	55	37	24	13
≤26	58	44	31	17

Figure 2. Kaplan-Meier curve analysis showing the difference in appropriate ICD therapy (primary endpoint) between patients with a large (summed score >26) or small (summed score ≤26) late 123-I MIBG SPECT defect.

early 123-I MIBG SPECT defect score was excluded for multivariable analysis as it showed strong interrelation (r=0.82) with the late 123-I MIBG SPECT defect score.

Subsequently, multivariable analysis demonstrated that ICD indication (secondary vs. primary prevention) (HR 3.85, 95% CI 1.43-10.37, p<0.01) and late 123-I MIBG SPECT defect score (HR 1.13, 95% CI 1.05-1.21, p<0.01) were independent predictors for appropriate ICD therapy.

Risk stratification for appropriate ICD therapy

Twenty-two (40%) patients with a large late 123-I MIBG SPECT defect (summed score >26) versus 2 (3%) patients with a small late 123-I MIBG SPECT defect (summed score ≤26) received appropriate ICD therapy (p<0.01).

The cumulative event rate at 3-year follow-up for appropriate ICD therapy was 52% (95% CI 36-68%) for patients with a large late 123-I MIBG SPECT defect versus 5% (95% CI 0-11%) for patients with a small late 123-I MIBG SPECT defect (Figure 2). Appropriate ICD therapy was significantly more often documented in patients with a large late 123-I MIBG SPECT defect when compared to patients with a small late 123-I MIBG SPECT defect during a mean follow-up of 23±15 months (log rank test, p<0.01). Moreover, the risk for appropriate ICD therapy was 13 times higher in patients with a large late 123-I MIBG SPECT defect as compared to patients with a small defect (HR 12.81, 95% CI 3.01-54.50, p<0.01).

Secondary endpoint: appropriate ICD therapy or cardiac mortality

Appropriate ICD therapy or cardiac mortality was documented in 32 (28%) patients. In total, 24 (21%) patients received appropriate ICD therapy and 8 (7%) patients died of progressive heart failure without previous appropriate ICD therapy. In total, cardiac death was documented in 13 (11%) patients, including 5 (4%) patients who received appropriate ICD therapy before cardiac death.

Univariable analysis demonstrated that ICD indication (secondary vs. primary prevention), ischemic cardiomyopathy, delayed H/M ratio, early 123-I MIBG SPECT defect score, late 123-I MIBG SPECT defect score and 123-I MIBG/perfusion mismatch score were significant predictors for the secondary endpoint (Table 4). Since early and late 123-I MIBG SPECT defect score were strongly interrelated ($r=0.82$), early 123-I MIBG SPECT defect score was excluded for multivariable analysis.

Late 123-I MIBG SPECT defect score (HR 1.12, 95% CI 1.05-1.19, $p<0.01$) was the only independent predictor in multivariable analysis.

Risk stratification for appropriate ICD therapy or cardiac mortality

Appropriate ICD therapy or cardiac mortality was documented in 28 (51%) patients with a large late 123-I MIBG SPECT defect (summed score >26) and in 4 (7%) patients with a small late 123-I MIBG SPECT defect (summed score ≤26) ($p<0.01$).

The cumulative event rate at 3-year follow-up for appropriate ICD therapy or cardiac mortality was 57% (95% CI 43-72%) for patients with a large late 123-I MIBG SPECT defect as compared to 10% (95% CI 0-20%) for patients with a small defect (Figure 3). Appropriate ICD therapy or cardiac death was significantly more documented in patients with a large late 123-I MIBG SPECT defect as compared to patients with a small defect during a mean follow-up of 23±15 months (log rank test, $p<0.01$). Moreover, the risk for appropriate ICD therapy or cardiac death was 8 times higher in patients with a large late 123-I MIBG SPECT defect than patients with a small defect (HR 8.29, 95% CI 2.91-23.63, $p<0.01$).

Discussion

The main findings of the study can be summarized as follows. Late 123-I MIBG SPECT defect score was an independent predictor for ventricular arrhythmias causing appropriate ICD therapy (primary endpoint) as well as the composite of appropriate ICD therapy or cardiac death (secondary endpoint). In addition, cumulative event rates for appropriate ICD therapy (52% vs. 5%, $p<0.01$) and appropriate ICD therapy or cardiac death (57% vs. 10%, $p<0.01$) were significantly higher in patients with a large late 123-I MIBG SPECT defect (summed score >26) as compared to patients with a small late 123-I MIBG SPECT

Table 4. Univariable and multivariable analyses of baseline variables for appropriate ICD therapy or cardiac death (secondary endpoint)

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (yrs)	1.02 (0.98 - 1.06)	0.4		
Male gender	1.03 (0.48 - 2.22)	0.9		
CRT-D	1.61 (0.49 - 5.27)	0.4		
ICD indication (secondary vs. primary prevention)	3.06 (1.37 - 6.81)	<0.01*	1.94 (0.81 - 4.63)	0.1
Ischemic cardiomyopathy	2.44 (0.94 - 6.35)	0.07*	1.51 (0.53 - 4.30)	0.4
NYHA functional class	1.24 (0.67 - 2.29)	0.5		
LVEF (%)	1.00 (0.96 - 1.05)	1.0		
Cardiovascular risk factors				
Diabetes	1.53 (0.63 - 3.72)	0.4		
Hypertension	0.89 (0.41 - 1.92)	0.8		
Hypercholesterolemia	1.08 (0.48 - 2.40)	0.9		
Smoking	1.22 (0.59 - 2.53)	0.6		
Positive family history of CAD	0.82 (0.38 - 1.78)	0.6		
Medication use				
Beta-blockade	0.93 (0.44 - 1.97)	0.9		
Amiodarone	1.63 (0.73 - 3.62)	0.2		
ACE-I / ATII antagonist	0.96 (0.37 - 2.50)	0.9		
Oral anticoagulant	0.63 (0.31 - 1.28)	0.2		
Statin	1.23 (0.57 - 2.67)	0.6		
Diuretic	1.54 (0.37 - 6.47)	0.6		
123-I MIBG imaging				
Early H/M ratio	0.25 (0.04 - 1.80)	0.2		
Late H/M ratio	0.17 (0.03 - 1.13)	0.07*	0.79 (0.10 - 6.10)	0.8
Cardiac washout rate (%)	1.03 (0.97 -1.09)	0.3		
Early 123-I MIBG SPECT defect score	1.08 (1.04 - 1.12)	<0.01*		
Late 123-I MIBG SPECT defect score	1.13 (1.08 - 1.18)	<0.01*	1.12 (1.05 - 1.19)	<0.01**
Myocardial perfusion imaging				
Rest perfusion defect score	1.02 (0.99 - 1.06)	0.2		
Stress perfusion defect score	1.02 (0.99 - 1.06)	0.2		
Summed perfusion difference score	1.04 (0.94 - 1.16)	0.5		
123-I MIBG/perfusion mismatch score	1.05 (1.02 - 1.08)	<0.01*	1.00 (0.97 - 1.04)	0.9

* Significant association with appropriate ICD therapy at a level of p<0.15 in univariate analysis. **Significant association with appropriate ICD therapy in multivariate analysis. ACE-I = angiotensin converting enzyme - inhibitor; AT = angiotensin; CAD = coronary artery disease; CRT-D = cardiac resynchronization therapy - defibrillator; H/M ratio = heart-to-mediastinum ratio; 123-I MIBG = 123-iodine metaiodobenzylguanidine; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SPECT = single photon emission computed tomography.

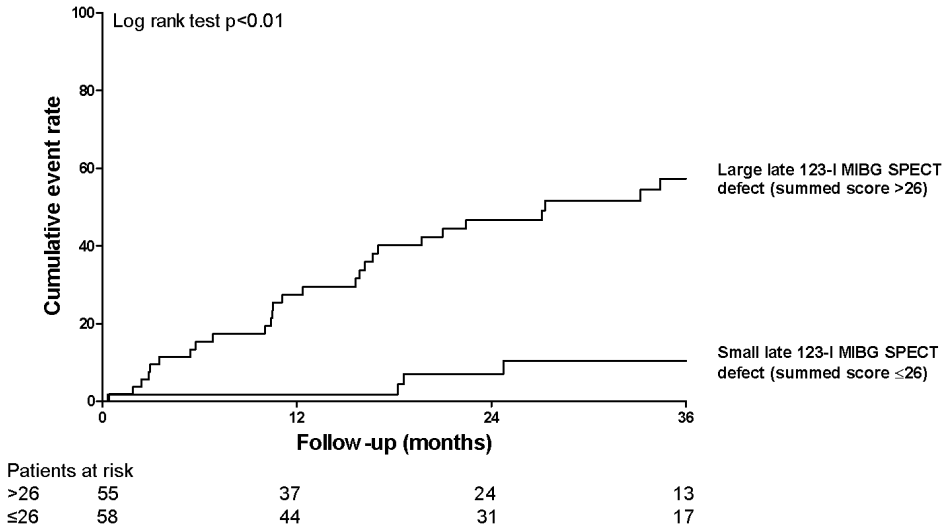


Figure 3. Kaplan-Meier curve analysis showing the difference in appropriate ICD therapy or cardiac death (secondary endpoint) between patients with a large (summed score >26) or small (summed score ≤26) late 123-I MIBG SPECT defect.

defect (summed score ≤26) at 3-year follow-up. Importantly, only 2 (3%) patients with a small late 123-I MIBG SPECT defect received appropriate ICD therapy during follow-up.

Sudden cardiac death and substrate imaging

ICD therapy has become a cornerstone treatment in patients at high risk for sudden arrhythmic death.[4] Although the benefits of ICD treatment have been demonstrated, the question has been raised whether patient selection according to the current guidelines is adequate, as it is still unclear which patients will benefit from ICD treatment.[2,3,5] Post-hoc analysis of the second Multicenter Automated Defibrillator Implantation Trial (MADIT II) population demonstrated that 35% of patients received appropriate ICD therapy after 3-year follow-up.[5] Moreover, the majority of arrhythmic deaths occurs in patients without ICD indication.[6]

Accordingly, attention has shifted towards improved risk stratification of patients currently indicated for ICD therapy. Recently, the AHA/ACC/HRS scientific statement on the noninvasive risk stratification in patients at risk for sudden arrhythmic death was published, indicating that the optimal method for risk stratification is unclear.[15] Although an LV ejection fraction (LVEF) of <40% is most commonly used for stratification of patients at risk for ventricular arrhythmias, it does not allow accurate discrimination of patients with or without sudden arrhythmic death.[15] Moreover, sudden arrhythmic death is often occurred in patients with an LVEF of >40%.[6,15]

Since the majority of patients with documented arrhythmic death is diagnosed with structural heart disease, predominantly coronary artery disease, risk stratification should

focus on further identification of the underlying substrate for arrhythmic death.[15,16] Although the exact mechanisms of ventricular arrhythmias have been a matter of debate, it has been recognized that scar tissue and myocardial ischemia may serve as important substrates for ventricular arrhythmias. In acute myocardial infarction, ischemia may serve as a substrate for ventricular arrhythmias by inducing electrical instability.[17] In chronic myocardial infarction, areas of slow conduction are present that facilitate the development of reentrant tachycardia.[17]

Different imaging techniques (predominantly myocardial perfusion imaging) have been used to provide information on the underlying substrate. Borger van der Burg et al.[18] evaluated the occurrence of ventricular arrhythmia and cardiac death in relation to ischemia, viability and scar tissue in 156 survivors of sudden arrhythmic death. Extent of scar tissue and reduced LV function (LVEF ≤30%) were significantly associated with occurrence of ventricular arrhythmias and cardiac death in univariable and multivariable analysis. In the present study, ischemia (summed perfusion difference score) was significantly associated with appropriate ICD therapy in univariable analysis. However, myocardial infarction (resting perfusion defect score) and ischemia were not significantly associated with both endpoints in multivariable analysis. One of the potential explanations for these findings is the fact that the current study included patients with nonischemic cardiomyopathy, whereas in the study performed by Borger van der Burg et al.[18] all patients were diagnosed with significant coronary artery disease.

The autonomic nervous system may also play an important role in the pathogenesis of ventricular arrhythmias.[7,8] Observational studies have associated the occurrence of ventricular arrhythmias with abnormalities in cardiac sympathetic innervation.[9,10] Although the pathophysiologic mechanisms are unclear, it has been suggested that denervated but viable myocardium may be hypersensitive to circulating catecholamines. As compared to regions with normal cardiac innervation, denervated myocardium may respond differently to sympathetic activation with increased automaticity and enhanced triggering.[7] In particular, the borderzone of infarct tissue may be predisposed to develop reentrant circuits as these regions are viable but may have damaged sympathetic nerves. Viable myocardium may already exhibit areas of denervation (innervation/perfusion mismatch), as sympathetic nerve fibers are more susceptible to myocardial ischemia than cardiac tissue.[19,20]

Recently, the innervation/perfusion mismatch score was assessed in 50 patients with LV systolic dysfunction referred for electrophysiologic testing.[10] The innervation/perfusion mismatch score was not significantly associated with inducibility of tachyarrhythmias in univariable and multivariable analysis.[10] Although the current study showed that 123-I MIBG/perfusion mismatch score was associated with the occurrence of ventricular arrhythmias in univariable analysis, no significant association was found in multivariable analysis.

Risk stratification in heart failure patients with 123-I MIBG imaging

Several studies using 123-I MIBG imaging have demonstrated that abnormalities in global cardiac innervation were predictive for overall cardiac mortality in heart failure patients.[21,22] Merlet et al.[22] showed that impaired cardiac sympathetic innervation, as assessed with planar 123-I MIBG imaging, was associated to adverse cardiac outcomes in 112 patients with heart failure and a poor LV function. Over a mean follow-up of 27±20 months, the only independent predictors for adverse cardiac events (cardiac transplantation and cardiac death) were low 123-I MIBG uptake ($p<0.01$) and LV function ($p=0.02$). Recently, Agostini et al.[11] confirmed the predictive value of cardiac 123-I MIBG imaging in 290 patients with moderate-to-severe heart failure. Most important, the study showed that patients with normal 123-I MIBG uptake showed a significant higher 2-year event-free survival as compared to patients with reduced 123-I MIBG uptake (95% vs. 62%, $p<0.01$).

123-I MIBG imaging to predict ventricular arrhythmia

Various studies have related sympathetic denervation to the occurrence of ventricular arrhythmias.[9,10] Arora et al.[23] performed a pilot study that evaluated cardiac sympathetic innervation in 17 patients with ICD treatment. ICDs were implanted because of sustained ventricular tachycardia or ventricular fibrillation. Patients with a documented ICD discharge showed significantly more global (early H/M ratio) and regional sympathetic denervation (early and late 123-I MIBG defect score) than patients without an ICD discharge. In addition, Nagahara et al.[24] evaluated in a small study population whether abnormalities in cardiac sympathetic innervation were related to appropriate ICD therapy or lethal cardiac events. During a mean follow-up of 15 months, global cardiac sympathetic innervation (assessed with delayed H/M ratio) was independently associated with appropriate ICD therapy. More recently, the relation between cardiac sympathetic innervation and inducibility of ventricular arrhythmias during electrophysiologic testing was evaluated in 50 patients with previous myocardial infarction and reduced LV systolic function.[10] Although no significant association between global cardiac denervation and inducible ventricular arrhythmias was found, regional cardiac denervation was significantly higher in patients with positive electrophysiologic tests than patients with negative electrophysiologic tests. In addition, Mitrani et al.[9] evaluated whether patients with documented ventricular arrhythmias showed abnormal sympathetic innervation. Patients with ventricular tachycardia showed significantly more regional sympathetic denervation as compared to patients without ventricular tachycardia. Likewise, this study demonstrated that regional cardiac sympathetic denervation derived from late 123-I MIBG SPECT was significantly associated with ventricular arrhythmias causing appropriate ICD therapy. Moreover, late 123-I MIBG SPECT defect score was an independent predictor for appropriate ICD therapy. Importantly, the risk for appropriate ICD therapy was 13 times higher in patients with a large late 123-I MIBG SPECT defect than patients with a small defect.

Limitations

Although the current study clearly demonstrated that cardiac sympathetic denervation on late 123-I MIBG SPECT imaging was predictive for both study endpoints, some limitations need to be considered. In this study, a heterogeneous patient population was enrolled, including patients with ischemic and nonischemic cardiomyopathy. Additional studies are needed to establish the specific role of 123-I MIBG imaging in these subpopulations. In addition, innervation and perfusion scans were scored visually, whereas an automatic quantitative approach would be preferred.

Conclusion

Cardiac sympathetic denervation on late 123-I MIBG imaging predicts ventricular arrhythmia causing appropriate ICD therapy (primary endpoint) as well as the composite of appropriate ICD therapy or cardiac death (secondary endpoint). Cardiac sympathetic denervation as assessed with delayed 123-I MIBG SPECT imaging may improve risk stratification for arrhythmic death in patients who have an indication for ICD treatment.

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