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Cardiac ^{123}I-*m*IBG scintigraphy is associated with freedom of appropriate ICD therapy in stable chronic heart failure patients

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ABSTRACT

Aim: Chronic heart failure (CHF) is a life-threatening clinical syndrome, partly due to sudden cardiac death (SCD). Implantable cardioverter defibrillators (ICD) for primary prevention of SCD have improved overall survival of CHF patients. However, a high percentage of patients never receives appropriate ICD therapy. This prospective multicentre study evaluated whether cardiac sympathetic activity assessed by ^{123}I-*m*IBG scintigraphy could be helpful in selecting patients for ICD implantation.

Materials and methods: 135 stable CHF subjects (age 64.5 ± 9.3 years, 79% male, LVEF 25 ± 6%) referred for prophylactic ICD implantation were enrolled in 13 institutions. All subjects underwent planar and SPECT ^{123}I-*m*IBG scintigraphy. Early and late heart-to-mediastinum (H/M) ratio, ^{123}I-*m*IBG washout (WO) and late summed scores were calculated. The primary endpoint was appropriate ICD therapy. The secondary endpoint was defined as the combined endpoint of all first cardiac events: appropriate ICD therapy, progression of heart failure (HF) and cardiac death.

Results: During a median follow-up of 30 months (6–68 months), 24 subjects (17.8%) experienced a first cardiac event (appropriate ICD therapy [12], HF progression [6], cardiac death [6]). Late H/M ratio and defect size of ^{123}I-*m*IBG SPECT were not associated with appropriate ICD therapy. However, late H/M ratio was independently associated with the combined endpoint (HR 0.135 [0.035–0.517], $p = 0.001$). Post-hoc analysis showed that the combination of late H/M ratio (HR 0.461 [0.281–0.757]) and LVEF (HR 1.052 [1.021–1.084]) was significantly associated with freedom of appropriate ICD therapy ($p < 0.001$).

Conclusion: ^{123}I-*m*IBG scintigraphy seems to be helpful in selecting CHF subjects who might not benefit from ICD implantation.

1. Introduction

Despite therapeutic improvements the prognosis of chronic heart failure (CHF) remains unfavorable partly due to sudden cardiac death (SCD). The introduction of implantable cardioverter defibrillators (ICD) has improved overall survival of CHF patients [1,2]. Based on large randomized trials, current European guidelines recommend ICD implantation for primary prevention of fatal arrhythmias in symptomatic CHF subjects with New York Heart Association (NYHA) class ≥2 under optimal pharmacological therapy and a left ventricular ejection fraction (LVEF) <35% [3]. ICDs applied for primary or secondary prevention of SCD reduce the relative risk of death by 20%. However, three years after ICD implantation for primary prevention, a remarkably high percentage (65%) of patients had never received appropriate ICD therapy [4]. Moreover, the risk of malfunction, (post)operative complications [5] and the relatively high cost of these devices urges for optimization of current ICD selection criteria for primary prevention.

Cardiac sympathetic activity can non-invasively be assessed with *meta*-iodobenzylguanidine (^{123}I-*m*IBG) [6]. The past decades, myocardial

Abbreviations: ATP, anti-tachycardia pacing; β-AR, β-adrenergic receptors; CE, combined endpoint; CHF, chronic heart failure; H/M, heart-to-mediastinum; HR, hazard ratio; NE, norepinephrine; NET, norepinephrine transporter; NT-proBNP, N-terminal pro B-type natriuretic peptide; ROI, region of interest; WO, washout.

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^{123}I-*m*IBG scintigraphy has been shown to predict prognosis in CHF patients [7,8]. A predefined LEHR (low energy high resolution) collimator derived late heart-to-mediastinum (H/M) ratio < 1.6 has been suggested to be a predictor of ventricular arrhythmia [9]. Furthermore, decreased ^{123}I-*m*IBG uptake and increased wash-out (WO) are associated with increased incidence of SCD or appropriate ICD therapy [10–12]. Most of these studies have been conducted in various populations, both with primary and secondary prevention of SCD. In addition, extrapolation of the obtained data is hampered by the fact that these data were not corrected for differences in gamma camera-collimators [13]. Therefore, the aim of this prospective study was to evaluate whether ^{123}I-*m*IBG scintigraphy assessed cardiac sympathetic activity could identify high-risk CHF patients most likely to undergo appropriate ICD therapy for primary prevention of SCD.

2. Methods

The study was approved by the local institutional review boards and conducted according to the principles of the International Conference on Harmonization–Good Clinical Practice. All subjects provided written informed consent before participation. The study was registered on www.trialregister.nl (registration number NTR2735). The study started in two institutions in the Netherlands (Academic Medical Center (AMC) and Onze Lieve Vrouwe Gasthuis with image acquisition at the AMC) with the expectation to include 300 subjects. Assuming a 10% appropriate ICD response per year this would result in approximately 60 subjects with an appropriate ICD therapy at 2-years follow-up. However, a slow inclusion rate at the initial sites made us decide to expand the number of participating institutions. (see "Appendix" for list of all participating institutions). Consequently, correction for different gamma camera-collimator combinations was needed. To convert to standardized ME collimator conditions we used conversion coefficients from our previous studies [13,14]. However despite this effort inclusion rate remained slow and it was decided to stop the inclusion at 135 patients. From the 334 potential subjects screened for participation, only 269 subjects were eligible for inclusion. However, 134 subjects could not be included due to logistics (i.e. transportation to hospital or participating in competing studies ($n = 76$) or did not give informed consent ($n = 58$)).

2.1. Design

All included patients underwent cardiac ^{123}I-*m*IBG scintigraphy within 2 weeks prior to ICD implantation and were followed for the occurrence of the primary and secondary endpoints.

The primary endpoint for this study was appropriate ICD therapy: ICD therapy to overcome potentially fatal ventricular arrhythmias: i.e. anti-tachycardia pacing (ATP) or shock triggered by ventricular tachycardia or fibrillation. The secondary endpoint was defined as the combined endpoint of all first cardiac events: appropriate ICD therapy, progression of heart failure (HF) and cardiac death.

2.2. Subjects

Patients with stable CHF (ischemic or non-ischemic) who were referred for ICD implantation for primary prevention of SCD were enrolled between July 2010 and October 2015. The inclusion criteria were: 1. LVEF <35%, 2. NYHA functional class II or III, 3. Pacemaker-naive, 4. Stable and treated with optimal medical therapy for at least 3 months according to the European HF guidelines [3]. Exclusion criteria were: 1. History of defibrillation to treat a previous ventricular arrhythmic event, 2. History of acute myocardial infarction within the previous 30 days.

As part of the workup for ICD implantation all subjects underwent complete clinical evaluation including echocardiography and blood sample analysis.

2.3. ^{123}I-mIBG scintigraphy acquisition and analysis

To block the uptake of free ^{123}I by the thyroid gland, subjects were pretreated with 250 mg oral potassium iodide 30 min before intravenous (IV) injection of 185 MBq^{123}I-*m*IBG (Adreview®, GE, Healthcare). Fifteen minutes (early acquisition) and 4 h (late acquisition) after administration of ^{123}I-*m*IBG, 10-min planar images were acquired from an anterior thoracic view (256 × 256 matrix) with the subjects in supine position. A 20% window was centred at 159 keV. Additional SPECT ^{123}I-*m*IBG images, without attenuation correction, were acquired after the late planar acquisitions (128 × 128 matrix).

All ^{123}I-*m*IBG data were anonymized and sent to the study coordinating centre (Academic Medical Center, Amsterdam, the Netherlands). Planar data were analysed by one experienced observer (D.O.V.) blinded to patient data using post-processing software. Heart-to-mediastinum (H/M) ratio was calculated from planar ^{123}I-*m*IBG images using a manually drawn region-of-interest (ROI) over the heart and a fixed rectangular mediastinal ROI [15]. To correct for differences in gamma camera-collimator combination, institutional early and late planar H/M ratios were converted to standardized ME collimator values by using conversion coefficients from our previous ^{123}I-*m*IBG cross-calibrated phantom study [13,14]. The washout (WO) was defined by:

$$WO = \left\{\frac{(\text{early H/M} - \text{late H/M})}{(\text{early H/M})}\right\}^{*} 100$$

All late SPECT ^{123}I-*m*IBG images were analysed by two experienced observers (B.L.v.E.S. and H.J.V.) blinded to patient data according a previous published protocol [16]. Summed scores (range 0–68) were derived by the standard 17-segment model and 5-point scoring method [17].

2.4. ICD implantation

After myocardial ^{123}I-*m*IBG imaging transvenous or subcutaneous ICDs were implanted in the participating institutions. Testing of sensing, pacing and defibrillation thresholds was performed according to local protocols. In case of patient eligibility for cardiac resynchronization therapy (CRT), a combined CRT-D device was implanted. Settings for detection of ventricular tachycardias or fibrillation were at the discretion of the implanting physician.

2.5. Clinical follow-up and event adjudication

Follow-up was based on telephone interviews (D.O.V.) and medical records. All subjects received standard clinical care and were followed up until: 1. subjects death was confirmed by medical records of the general practitioner; 2. the trial was terminated (30th of April 2016). The Clinical Adjudication Committee, whose members were unaware of the scintigraphy data, reviewed all data from case record forms and source documents to confirm occurrence of cardiac events, specifically: 1. HF progression: increase in NYHA functional class, or admission due to HF progression; 2. Potentially life-threatening arrhythmic event, including documented episode of spontaneous sustained (30 s) ventricular tachyarrhythmia, resuscitated cardiac arrest, or appropriate ICD therapy: ATP or defibrillation); or 3. Cardiac death (further classified as due to terminal heart failure and SCD).

2.6. Comparison with a historical Japanese CHF cohort

To compare the mortality rate of our study population with other published data we used a risk model, based on a historical Japanese CHF cohort [18]. This model estimates the 2-years mortality risk based on four variables (NYHA class, age, LVEF and standardized late H/M ratio). Using the median 2-year mortality of 9%, patients were divided into 2 groups: mortality rate < 9% and ≥9%. Since the Japanese risk model was made using data from 1990, the effect of ICD therapy was not included and therefore appropriate ICD therapy was scored as a fatal event. As this mortality risk model assumes complete 2-year follow-up, patients who had a follow-up <2 years and were alive were excluded for this analysis.

2.7. Statistical analysis

All continuous variables are expressed as mean ± standard deviation. Difference between groups for continuous data we compared using analysis of variance (ANOVA) with post-hoc Bonferroni. Efficacy analysis used univariate and multivariate Cox proportional regression hazards models for primary and secondary endpoint using age, NYHA class, LVEF, early and late standardized H/M ratio, ^{123}I-*m*IBG WO and SPECT summed score as variables. Post-hoc analysis was performed for freedom of appropriate ICD therapy. Forward elimination determined the combination of variables that most influenced the time-over-event model. The χ^2 test, Cox's proportional hazard regression coefficient and exponent were used to describe the model and relative contribution of the parameters to the model. The hazard ratio (HR) expresses the predicted change in hazard for a unit change in the predictor. A p-value <0.05 was considered to indicate a statistically significant difference. Statistical analyses were performed with SPSS, release 22.0 (SPSS Inc., Chicago, USA 2003).

3. Results

3.1. Subjects

A total of 135 stable CHF patients (79% men, age 64.5 ± 9.3) were enrolled. Baseline characteristics of the study population are shown in Table 1A. Almost 60% of the patients had ischemic heart disease. Mean NYHA class was 2.2 ± 0.4 and mean LVEF was 25.0 ± 6.2%. The mean early standardized H/M ratio was 2.05 ± 0.39, the late standardized H/M ratio was 1.79 ± 0.38 and ^{123}I-*m*IBG WO was 12.4 ± 9.2%. The mean SPECT summed score was 39.4 ± 15.5.