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# The relation between cardiac $^{123}$I-*m*IBG scintigraphy and functional response 1 year after CRT implantation

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**Aims** Cardiac resynchronization therapy (CRT) is a disease-modifying therapy in patients with chronic heart failure (CHF). Current guidelines ascribe CRT eligibility on three parameters only: left ventricular ejection fraction (LVEF), QRS duration, and New York Heart Association (NYHA) functional class. However, one-third of CHF patients does not benefit from CRT. This study evaluated whether $^{123}$I-*meta*-iodobenzylguanidine ($^{123}$I-*m*IBG) assessed cardiac sympathetic activity could optimize CRT patient selection.

**Methods and results** A total of 78 stable CHF subjects (age 66.8 ± 9.6 years, 73% male, LVEF 25.2 ± 6.7%, QRS duration 153 ± 23 ms, NYHA 2.2 ± 0.7) referred for CRT implantation were enrolled. Subjects underwent $^{123}$I-*m*IBG scintigraphy prior to implantation. Early and late heart-to-mediastinum (H/M) ratio and $^{123}$I-*m*IBG washout were calculated. CRT response was defined as either an increase of LVEF to >35%, any improvement in LVEF of >10%, QRS shortening to <150 ms, or improvement in NYHA class of >1 class. In 33 patients LVEF increased to >35%, QRS decreased <150 ms in 36 patients, and NYHA class decreased in 33 patients. Late H/M ratio and hypertension were independent predictors of LVEF improvement to >35% ($P = 0.0014$ and $P = 0.0149$, respectively). In addition, early H/M ratio, LVEF, and absence of diabetes mellitus (DM) were independent predictors for LVEF improvement by >10%. No independent predictors were found for QRS shortening to <150 ms or improvement in NYHA class.

**Conclusion** Early and late H/M ratio were independent predictors of CRT response when improvement of LVEF was used as measure of response. Therefore, cardiac $^{123}$I-*m*IBG scintigraphy may be used as a tool to optimize selection of subjects that might benefit from CRT.

**Keywords** chronic heart failure • cardiac resynchronization therapy • response • $^{123}$I-*m*IBG scintigraphy • heart-to-mediastinum ratio • wash out

## Introduction

Chronic heart failure (CHF) is a life-threatening syndrome. Despite pharmacological therapy induced improvement, the prognosis remains poor with a mortality rate of 20% during the first years.[1] Left ventricular (LV) dyssynchrony with QRS prolongation is present in >25% of the subjects with CHF. LV dyssynchrony has emerged as an important marker for the progression of CHF and LV remodelling with detrimental effects on cardiac function, such as systolic and diastolic LV dysfunction. In addition, LV dyssynchrony appears to play a

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major role in the pathophysiology of CHF.[2] Cardiac resynchronization therapy (CRT) has been shown to improve left ventricular ejection fraction (LVEF), reduce hospitalization due to heart failure (HF), and decrease all-cause mortality in selected CHF patients.[3–5] CRT is currently recommended as a Class IA in symptomatic CHF subjects, when LVEF is ≤35%, sinus rhythm is present, and QRS is ≥150 ms.[6,7] However, one-quarter to one-half of the subjects who receive a CRT are 'non-responders' and do not benefit from CRT device implantation.[8,9] For example, the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial showed no therapeutic benefit of CRT in 33% of subjects using a clinical composite score including all-cause mortality, HF hospitalization, New York Heart Association (NYHA) functional class, and clinical performance scores.[10] Non-response to therapy has remained the Achilles' heel of CRT over the years and is clearly multifactorial involving multiple pre-, peri-, and post-implantation factors.[11] As the implantation of CRT devices is associated with the risk of device malfunction, peri-procedural complications,[12,13] and relatively high costs, the search for other discrimination factors to optimize the current selection criteria for CRT device implantation is essential.

Despite two decades of development of CRT, a consensus of who will respond to CRT has not been reached. In part, this can be explained by the fact that clinical trials and registries used a variety of different outcome measures without a unified/harmonized (composite) endpoint.[14] Early studies used parameters reflecting functional improvement (i.e. $VO_2$ max, 6-min walk test, and NYHA functional class).[15,16] More recent CRT trials used HF hospitalization and death as a more objective, hard clinical endpoints.[3,4] Besides clinical events and mortality, surrogate outcomes such as LV remodelling measures [i.e. improvement of LVEF, LV end-systolic volume (LVESV), and LV end-diastolic volume (LVEDV)] were also used in clinical trials. Because of the multiple available parameters and because of the lack of consensus in defining CRT response we used three different types of response: echocardiographic (improvement of LVEF), electrographic (QRS duration), and functional improvement (NYHA functional class).

The cardiac sympathetic system is one of the neurohormonal compensation mechanisms that play an important role in the pathogenesis of CHF with reduced LVEF. Patients with CHF have increased cardiac sympathetic activity with increased exocytosis of norepinephrine (NE) from the presynaptic vesicles. Initially, β-adrenergic receptor (AR) stimulation by increased NE levels helps to compensate for impaired myocardial function, but long-term NE excess gives rise to a downregulation and decrease in the sensitivity of post-synaptic β-AR.[17,18] This downregulation leads to LV remodelling and is associated with increased mortality and morbidity.[19] Cardiac $^{123}$I-*meta*-iodobenzylguanidine ($^{123}$I-*m*IBG) scintigraphy has been widely used for non-invasive assessment of cardiac sympathetic function in CHF. $^{123}$I-*m*IBG is an NE analogue which is concentrated and stored in the presynaptic sympathetic myocardial nerve terminals in a fashion similar to NE.[20] It has been demonstrated that impaired cardiac sympathetic activity as assessed with $^{123}$I-*m*IBG is associated with poor outcome in CHF.[21–24]

Several studies have shown that CRT improves $^{123}$I-*m*IBG assessed cardiac sympathetic activity. Available data demonstrated that CRT responders have a rebalance in cardiac autonomic function as structural reverse remodelling (i.e. increase of LVEF) may also induce reverse modulation of cardiac sympathetic activity and rebalance of cardiac autonomic activity.[25–28] Therefore, cardiac $^{123}$I-*m*IBG scintigraphy may have a potential role in predicting CRT response. As far as we know the association between cardiac sympathetic activity and CRT response defined as improvement of LVEF has never been evaluated previously in a multicentre study. Therefore, the purpose of the study was to evaluate whether $^{123}$I-*m*IBG assessed cardiac sympathetic activity could optimize CRT patient selection.

# Methods

## Study population

### Design

All subjects underwent planar cardiac $^{123}$I-*m*IBG scintigraphy prior to CRT implantation and were followed for the occurrence of the primary endpoint 1 year ± 2 months after CRT implantation. The primary endpoint for this study was response to CRT defined as increase of LVEF to >35%, any improvement in LVEF of >10%, QRS shortening to <150 ms, and improvement in NYHA functional class of at least one class.

We combined data from two previous prospective studies from the Netherlands[22] and Italy,[29] both evaluated the prognostic role of cardiac $^{123}$I-*m*IBG scintigraphy in subjects with stable CHF who were referred for implantable cardiac defibrillator (ICD) implantation. The inclusion criteria of both original studies were (i) LVEF ≤35%, (ii) NYHA functional Class II or III, (iii) stable HF and treated with optimal medical therapy for at least 3 months according to the European HF guidelines,[7] and (iv) pacemaker-naive. Both studies were 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. In the original studies, some subjects did not have an indication for ICD implantation only but were also eligible for CRT (i.e. QRS duration > 150 ms, LVEF ≤ 35%, NYHA functional Class II or III). Therefore, these subjects received an integrated device with ICD and CRT function (i.e. CRT-D) as recommend by the ESC guidelines.[6] In the current study, we only enrolled those subjects with CRT-D implantation. The follow-up data of LVEF, QRS duration, and NYHA functional class in the original studies were prospectively collected from outpatient visits, medical reports, and telephone calls.

### $^{123}$I-*m*IBG scintigraphy acquisition and analysis

To block uptake of free $^{123}$I by the thyroid gland, subjects were pretreated with 250 mg oral potassium iodide or 5% Lugol solution 30 min before intravenous injection of 150–185 MBq $^{123}$I-*m*IBG (Adreview®, GE Healthcare). Fifteen minutes (i.e. early) and 4 h (i.e. late) after administration of $^{123}$I-*m*IBG, 10-min planar images were acquired from an anterior thoracic view (128 × 128 or 256 × 256 matrix) with the subject in supine position using a 20% window centred at 159 keV.

All planar $^{123}$I-*m*IBG were analysed by two experienced observers (D.O.V. and V.F.). 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 (*Figure 1*).[30] To correct for differences in gamma camera-collimator combination, institutional early and late planar H/M ratios were converted to standardized medium energy (ME) collimator values by using conversion coefficients from our previous $^{123}$I-*m*IBG cross-calibration phantom study.[31] The washout (WO) was defined by:

$$\mathrm{WO} = \left\{ \frac{(\text{early H/M} - \text{late H/M})}{(\text{early H/M})} \right\} \times 100.$$

### CRT implantation

After myocardial $^{123}$I-*m*IBG imaging, the CRT-D device was implanted in the participating institutions. Although pacemaker -lead placement was at the discretion of each institution, placement in infarcted segments was not recommended and avoided as much as possible. Testing of sensing and pacing, as well as defibrillation thresholds was performed according to local protocols.

### Clinical follow-up

All subjects received standard clinical care and were followed up 1 year after CRT implantation with evaluation by echocardiography (LVEF), electrocardiogram, and NYHA functional capacity. Changes in LVEF, QRS duration, and NYHA functional class between baseline and 1-year follow-up were used as parameters of CRT response.

## Statistical analysis

All continuous variables are expressed as mean ± standard deviation. Differences between groups for continuous data were compared using unpaired *T*-test. Efficacy analysis was performed using logistic regression for the primary endpoint with a variety of parameters [i.e. age, hypertension, DM, QRS duration, NYHA functional class, LVEF, early and late standardized H/M ratio, $^{123}$I-*m*IBG WO]. Forward elimination determined the combination of parameters that most influenced the model. A *P*-value <0.05 was considered to indicate a statistically significant difference. Receiver operating characteristic (ROC) analysis was performed using parameters listed above to predict any improvement in LVEF >10% and improvement of LVEF to >35%. ROC curves were created with multiple significant variables combined, and areas under the curve (AUC) with 95% confidence interval (CI) were calculated. The differences in AUC for the different ROC curves were compared using whole model tests and pairwise comparisons. The probability of CRT response was assessed using the ROC-derived optimal cut-off values and the associated logistic curves. The response rate to CRT treatment was analysed by a multi-variable logistic regression model.[32] Mathematical calculation for creating ROC analysis and models was based on Mathematica 12 (Wolfram Research Inc., Champaign, IL, USA). Other statistical analyses were performed with SPSS, release 25.0 (SPSS Inc., Chicago, IL, USA 2017).

# Results

In total, 78 stable CHF subjects [the Netherlands ($n = 42$) and Italy ($n = 36$)] referred for CRT-D implantation were enrolled. Baseline characteristics of the study population are shown in *Table 1*. The mean age was 66.8 ± 9.6 years and 73% was male. Almost 56% of the subjects had ischaemic heart disease. Mean baseline NYHA functional class was 2.4 ± 0.6 and mean LVEF was 25.2 ± 6.7%. The mean early standardized H/M ratio was 2.04 ± 0.37, late standardized H/M ratio was 1.82 ± 0.36, and $^{123}$I-*m*IBG WO was 10.6 ± 10.8. There was a difference in early and late H/M ratio between the population in the Netherlands and Italy. The incidence of hypertension was higher in the Italian subjects. Seventy-six subjects completed the 1-year follow-up. Two subjects died during follow-up due to sudden cardiac death (SCD), 9 (late H/M ratio: 1.56) and 11 (late H/M ratio: 1.26) months after enrolment, respectively. These two subjects were qualified as 'non-responder' in the statistical analysis.

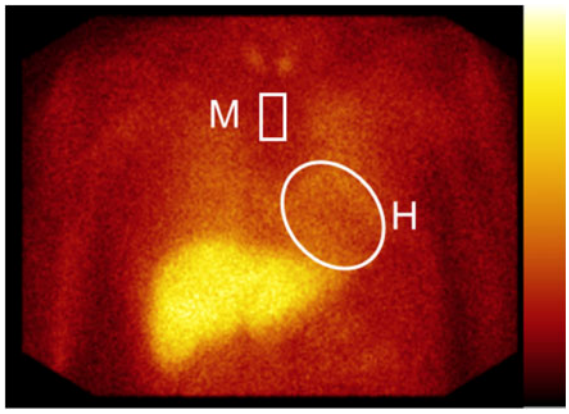


**Figure 1** Example of planar $^{123}$I-*m*IBG images of 68-year-old patient with ischaemic heart failure with a calculated standardized H/M ratio of 1.62. A manual drawn ROI is placed over the heart (H). A fixed rectangular ROI is positioned in the mediastinum (M) in relation to the lung apex, the lower boundary of the upper mediastinum, and the midline between the lungs.

## Predictors of CRT response after 1-year follow-up

### Response defined as increase of LVEF

In eight subjects no follow-up echocardiography was performed due to transfers to other institutions. In total, 53 subjects showed any improvement of LVEF 1 year after CRT device implantation. A substantial part of the observed changes in LVEF after 1-year follow-up was well within the echocardiographic intra- and inter-observer variation (i.e. 7.6% and 8.3%, respectively).[33] The mean change in LVEF was 4.6 ± 15.3% (*Figure 2*). In total, 33 subjects showed an LVEF >35% after 1-year follow-up. The baseline characteristics of responders and non-responders are shown in *Table 2*. There was a significant difference in late H/M ratio between responders and non-responders (2.00 ± 0.40 vs. 1.67 ± 0.25, respectively, $P = 0.008$). When improvement in LVEF was dichotomized ≤35% (non-responder) and >35% (responder), logistic regression analysis showed that late H/M ratio [OR 18.19 (95% CI 3.06–108.23), $P = 0.0014$] and hypertension [OR 0.23 (95% CI 0.07–0.75), $P = 0.0149$] were independent predictors of CRT response. This outcome is mainly driven by the results of the Dutch population (data not shown). *Figure 3A* shows ROC AUC curves for late H/M and hypertension in relation to late H/M ratio. Although the ROC AUC was higher for the combination of late H/M and hypertension compared with late H/M ratio alone, the difference in ROC AUC did not reach statistical significance [0.802 (95% CI 0.671–0.889) vs. 0.746 (95% CI 0.608–0.847), $P = 0.16$] (*Figure 3A*). When CRT response was defined as any improvement in LVEF of >10%, early H/M ratio [OR 51.51 (95% CI 5.81–456.81), $P = 0.0004$], DM [0.15 (95% CI 0.04–0.56), $P = 0.0049$], and baseline LVEF [OR 0.89 (95% CI 0.80–0.99), $P = 0.0281$] were independent predictors of CRT response. When ROC analysis was performed with these three variables (a) the combination of early H/M ratio, DM, and baseline LVEF, (b) early H/M ratio, and (c) LVEF separately, the AUC was 0.838 (95% CI 0.726–0.911), 0.755 (95% CI 0.623–0.851), and 0.635

**Table 1 Patients baseline characteristics of total patient population and per institution**

| | All ($n = 78$) | Netherlands ($n = 42$) | Italy ($n = 36$) | $P$-value |
|---|---|---|---|---|
| Age (years) | 66.8 ± 9.6 | 65.3 ± 8.5 | 68.6 ± 10.5 | 0.118 |
| Male gender (%) | 57 (73) | 30 (71) | 27 (75) | 0.723 |
| Ischaemic heart disease (%) | 34 (44) | 16 (38) | 18 (50) | 0.291 |
| NYHA class | 2.4 ± 0.6 | 2.3 ± 0.5 | 2.4 ± 0.8 | 0.707 |
| LVEF (%) | 25.2 ± 6.7 | 22.9 ± 6.5 | 28.0 ± 6.0 | 0.756 |
| QRS time (ms) | 157 ± 26 | 153 ± 23 | 163 ± 29 | 0.254 |
| Medical history | | | | |
| Hypertension (%) | 51 (66) | 20 (48) | 31 (86) | <0.001 |
| Diabetes mellitus (%) | 28 (36) | 12 (29) | 16 (44) | 0.145 |
| Dyslipidaemia (%) | 31 (40) | 13 (31) | 18 (50) | 0.087 |
| Medication | | | | |
| Beta-blocker (%) | 66 (85) | 36 (86) | 30 (83) | 0.771 |
| ACE-I/ARB (%) | 63 (81) | 38 (91) | 25 (69) | 0.019 |
| MRA (%) | 30 (39) | 14 (33) | 16 (44) | 0.315 |
| Loop diuretics (%) | 64 (82) | 31 (74) | 33 (92) | 0.080 |
| Planar $^{123}$I-*m*IBG | | | | |
| Early H/M ratio | 2.04 ± 0.37 | 2.14 ± 0.41 | 1.93 ± 0.27 | 0.020 |
| Late H/M ratio | 1.82 ± 0.46 | 1.86 ± 0.41 | 1.77 ± 0.29 | 0.015 |
| $^{123}$I-*m*IBG WO | 10.6 ± 10.8 | 12.8 ± 10.1 | 8.1 ± 11.2 | 0.299 |

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensine receptor blocker; MRA, mineralocorticoid receptor antagonist.

(95% CI 0.498–0.754), respectively ($P = 0.0056$ for a vs. c; $P = 0.065$ for a vs. b; $P = 0.21$ for b vs. c) (*Figure 3B*). *Figure 4* illustrates that when CRT response was defined as any improvement in LVEF of >10%, response rate is higher when DM is not present, early H/M ratio is high, and baseline LVEF is low.

The probability of LVEF improvement to >35% and any improvement in LVEF >10% using H/M ratio are shown in *Figure 5A*. The optimal H/M ratio for LVEF improvement was 2.0 with a ROC AUC was 0.746 and 0.755 for both late and early H/M ratios, respectively (*Figure 5B*). The probability of CRT response using the ROC-derived optimal cut-off values showed that a 2.0 threshold for the late H/M ratio corresponded with a 60% probability of LVEF improvement to >35%. More important is that higher late H/M thresholds result in higher probability of CRT response. For example, the probability of CRT response increased to 80% at a threshold of 2.5 for the late H/M ratio (*Figure 5A*).

### Response defined as shortening of QRS duration

The mean shortening of QRS duration was 12.0 ± 26.0 ms. In total, 36 subjects showed shortening of QRS <150 ms duration 1 year after CRT implantation. There was no significant difference in early and late H/M ratio and $^{123}$I-*m*IBG WO between responders and non-responders (data not shown). When shortening of QRS duration was used as a measure of CRT response, logistic regression analysis was not able to identify an independent predictor of response (data not shown).

### Response defined as decrease of NYHA functional class

In total, 33 subjects reported improvement of NYHA functional class with at least one class 1 year after CRT implantation. There was no significant difference in early and late H/M ratio and $^{123}$I-*m*IBG WO between responders and non-responders (data not shown). When improvement in NYHA functional class was used as a marker of CRT response, logistic regression analysis was not able to identify an independent predictor of CRT response (data not shown).

### Response defined as increase of LVEF to ≥35%, decrease of QRS duration ≤150 ms, or decrease of NYHA functional class

In total, 65 subjects showed improvement 1 year after CRT implantation of at least one of the following variables: LVEF >35%, QRS duration <150 ms, or NYHA functional class. There was no significant difference in early and late H/M ratio and $^{123}$I-*m*IBG WO between responders and non-responders (data not shown). Using these combined response criteria, logistic regression analysis was not able to identify an independent predictor of CRT response (data not shown).

## Discussion

Our study is the first multicentre study that evaluated cardiac $^{123}$I-*m*IBG scintigraphy in relation CRT response 1 year after CRT implantation using standardized H/M ratios. The results of this study show that a late H/M ratio is an independent predictor of CRT response defined as increase of LVEF to >35%. Although hypertension was also shown to be an independent predictor, the combination of hypertension and late H/M ratio did not result in a statistical significant change in the ROC AUC.

LVEF is a strong predictor of prognosis in HF patients. Agra Bermejo *et al.*[34] showed that HF patients with a reduced LVEF

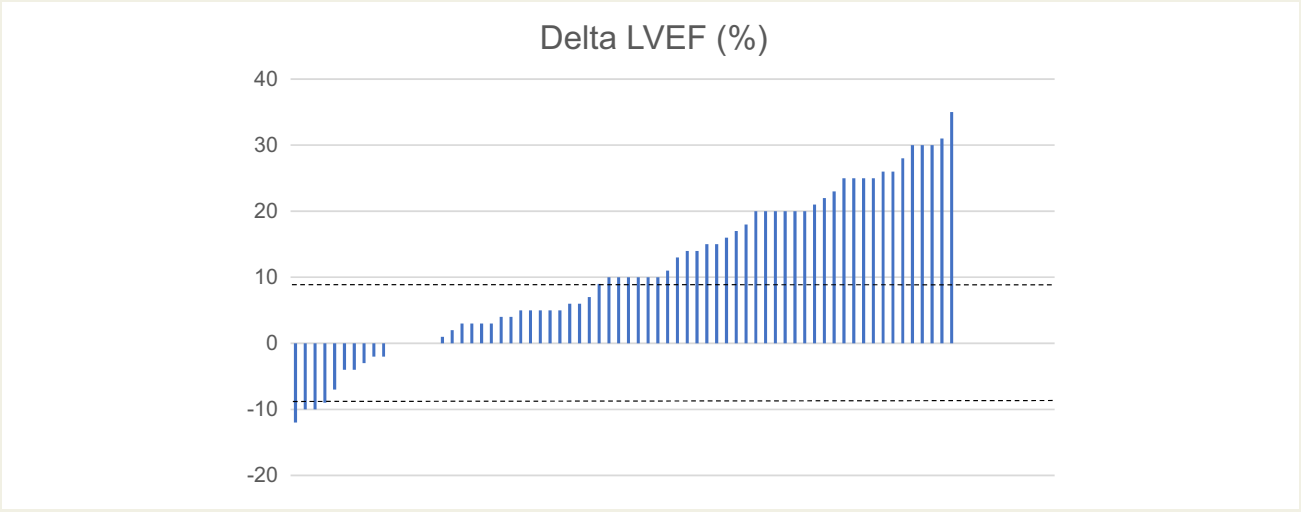


**Figure 2** Waterfall plot of change of LVEF between baseline and 1-year follow-up. Dashed blacklines indicate the boundaries of the echocardiographical intra- and inter-observer variation.

**Table 2 Patients baseline characteristics of CRT responders vs. CRT non-responders using LVEF improvement to >35%**

| | All ($n = 78$) | Responders ($n = 33$) | Non-responders ($n = 37$) | *P*-value |
|---|---|---|---|---|
| Age (years) | 66.8 ± 9.6 | 68.0 ± 8.6 | 64.7 ± 10.4 | 0.476 |
| Male gender (%) | 57 (73) | 21 (64) | 28 (76) | 0.273 |
| Ischaemic heart disease (%) | 34 (44) | 11 (33) | 20 (54) | 0.081 |
| NYHA class | 2.4 ± 0.6 | 2.5 ± 0.7 | 2.2 ± 0.6 | 0.193 |
| LVEF (%) | 25.2 ± 6.7 | 25.0 ± 6.8 | 26.0 ± 7.1 | 0.591 |
| QRS time (ms) | 157 ± 26 | 162 ± 26 | 152 ± 27 | 0.748 |
| Medical history | | | | |
| Hypertension (%) | 51 (66) | 17 (52) | 30 (81) | 0.004 |
| Diabetes mellitus (%) | 28 (36) | 8 (24) | 19 (51) | 0.020 |
| Dyslipidaemia (%) | 31 (40) | 9 (27) | 20 (54) | 0.023 |
| Medication | | | | |
| Beta-blocker (%) | 66 (85) | 28 ( 85) | 31 (84) | 0.903 |
| ACE-I/ARB (%) | 63 (81) | 28 (85) | 28 (75) | 0.338 |
| MRA (%) | 30 (39) | 11 (33) | 15 (41) | 0.533 |
| Loop diuretics (%) | 64 (82) | 26 (79) | 33 (89) | 0.233 |
| Planar $^{123}$I-*m*IBG | | | | |
| Early H/M ratio | 2.04 ± 0.37 | 1.91 ± 0.28 | 2.18 ± 0.39 | 0.127 |
| Late H/M ratio | 1.82 ± 0.46 | 2.00 ± 0.40 | 1.67 ± 0.25 | 0.008 |
| $^{123}$I-*m*IBG WO | 10.6 ± 10.8 | 11.5 ± 1.89 | 8.8 ± 10.4 | 0.727 |

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensine receptor blocker; MRA, mineralocorticoid receptor antagonists.

who had significant improvement of LVEF after treatment, had a more favourable prognosis (less hospitalization and mortality) compared with patients without improvement of LVEF. Recently a meta-analysis, including 24 observational studies with total 11 018 CHF subjects treated according to recommended drug therapy, CRT, and/or intra-cardiac defibrillator, showed that CHF patients with improved LVEF ($n = 2663$) had significantly lower risks of mortality and appropriate shocks compared with patients with persistently reduced LVEF ($n = 8355$).[35] This suggests that improvement of LVEF is a relevant parameter for survival and should therefore be included in the definition of CRT response. In the present study, we evaluated increase of LVEF to >35% and any improvement in LVEF of >10% as LVEF response criteria. As an LVEF of 35% is the cut-off point for the decision whether a CRT or ICD device should be implanted or replaced (i.e. end of life battery) in subjects with CHF, the first tested LVEF response

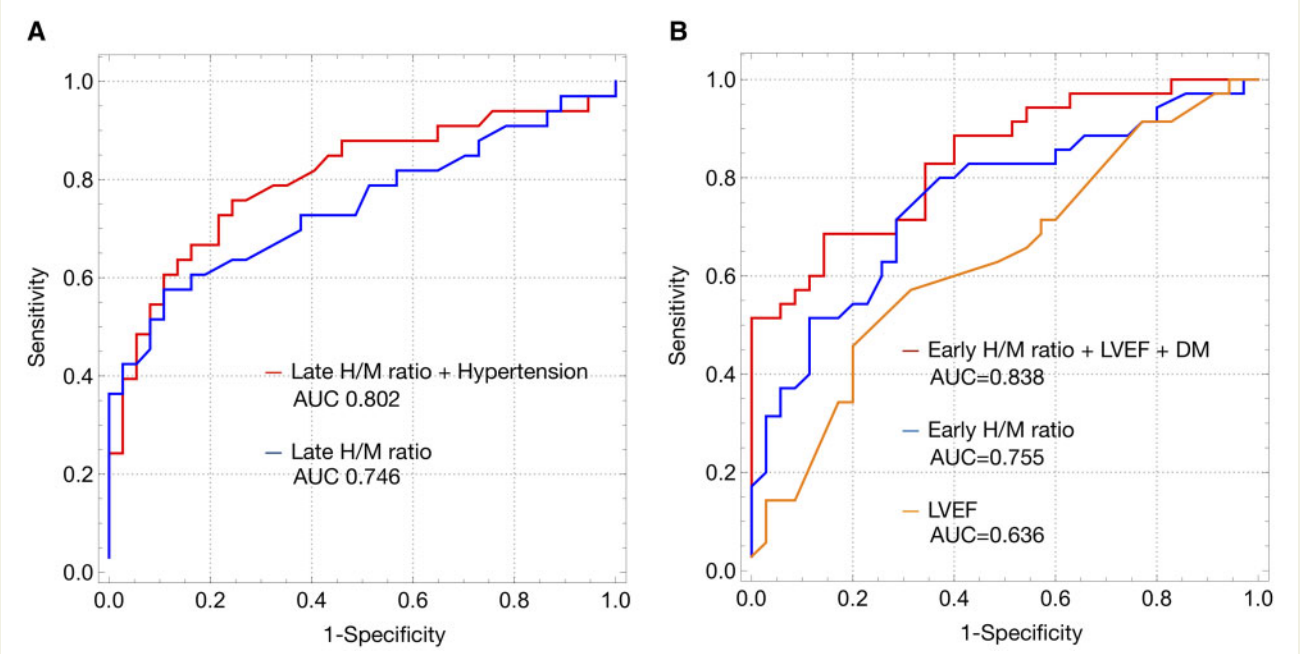


**Figure 3** (*A*) AUC curves for late H/M ratio (blue) and combination of late H/M ratio and hypertension (red) for predicting increase of LVEF to >35%. (*B*) AUC curves for combined use of early H/M ratio, LVEF, and diabetes mellitus (DM) (red), early H/M ratio (blue), and LVEF (yellow) for predicting increase of LVEF by >10%.

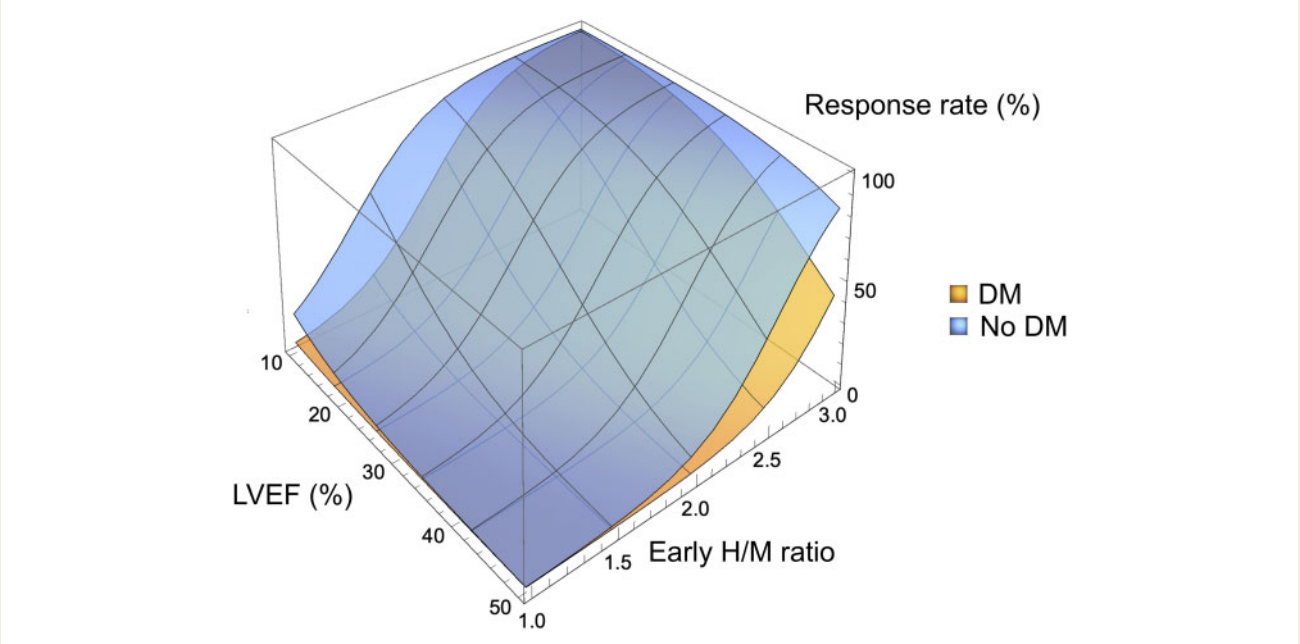


**Figure 4** Prediction model of increase of LVEF with ≥10% created using the three-variable logistic model with baseline LVEF, early H/M ratio, and diabetes mellitus (DM). The response rate is higher when DM is not present, early H/M ratio is higher, and baseline LVEF is lower.

criterion (i.e. increase of LVEF to >35%) could be of clinical importance.

In the landmark trials, the selection of patients was mainly based on QRS duration.[3,36] Retrospective analyses have shown that patients with left bundle branch block morphology have a higher chance to respond to CRT.[37,38] As a consequence, both QRS duration and morphology are mentioned as an one of the inclusion criteria for CRT in the most recent guidelines.[6,7] However, a substantial

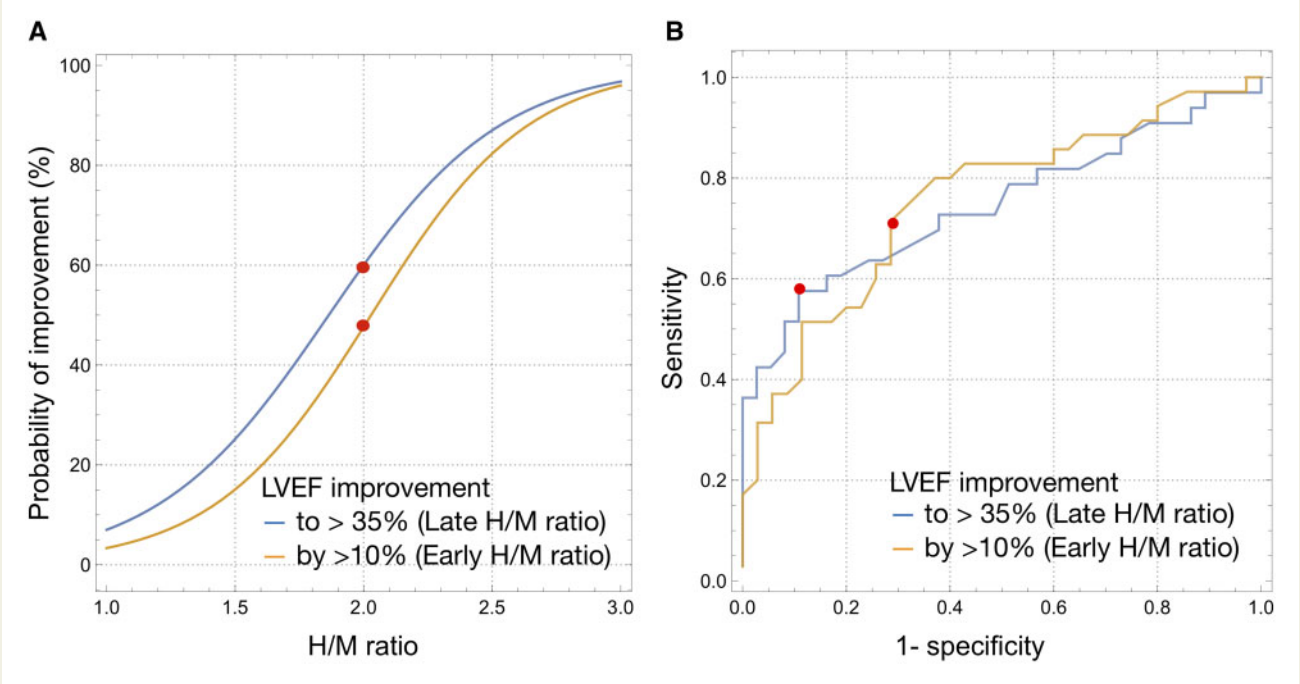


**Figure 5** (*A*) Probability of LVEF improvement to >35% using late H/M ratio (blue) and LVEF improvement by >10% (orange) using early H/M ratio. The optimal threshold of 2.0 for late H/M ratio corresponded with 60% probability of LVEF improvement to >35%. For early H/M ratio a threshold corresponded with 49% probability of LVEF improvement by >10%. (*B*) ROC analysis red dots denote the probability of LVEF improvement when H/M ratio is 2.0. ROC AUC was 0.746 and 0.755 using late and early H/M ratios, respectively.

percentage of CHF patients does not benefit from CRT implantation, so-called 'non-responders'.[8–10] It is anticipated that number of CHF subjects with a CRT indication will increase.[13,39] Therefore, the problem of non-response to CRT will be increasingly important, at least from a numerical point of view. The response to CRT is multifactorial, including pre-implantation factors such as aetiology of CHF, QRS duration, and mechanical dyssynchrony.[14,40,41] In addition, peri-implantation factors such an optimal delivery of CRT and targeted lead position are essential for response to CRT. Myocardial scar in the region of the LV pacing lead is an independent determinant of long-term prognosis in ischaemic HF.[42] Finally, post-implantation factors such as arrhythmia and device programming influence the response to CRT.[14] Several clinical and echocardiographic variables have been evaluated to predict response to CRT. Ischaemic aetiology, male gender, NYHA functional Class IV, severe mitral regurgitation, left atrial dilatation, and a short interventricular mechanical delay have been associated with worse echocardiographic and clinical outcomes.[4,43] However, their contributions to the selection of patients are limited as most of these variables were not independent predictors of the response to CRT.

Previous studies that evaluated cardiac $^{123}$I-*m*IBG scintigraphy in relation to long-term CRT response were single centre with relative small numbers of CHF patients.[25–28,44–46] Recently, the large single centre BETTER-HF study showed in CHF patients ($n = 121$) that the late H/M ratio was an independent predictor of CRT response defined as LV remodelling with 15% reduction of LVESV (regression coefficient 2.906, 95% CI 0.293–3.903, $P = 0.029$).[47] These results are in line with our study showing that LV remodelling (i.e. improvement of LVEF) was associated with the late H/M ratio. Furthermore, the BETTER-HF study showed that the late H/M ratio was an independent predictor of long-term clinical outcome (combined endpoint of cardiac mortality, cardiac transplantation, HF hospitalization: hazard ratio 0.033, 95% CI 0.005–0.880, $P = 0.040$). Tanaka *et al.*[48] showed that in CHF ($n = 50$) mechanical dyssynchrony is associated with $^{123}$I-*m*IBG assessed cardiac sympathetic activity. In patient with dyssynchrony late H/M ratio was lower compared to patients without dyssynchrony ($1.62 \pm 0.31$ vs. $1.82 \pm 0.36$, $P < 0.05$). Furthermore, patients with both dyssynchrony and late H/M ratio ≥1.6 had a higher frequency of CRT response and a favourable outcome after 3 years. Interestingly, Erol-Yilmaz *et al.*[25] showed that parallel to significant functional (NYHA class) improvement and echocardiographic reverse remodelling, CRT induces favourable changes in the neurohumoral system (i.e. increase of late H/M ratio), supporting the notion that structural reverse remodelling (i.e. increase of LVEF) may also induce reverse modulation of cardiac sympathetic activity and rebalance of cardiac autonomic activity.

In line with the previous studies, the results of our study showed that late H/M ratio is an independent predictor of reverse remodelling of LVEF (i.e. increase of LVEF to >35%). However, late H/M ratio is not associated with increase of LVEF >10%. In addition to baseline LVEF and DM, early H/M was an independent predictor for increase of LVEF >10%. Although the precise mechanism is unknown, the correlation between cardiac innervation (i.e. H/M ratio) and CRT response is highly interesting. Although a number of other variables have been suggested to improve CRT patient selection, only a few have seen wide-spread implementation. Most other imaging

modalities focus on mechanical and anatomical information, whereas the neurohumoral information gained from cardiac $^{123}$I-*m*IBG scintigraphy adds a unique perspective on the pathophysiology of HF in general and most likely for CRT response in particular.

Our study has some limitations. We used data from two cohort studies and analysed them retrospectively. As data about LVESV and LVEDV were not recorded we have only the LVEF as echocardiographic measurement. Furthermore, the loss of echocardiographic data of eight subjects during follow-up may have influenced the outcome. For assessment of functional impact we used the relatively subjective NYHA functional class, although a 6-min walk test would be more objective. However, these data were not available. In addition, we qualified two subjects that died during follow-up due to SCD as 'non-responder'. This qualification could potentially influence outcome. However, exclusion of these two subjects from the analyses did not change the outcome of the analyses (data not shown). Infarct size and location can be of influence of lead implantation and consequently with response. Pacemaker leads were placed according to the discretion of the cardiologist responsible of the CRT-D implantation and in line with the most recent guidelines, avoiding as much as possible infarcted myocardial areas. However, in a large number subjects exact information on the pacemaker lead in relation possible myocardial scar could not be retrieved in this retrospective study. Therefore, the available data were too small to perform an adequate multivariate analysis. We were therefore not able to assess the impact of pacemaker lead placement on CRT response. Remains that myocardial perfusion imaging with single-photon-emission computed tomography or positron emission tomography could be of help to locate possible infarcted myocardium and thereby help guide pacemaker lead placement.

Nonetheless, we feel that despite these limitations our data reflect clinical practice and could be useful to better identify CRT responders from non-responders.

# Conclusion

In stable CHF $^{123}$I-*m*IBG assessed cardiac sympathetic activity predicts CRT response defined as improvement of LVEF after follow-up of 1 year. Therefore, these results may help selecting CHF patients eligible for CRT and consequently reduce the percentage of non-response to CRT.

Trying to put our findings in a clinical perspective, we conclude that for CHF patients eligible for CRT based on the current criteria in combination with a late H/M ratio of at least 2.0 there is little doubt about clinical response and therefore strengthens the CRT indication (i.e. predicted response increasing from 60% and higher with higher late H/M ratios). However, in CHF patients with a late H/M ratio of 1.8 or less CRT indication should be reconsidered (i.e. predicted response declining from 50% and lower with lower late H/M ratios).

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