ESC HEART FAILURE
ESC Heart Failure 2015; **2**: 116–121
Published online 17 August 2015 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12057

ORIGINAL RESEARCH ARTICLE

Risk stratification of patients with chronic heart failure using cardiac iodine-123 metaiodobenzylguanidine imaging: incremental prognostic value over right ventricular ejection fraction

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Abstract

Aims Right ventricular (RV) systolic dysfunction has been shown to be an independent predictor of clinical outcome in patients with chronic heart failure (CHF), and cardiac metaiodobenzylguanidine (MIBG) imaging also provides prognostic information. We aimed to evaluate the long-term predictive value of combining RV systolic dysfunction and abnormal findings of cardiac MIBG imaging on outcome in CHF patients.

Methods and results We enrolled 63 CHF outpatients with left ventricular ejection fraction (EF) $<$40% in a prospective cohort study. At entry, RVEF was measured by radionuclide angiography. Furthermore, cardiac MIBG imaging was performed, and the cardiac MIBG washout rate (WR) was calculated. Reduced RVEF was defined as $\leq$37%, and abnormal WR was defined as $>$27%. The study endpoint was unplanned hospitalization for worsening heart failure (WHF) and cardiac death. During a follow-up period of 8.9 ± 4.3 years, 19 of 63 patients had unplanned hospitalization for WHF, and 19 of 63 patients had cardiac death. In multivariate analysis, both WR and RVEF were independent predictors of unplanned WHF hospitalization, while WR was also an independent predictor of cardiac death. A risk-stratification model based on independent predictors of unplanned WHF hospitalization separated the patients into those with low (absence of the predictors), intermediate (one of the predictors), and high (two or more of the predictors) risk of unplanned WHF hospitalization ($P < 0.0001$) or cardiac death ($P = 0.0113$).

Conclusions Cardiac MIBG imaging provides incremental value when it is used along with RV systolic dysfunction to predict clinical outcome in patients with CHF.

Keywords Chronic heart failure; Reduced left ventricular ejection fraction; Prognosis; Cardiac metaiodobenzylguanidine imaging; Right ventricular systolic function; Nuclear cardiology

Received: 28 February 2015; Revised: 24 June 2015; Accepted: 9 July 2015
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Introduction

Chronic heart failure (CHF) is an increasing socioeconomic burden on health-care systems, and hospitalizations due to heart failure make a significant contribution to the overall cost.[1,2] Therefore, reliable risk stratification to identify CHF patients at risk of admission for worsening heart failure (WHF) is of great importance. Previous studies demonstrated that right ventricular (RV) systolic dysfunction predicts poor prognosis in CHF patients.[3–6] In addition, cardiac iodine-123 (I-123) metaiodobenzylguanidine (MIBG) imaging also predicts poor outcome in CHF patients.[7–11] However, little is known about the predictive value of combining RV systolic dysfunction and MIBG imaging on long-term outcome in CHF patients.

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Aims

The aim of the current study was to investigate whether cardiac I-123 MIBG imaging provides additional prognostic information over RV systolic dysfunction in patients with CHF.

Methods

Patients

Sixty-three CHF outpatients with radionuclide left ventricular (LV) ejection fraction (EF) <40% were enrolled in a prospective cohort study. CHF was defined according to Framingham criteria.[12] Patients were required to be stable for ≥3 months on conventional therapy. Patients with significant renal failure (serum creatinine >3.0 mg/dL), insulin-dependent diabetes mellitus, or autonomic neuropathy were excluded. None had had implantable cardioverter defibrillators, biventricular pacemakers, or biventricular defibrillators at enrollment. At entry, radionuclide angiography, cardiac MIBG imaging, and echocardiography were performed; and a venous blood sample was drawn. All patients gave written informed consent. The study complied with the Declaration of Helsinki and was approved by our institutional review committee. The primary endpoint of this study was unplanned hospitalization for WHF. Cardiac death was the other study endpoint.

Radionuclide angiography

Patients underwent electrocardiogram-gated blood-pool scintigraphy with a conventional rotating gamma camera (Prism 2000, Picker, Bedford, OH, USA). Patients were given 740 MBq of technetium-99m-labelled human serum albumin (Nihon Medi-Physics, Nishinomiya, Japan). Reduced RVEF was defined as ≤37%.[6]

Cardiac MIBG imaging

Myocardial imaging with I-123 MIBG (Daiichi Radioisotope Laboratory, Tokyo, Japan) was performed with the same gamma camera as that used for radionuclide angiography. A 111 MBq dose of I-123 MIBG was injected intravenously at rest after an overnight fast. Initial and delayed image acquisitions were performed in the anterior chest view at 20 and 200 min after isotope injection. The heart-to-mediastinum ratio and the cardiac MIBG washout rate (WR) were calculated; an abnormal WR was defined as >27%.[8]

Echocardiography

Two-dimensional echocardiography was performed to measure LV end-diastolic and end-systolic dimensions and left atrial dimension, and the severity of mitral regurgitation (MR) was graded as previously described.[8,13]

Statistics

Data are presented as the mean ± SD. A Student's *t*-test and Fisher's exact test were used to compare differences in continuous and discrete variables, respectively. The prognostic value of baseline characteristics was assessed with a Cox proportional hazards regression analysis. Event-free survival rates were calculated using the Kaplan–Meier method, and the differences in survival rates were compared between groups with the log-rank test. A *P* value <0.05 was considered significant.

Results

Comparison of baseline characteristics

During a follow-up period of 8.9 ± 4.3 years, 19 of 63 patients had unplanned hospitalization for WHF, and 19 of 63 patients had cardiac death. Although atrial fibrillation was more often observed in patients with cardiac event (unplanned hospitalization for WHF and/or cardiac death), there was no significant difference in the other baseline clinical characteristics between the patients with and without cardiac event (*Table 1*). Patients

Table 1 Baseline clinical characteristics in the study patients with and without cardiac event (unplanned hospitalization for worsening heart failure and/or cardiac death)

	With cardiac event (*n* = 28)	Without cardiac event (*n* = 35)	*P*-value
Follow-up time, years	7.3 ± 4.3	10.2 ± 3.9	0.0082
Age, years	63 ± 14	62 ± 13	0.6264
Male sex, %	86	63	0.0506
Ischemic origin, %	39	63	0.0790
Diabetes mellitus, %	18	34	0.1660
Atrial fibrillation, %	39	9	0.0054
Body mass index, kg/m^2	22.7 ± 3.6	23.6 ± 3.0	0.2891
Medication			
Diuretics			
Loop, %	89	71	0.1190
Spironolactone, %	71	63	0.5931
Digitalis, %	64	54	0.5963
ACE inhibitor/ARB, %	86	89	0.9999
β-Blocker[a], %	79	89	0.3180
NYHA functional class	2.2 ± 0.7	2.1 ± 0.4	0.3728
Heart rate, beats/min	75 ± 14	74 ± 10	0.7840
Systolic blood pressure, mmHg	125 ± 20	130 ± 19	0.3037

ACE, angiotensin-converting enzyme; ARB, angiotensin II type 1 receptor blocker; NYHA, New York Heart Association; WHF, worsening heart failure.
Data are presented as the mean value ± SD or percentage of patients
[a]Use of β-blocker (carvedilol), as scored at the last follow-up visit.

with cardiac event had significantly larger left atrial dimensions, significantly higher MR grade, significantly lower serum sodium levels, significantly higher serum uric acid levels, and significantly higher plasma noradrenaline levels. Radionuclide RVEF was significantly lower, and WR was significantly higher in patients with than without cardiac event (*Table 2*).

Prognostic analysis

Univariate and multivariate Cox proportional hazard analyses for unplanned hospitalization for WHF and cardiac death are shown in *Table 3*. In multivariate analysis, WR was the independent predictor of both endpoints. In addition, RVEF and New York Heart Association (NYHA) functional class predicted unplanned hospitalization for WHF, and LVEF and the presence of atrial fibrillation predicted cardiac death.

Kaplan–Meier analysis showed that patients with an abnormal WR had a significantly higher risk of unplanned hospitalization for WHF regardless of the presence or absence of a reduced RVEF (*Figure 1*), although this was not the case for cardiac death (*Figure 2*).

To better define the risk in individual patients, a predictive model was constructed based on three independent predictors of unplanned hospitalization for WHF identified by multivariate Cox analysis: the presence of abnormal WR, reduced RVEF, and NYHA functional class III/IV. Low-risk, intermediate-risk, and high-risk groups of unplanned hospitalization for WHF (none: 6%, one: 20%, two or three: 80%) or cardiac death (none: 6%, one: 33%, two or three: 53%) were identified according to the number of risk factors (*Figure 3*).

Table 2 Baseline characteristics in the study patients with and without cardiac event (unplanned hospitalization for worsening heart failure and/or cardiac death)

	With cardiac event (n = 28)	Without cardiac event (n = 35)	P-value
Radionuclide angiography			
LVEF, %	28.0 ± 7.6	31.6 ± 6.8	0.0582
RVEF, %	43.4 ± 11.9	49.6 ± 10.2	0.0307
Echocardiography			
LVEDD, mm	65.7 ± 7.8	62.1 ± 7.1	0.0588
LVESD, mm	54.5 ± 7.7	51.3 ± 8.2	0.1261
LAD, mm	47.5 ± 8.8	40.6 ± 5.5	0.0004
MR grade	1.3 ± 0.7	0.9 ± 0.6	0.0153
Sodium, mEq/L	138 ± 3	140 ± 3	0.0239
Creatinine, mg/dL	1.00 ± 0.29	0.86 ± 0.26	0.0552
eGFR, mL/min/1.73m^2	58.7 ± 16.2	65.5 ± 20.3	0.1516
Uric acid, mg/dL	7.6 ± 2.1	6.3 ± 1.5	0.0043
Noradrenaline, pg/mL	535 ± 254	400 ± 250	0.0403
Cardiac MIBG imaging			
H/M(e)	1.78 ± 0.29	1.82 ± 0.25	0.5066
H/M(d)	1.59 ± 0.27	1.74 ± 0.32	0.0501
WR, %	39.3 ± 13.5	25.0 ± 11.2	$<$0.0001

eGFR, estimated glomerular filtration rate; H/M(d), heart-to-mediastinum metaiodobenzylguanidine uptake ratio on the delayed images; H/M(e), heart-to-mediastinum metaiodobenzylguanidine uptake ratio on the early images; LAD, left atrial dimension; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; MIBG, metaiodobenzylguanidine; MR, mitral regurgitation; RVEF, right ventricular ejection fraction; WHF, worsening heart failure; WR, washout rate of cardiac metaiodobenzylguanidine.
Data are presented as the mean value ± SD.

Discussion

Increased sympathetic nerve activity in patients with CHF has been shown to be associated with a poor prognosis,[14] and cardiac MIBG imaging has been introduced as a useful tool for the estimation of cardiac adrenergic nerve activity.[15] Since the first report by Merlet *et al.*[7] that showed the prognostic value of cardiac MIBG imaging in patients with CHF, the predictive value of MIBG imaging has been confirmed in several studies including ours.[8–11] The present long-term, prospective, observational study expands on previous research by demonstrating that cardiac I-123 MIBG imaging can provide incremental value when it is combined with RV systolic dysfunction to predict clinical outcome in patients with CHF.

Although our result was in line with previous reports showing that RV systolic dysfunction is a predictor of poor prognosis in CHF patients,[3,5,6] we did not observe a significant association between RV systolic dysfunction and cardiac mortality. This might be explained by the difference in the patients' background. In our study, patients had mild to moderate symptoms of CHF, and only 15 patients (24%) were in NYHA class III/IV compared with 100% in the study by Meyer *et al.*[5] Unlike in the study by De Groote *et al.*,[6] most of the study patients were enrolled before the beta-blocker era in our study. Moreover, the mean age of our study patients (62 years) was relatively higher than that of previous reports.[3,6]

Our study was consistent with the report by Manrique *et al.*[4] in that cardiac sympathetic dysfunction as assessed by cardiac MIBG imaging was an independent predictor of cardiac mortality, while RV systolic dysfunction was not. In addition to the results by Manrique *et al.*, our study demonstrated that cardiac MIBG imaging provided incremental value when it was used along with RV systolic dysfunction to predict poor outcome in CHF patients, showing that a simple risk-stratification model based on the independent predictors of unplanned WHF hospitalization was useful not only for the prediction of heart failure admission but also for that of cardiac death.

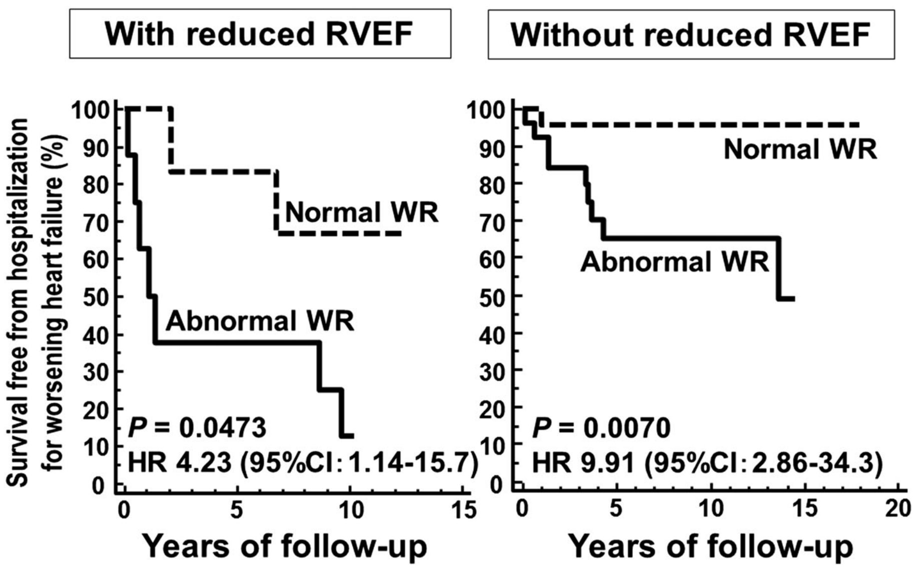
Although RVEF measurement by radionuclide angiography has been considered the gold standard for RV systolic function,[3–6] new RV systolic parameters, such as RVEF measured by magnetic resonance imaging or echocardiographic indices, are currently under evaluation.[6] Further research is needed to identify the best index of RV systolic function and to

Table 3 Univariate and multivariate Cox proportional hazard analyses for the identification of patients at risk for unplanned hospitalization for worsening heart failure and cardiac death

	Univariate analysis		Multivariate analysis	
	P-value	HR (95% CI)	*P*-value	HR (95% CI)
Cox proportional hazard model for unplanned hospitalization for worsening heart failure				
WR	0.0002	1.059 (1.028–1.092)	0.0110	1.039 (1.009–1.070)
LAD	0.0015	1.089 (1.034–1.148)	—	—
RVEF	0.0037	0.930 (0.886–0.976)	0.0204	0.929 (0.873–0.988)
Sodium	0.0178	0.838 (0.725–0.969)	—	—
NYHA functional class (III/IV)	0.0228	2.900 (1.165–7.214)	0.0495	2.739 (1.007–7.448)
MR grade (≧grade 2)	0.0242	3.102 (1.165–8.257)	—	—
Uric acid	0.0301	1.248 (1.023–1.522)	—	—
Atrial fibrillation	0.0423	2.675 (1.040–6.884)	—	—
Cox proportional hazard model for cardiac death				
WR	0.0004	1.057 (1.025–1.089)	0.0118	1.047 (1.010–1.085)
Atrial fibrillation	0.0015	4.349 (1.766–10.708)	0.0293	2.999 (1.123–8.008)
LAD	0.0120	1.066 (1.014–1.120)	—	—
LVEF	0.0125	0.927 (0.874–0.984)	0.0091	0.919 (0.862–0.979)
Creatinine	0.0273	4.313 (1.186–15.692)	—	—
Uric acid	0.0297	1.305 (1.028–1.658)	—	—

HR, hazard ratio; CI, confidence interval; LAD, left atrial dimension; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; RVEF, right ventricular ejection fraction; WR, washout rate of cardiac metaiodobenzylguanidine.

Figure 1 Survival rates from unplanned heart failure hospitalization in patients with and without reduced RVEF. RVEF, right ventricular ejection fraction; CI, confidence interval; HR, hazard ratio; WR, washout rate of cardiac metaiodobenzylguanidine.



compare its prognostic value with that of cardiac MIBG imaging in CHF patients.

Limitations of the study

There are several limitations to this study. First, this is a single-centre study, and the number of the study subjects is small. Second, because we included only stable outpatients with mild to moderate heart failure symptoms, one should not generalize our results to patients with severe CHF. Third, we could not include several echocardiographic indices that have been shown to be predictive of clinical outcome of CHF patients[6,16] in the analysis. Lastly, because most of the study patients were included in our placebo-controlled study where the efficacy of carvedilol or amlodipine was evaluated last century (T. Yamada *et al.*, unpublished study, 1995 to 1999), no study patient received beta-blocker therapy at entry. As previously reported, results of cardiac MIBG imaging is influenced by heart failure medications.[17,18] Therefore, caution should be made when generalizing our results to the recent patients with CHF.

Figure 2 Survival rates from cardiac death in patients with and without reduced RVEF. RVEF, right ventricular ejection fraction; CI, confidence interval; HR, hazard ratio; WR, washout rate of cardiac metaiodobenzylguanidine.

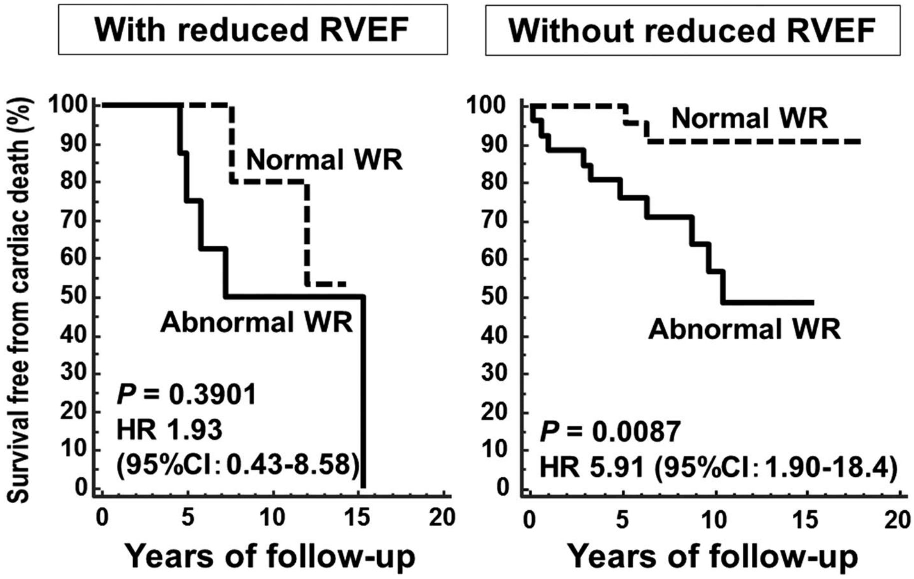
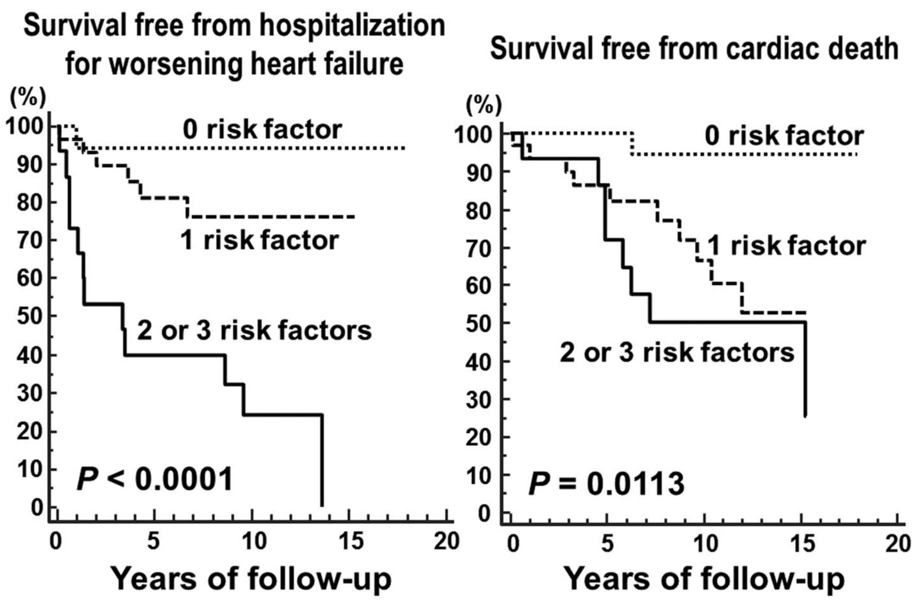


Figure 3 Risk-stratification model based on abnormal cardiac metaiodobenzylguanidine washout rate, reduced right ventricular ejection fraction, and New York Heart Association functional class III/IV.



Conclusions

We demonstrated that in patients with CHF, cardiac MIBG imaging provided additional prognostic value when it was combined with RV systolic dysfunction. In addition, our result suggested that cardiac MIBG imaging was a more potent predictor of cardiac mortality in CHF patients compared with RV systolic dysfunction. Further studies are needed to compare prognostic value of cardiac MIBG imaging with that of RV systolic parameters and to better risk stratify the patients with CHF.

Conflict of interest

All authors declare that they have no conflict of interest.

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