A simplified wall-based model for regional innervation/perfusion mismatch assessed by cardiac ^{123}I-*m*IBG and rest ^{99m}Tc-tetrofosmin SPECT to predict arrhythmic events in ischaemic heart failure

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Aims	Cardiac ^{123}iodine-*meta*-iodobenzylguanidine (^{123}I-*m*IBG) single-photon emission computed tomography (SPECT) imaging provides information on regional myocardial innervation. However, the value of the commonly used 17-segment summed defect score (SDS) as a prognostic marker is uncertain. The present study examined whether a simpler regional scoring approach for evaluation of ^{123}I-*m*IBG SPECT combined with rest ^{99m}Tc-tetrofosmin SPECT myocardial perfusion imaging could improve prediction of arrhythmic events (AEs) in patients with ischaemic heart failure (HF).
Methods and Results	Five hundred and two ischaemic HF subjects of the ADMIRE-HF study with complete cardiac ^{123}I-*m*IBG and rest ^{99m}Tc-tetrofosmin SPECT studies were included. Both SPECT image sets were read together by two experienced nuclear imagers and scored by consensus. In addition to standard 17-segment scoring, the readers classified walls (i.e. anterior, lateral, inferior, septum and apex) as normal, matched defect, mismatched (innervation defect > perfusion defect), or reverse mismatched (perfusion defect > innervation defect). Cox proportional hazards ratios (HRs) were used to determine if age, body mass index, functional class, left ventricular ejection fraction (LVEF), B-type natriuretic peptide (BNP), norepinephrine, ^{123}I-*m*IBG SDS, ^{99m}Tc-tetrofosmin SDS, innervation/perfusion mismatch SDS, and our simplified visual innervation/perfusion wall classification were associated with occurrence of AEs (i.e. sudden cardiac death, sustained ventricular tachycardia, resuscitated cardiac arrest, appropriate implantable cardioverter-defibrillator therapy). At 2-year median follow-up, 52 subjects (10.4%) had AEs. Subjects with 1 or 2 mismatched walls were twice as likely to have AEs compared with subjects with either 0 or 3–5 mismatched walls (16.3% vs. 8.3%, $P = 0.010$). Cox regression analyses showed that patients with a visual mismatch in 1-2 walls had an almost two times higher risk of AEs [HR 2.084 (1.109–3.914), $P = 0.001$]. None of the other innervation, perfusion and mismatch scores using standard 17 segments were associated with AEs. BNP (ng/L) was the only non-imaging parameter associated with AEs.

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Conclusion	A visual left ventricular wall-level based scoring method identified highest AE risk in ischaemic HF subjects with intermediate levels of innervation/perfusion mismatches. This simple technique for the evaluation of SPECT studies, which are often challenging in HF subjects, seems to be superior to the 17-segment scoring method.
Keywords	chronic heart failure • [123]I-*m*IBG scintigraphy • arrhythmia • innervation/perfusion mismatch

Introduction

Chronic heart failure (CHF) is a life-threatening syndrome with a growing incidence and prevalence worldwide.[1] Despite therapeutic improvements, the prognosis of CHF remains unfavourable partly due to arrhythmias and sudden cardiac death (SCD).[2] The introduction of implantable cardioverter-defibrillators (ICDs) has improved the overall survival of CHF patients.[3–5] Current guidelines recommend ICD implantation for primary prevention of fatal arrhythmias in symptomatic CHF subjects with New York Heart Association (NYHA) functional class ≥ 2 under optimal pharmacological therapy and a left ventricular ejection fraction (LVEF) $\leq 35\%$.[6] Although ICDs applied for primary or secondary prevention of SCD reduce the relative risk of death by 20%, a high percentage (65%) of patients had never received appropriate ICD therapy 3 years after implantation.[7] Moreover, the risk of malfunction (post)operative complications and the relatively high cost of these devices supports the need for optimization of current ICD selection criteria for primary prevention.

In the past decades, results of cardiac *meta*-iodobenzylguanidine ([123]I-*m*IBG) imaging have been shown to be of prognostic value in CHF.[8,9] Most published cardiac [123]I-*m*IBG studies have risk-stratified patients based on global cardiac uptake using the heart-to-mediastinum (H/M) ratio on planar images. In addition to global cardiac uptake, regional uptake can be assessed with single-photon emission computed tomographic (SPECT) imaging. In a prospective study including 116 CHF patients eligible for ICD implantation, SPECT was shown to be an independent predictor of appropriate ICD therapy and cardiac death.[10] Furthermore, it has been suggested that in ischaemic heart failure (HF) heterogeneity of sympathetic innervation may create a myocardial substrate particularly vulnerable to fatal arrhythmia.[11,12] This heterogeneity can reflect sympathetic denervation from infarction, as well as reversible ischaemia. A previous study showed that HF subjects with arrhythmias had a innervation/perfusion mismatch with a larger defect size on innervation SPECT than on myocardial perfusion imaging SPECT based on a 17-segment model compared to subjects without arrhythmias.[13] However, when total innervation and perfusion defect scores are used for analysis, significance of segmental mismatches may be obscured.

We hypothesized that assessing innervation/perfusion mismatch using a simple 5-segment wall-based model might be more convenient and equally as effective as the standard 17-segment scoring method. The objective of this study was to evaluate this new wall-based model to determine its utility in risk stratification for arrhythmic events (AEs) in ischaemic HF.
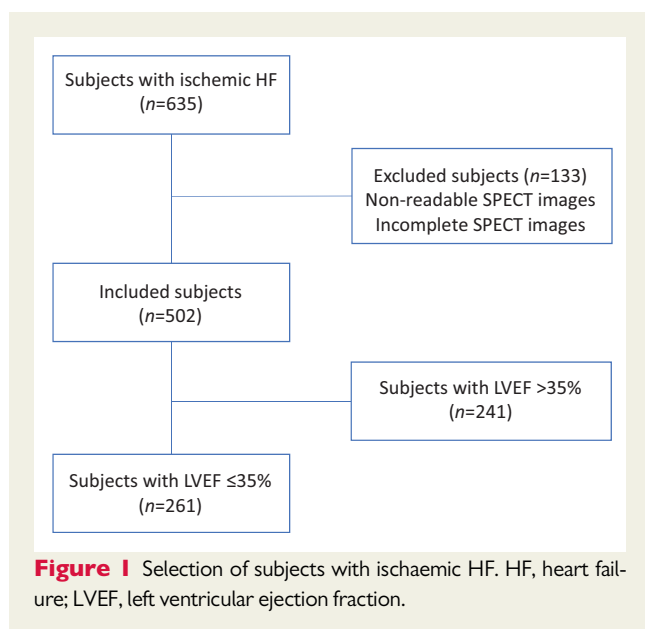
Materials and methods

Subjects

The study involved a re-analysis of previously collected patient data and images from the prospective multicentre ADMIRE-HF study, which was approved by institutional review boards and ethics committees at each centre, with all subjects signing written informed consents; specific study details have been reported previously.[9] The inclusion criteria of the ADMIRE-HF study were: ischaemic or non-ischaemic HF with a site-reported LVEF $\leq 35\%$, NYHA functional class II or III and receiving evidence-based medical therapy including a beta-blocker and angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. Exclusion criteria were: a functioning pacemaker or ICD implantation and prior cardiac electrical therapy for a ventricular arrhythmia, cardiac acute myocardial infarction (MI) within the previous 30 days, and serum creatinine >265 μmol/L.

It has been shown that the prognostic significance of patterns of [123]I-*m*IBG and ^{99m}Tc-tetrofosmin uptake differ between ischaemic and non-ischaemic HF.[14] Furthermore, in non-ischaemic HF, the significance of a ^{99m}Tc-tetrofosmin perfusion defect remains uncertain, and consequently it is unclear what an innervation/perfusion mismatch in relation to arrhythmia would mean. Therefore we evaluated subjects with ischaemic HF only. Of 635 ADMIRE-HF subjects with ischaemic heart HF and SPECT ([123]I-*m*IBG and ^{99m}Tc-tetrofosmin) images available in the primary efficacy population, readable SPECT images were available in 502 subjects. These 502 subjects were included in the current study (*Figure 1*).

For the inclusion of the original ADMIRE-HF study, a site-reported LVEF was used.[9] For quality assurance purposes, sites also submitted echocardiograms to an independent core laboratory for quantitative assessment of left ventricular volumes and LVEFs. Shah *et al.*[15] analysed the discrepancy between on-site LVEF measurements and echocardiographic LVEF measurements by the core laboratory of the original ADMIRE-HF study. It was shown that the on-site-reported LVEF assessment underestimated the LVEF compared to the core laboratory measurements. Although on-site measurement of LVEF reflects daily clinical practice, uniform LVEF assessment is to be preferred from a methodological point of view. Therefore, in this study, we only used core laboratory echocardiographic LVEF measurements. As a consequence some subjects had an LVEF >35%. As the current guidelines use an LVEF cut-off of $\leq 35\%$ for ICD implantation,[6] we separately analysed only those subjects with core laboratory LVEF $\leq 35\%$ ($n = 261$).

Clinical evaluation

Before imaging, all subjects underwent clinical evaluation including assessment of functional class and determination of plasma [B-type natriuretic peptide (BNP) and norepinephrine (NE) plasma levels.

Figure 1 Selection of subjects with ischaemic HF. HF, heart failure; LVEF, left ventricular ejection fraction.

Echocardiographic analysis

All echocardiograms were evaluated in a core laboratory blinded to both nuclear imaging and clinical status. Ventricular volumes were determined by the Simpson method in the apical four-chamber view, and LVEF was calculated from volumes in the standard manner.[16]

Nuclear image acquisition and processing

On separate days subjects underwent [123]I-*m*IBG and rest ^{99m}Tc-tetrofosmin imaging. Planar and SPECT [123]I-*m*IBG imaging was performed sequentially beginning approximately 3 h 50 min post-injection of [123]I-*m*IBG using low energy/high resolution collimators.[9] For this study, [123]I-*m*IBG SPECT data were reconstructed using ordered subsets-expectation maximization with deconvolution of septal penetration to correct for image contamination from high-energy ^{123}I photons.[17] There was no pre-construction filtering, but post-reconstruction three-dimensional filtering using a Butterworth low-pass filter (critical frequency 0.4 cycles/cm, power 10) was performed.[18] Images were processed and prepared for display and interpretation at a core laboratory (Emory University) using the Emory Cardiac Toolbox (ECTb).

[123]I-*m*IBG and ^{99m}Tc-tetrofosmin image analysis

For the current study, all SPECT images were re-analysed by six expert readers from the USA and Europe. The image sets were assigned in random order and interpreted by consensus of two primary readers with results recorded by consensus. In total, the data represent results from four different pairs of readers. SPECT interpretation was performed with access to selected clinical information (i.e. age, gender, and body mass index) to assist readers in identifying potential attenuation artefacts. Readers were blinded to additional diagnostic test results and clinical outcomes. [123]I-*m*IBG and conventionally reconstructed ^{99m}Tc-tetrofosmin image SPECT slices were displayed adjacent to each other.

17-segment model

Scoring was done by the standard 17-segment/5-point model used for SPECT myocardial perfusion imaging[19] (*Figure 2*). Readers were permitted to score individual segments as non-diagnostic. SDS (range 0–68) were derived for images of both radiotracers. The mismatch SDS ([123]I-*m*IBG SDS − ^{99m}Tc-tetrofosmin SDS) was subsequently calculated.

Wall-based model

In addition to standard 17-segment scoring, the readers classified walls (i.e. anterior, lateral, inferior, septum and apex) (*Figure 2*) as normal, matched defect, mismatched (innervation defect > perfusion defect), or reverse mismatched (perfusion defect > innervation defect). For this comparison of innervation and perfusion images, the assessment was based on the overall appearance of a wall on each image. For characterizing a defect as either matched or mismatched, a distinct difference between the innervation and perfusion images was required. If the size and severity of defects in a wall were judged equivalent, the category 'matched' was used, even in the presence of potentially small areas of mismatch. An example is shown in *Figure 3*.

Follow-up

In the original ADMIRE-HF, study subjects were followed for a maximum of 2 years after enrolment or until confirmed death, study withdrawal, loss to follow-up, or trial termination after a protocol-specified number of outcome events.[9] ADMIRE-HFX extended follow-up to 2 years for patients who had not previously reached it, and these data were used for this study.[20] A clinical adjudication committee had reviewed ADMIRE-HF CRFs and source documents to confirm AEs and deaths.[9,21] AEs were defined as documented episodes of spontaneous sustained (>30 s) ventricular tachycardia, resuscitated cardiac arrest, appropriate ICD therapy (i.e. anti-tachycardia pacing or defibrillation), and/or SCD, defined as an unexpected death in a previously stable patient including comatose subjects who died after attempted resuscitation and those for whom no other cause of death could be identified.

Statistical analysis

All continuous variables are expressed as mean ± standard deviation. Differences between groups for continuous data were compared using an unpaired *T*-test and for categorical data, a χ^2 test was used. Efficacy analysis used univariate and multivariate Cox proportional hazards models for the primary endpoint (AEs) using age, NYHA functional class, LVEF classified by core laboratory, BNP levels, NE levels, [123]I-*m*IBG SDS, ^{99m}Tc-tetrofosmin SDS, and innervation/perfusion mismatch SDS and the simplified visual innervation/perfusion wall classification. 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. In general, a *P*-value <0.05 was regarded as statistically significant. The statistical analyses were performed with SPSS, release 25.0 (SPSS Inc., Chicago, USA, 2017).

Results

In total, 502 subjects (mean age 64.9 ± 10.6 years, 86% male) were included. Baseline characteristics, including the number of mismatched walls per subject, are shown in *Table 1*. The majority had a history of an MI (82%), NYHA functional class 2 (85%), and the mean
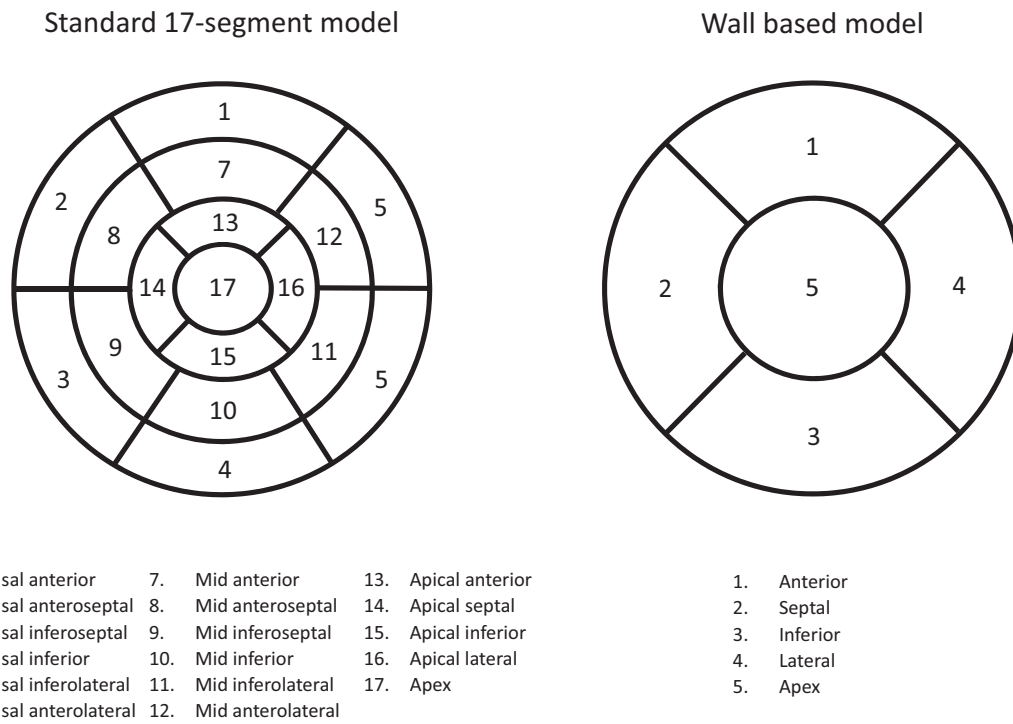
Standard 17-segment model

Wall based model

1.	Basal anterior	7.	Mid anterior	13.	Apical anterior
2.	Basal anteroseptal	8.	Mid anteroseptal	14.	Apical septal
3.	Basal inferoseptal	9.	Mid inferoseptal	15.	Apical inferior
4.	Basal inferior	10.	Mid inferior	16.	Apical lateral
5.	Basal inferolateral	11.	Mid inferolateral	17.	Apex
6.	Basal anterolateral	12.	Mid anterolateral		

1. Anterior
2. Septal
3. Inferior
4. Lateral
5. Apex

Figure 2 Display, on a circumferential polar plot, of the 17-segments model (left) and the wall-based model (right).
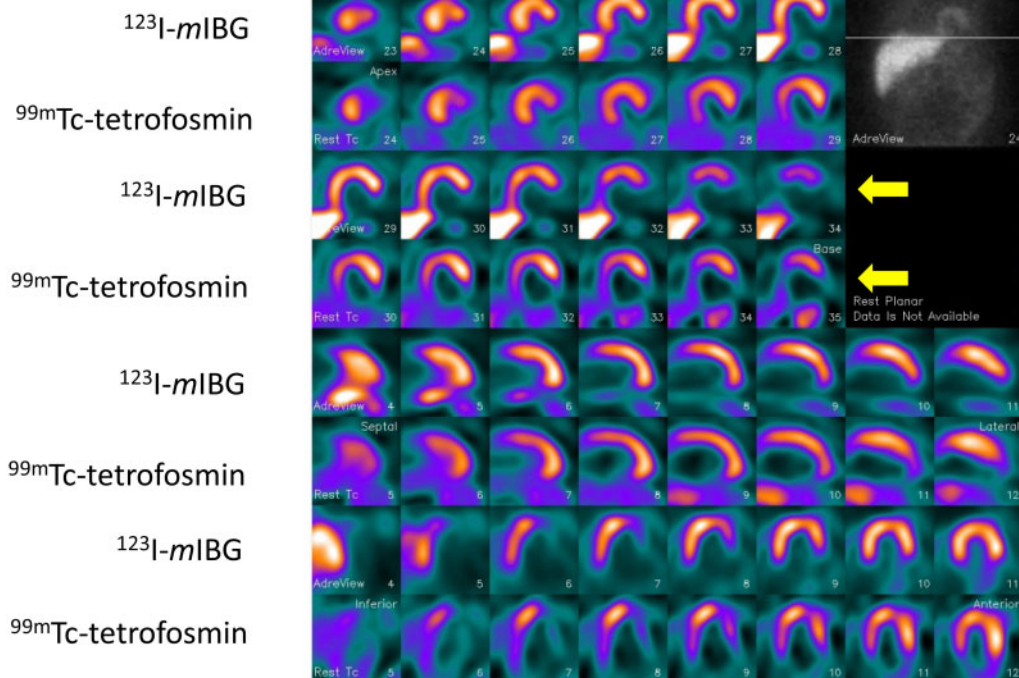

Figure 3 Example of a 68-year-old patient with infero-postero-lateral myocardial infarction showing an innervation/perfusion mismatch with a more pronounced [123]I-*m*IBG SPECT defect of the lateral wall compared to the ^{99m}Tc-tetrofosmin SPECT defect (indicated by the yellow arrows).

Table I Patient baseline characteristics

	All (n = 502)
Age (years)	64.9 ± 10.6
Male (%)	433 (86.3)
History of myocardial infarction (%)	413 (82.2)
BMI (kg/m^2) (n = 501)	28.4 ± 5.3
NYHA functional class 2/3 (%)	424 (84.5)/78 (15.5)
EDV (mL) (n = 460)	210 ± 51
LVEF (%) (n = 460)	34.5 ± 6.7
BNP (ng/L) (n = 478)	241 ± 363
NE (pg/mL) (n = 476)	677 ± 377
Number of mismatched walls (%)	
0	16 (3.1)
1	37 (7.4)
2	92 (18.3)
3	130 (25.9)
4	136 (27.1)
5	91 (18.1)
SPECT score	
^{123}I-*m*IBG SDS (n = 467)	41.2 ± 12.4
^{99m}Tc-tetrofosmin SDS (n = 499)	18.9 ± 11.4
Difference/mismatch score (n = 466)	22.4 ± 12.9
Clinical events	
AEs (%)	52 (10.4)

AEs, arrhythmic events; BMI, body mass index; BNP, B-type natriuretic peptide; Difference/mismatch score, ^{123}I-*m*IBG SDS − ^{99m}Tc-tetrofosmin SDS; EDV, end-diastolic volume; LVEF, left ventricular ejection fraction; NE, norepinephrine; NYHA, New York Heart Association; SDS, summed defect score.

core laboratory LVEF was 34.5 ± 6.7%. The mean ^{123}I-*m*IBG SDS was 41.2 ± 12.4, mean ^{99m}Tc-tetrofosmin SDS 18.9 ± 11.4, and mean mismatch SDS was 22.4 ± 12.9.

Arrhythmic events

At 2-year median follow-up, no subject was lost to follow-up. Thirty-four subjects (6.8%) had a cardiac death of whom 14 subjects (2.8%) could be classified as SCD. In total, 52 subjects (10.4%) of the total study population experienced AEs. The absolute and relative number of AEs per mismatched walls are shown in *Table 2*. *Figure 4* clearly illustrates there was no linear correlation between the number of mismatched walls and AEs. Most AEs occurred in subjects with 1-2 mismatched walls. We therefore dichotomized the study population

Table 2 AEs per number of mismatched walls based on the wall-based model

Number of mismatched walls	AEs (%)
0 (n = 16)	1 (6.3)
1 (n = 37)	6 (16.2)
2 (n = 92)	15 (16.3)
3 (n = 130)	10 (7.7)
4 (n = 136)	9 (6.6)
5 (n = 91)	11 (12.1)

into subjects with 1-2 mismatched walls and those subjects without 1-2 mismatched walls (i.e. either 0 or 3–5 mismatched walls).

Predictors of arrhythmic events in total study population

Subjects with 1 or 2 mismatched walls were twice as likely to have AEs compared to subjects with either 0 or 3–5 mismatched walls (16.3% vs. 8.3%, P = 0.010) (*Table 3*). *Figure 5A* shows the Kaplan–Meier curves of AEs by number of dichotomized mismatched walls according the new wall-based model. Multivariate cox regression analyses showed that that the BNP (ng/L) [HR 1.001 (1.000–1.001), P = 0.005] and presence of visual mismatch in 1-2 walls [HR 2.084 (1.109–3.914), P = 0.001] were the only independent predictor of AEs (*Table 4*). None of the other innervation, perfusion and mismatch scores using standard 17 segments were associated with AEs. Furthermore, the differences in AEs between patients with (n = 413) and without (n = 89) a previous MI have been analysed. In total, 48 (11.6%) patients in the MI group experienced an AE vs. 4 (4.5%) patients in the group without a previous MI. Multivariate Cox-regression analysis showed that in the MI group BNP (HR 1.001), 1-2 mismatched segments (HR 1.911), NYHA class (HR 0.446), LVEF (HR 0.930), and ^{123}I-*m*IBG SDS (HR 0.968) were independent predictors for arrhythmia. In patients without a previous MI multivariate Cox-regression analysis could not identify an independent predictor of arrhythmia, most likely related to the low event rate in this group.

Predictor of arrhythmic events in subjects with LVEF ≤35%

Of the 261 subjects with an LVEF ≤35% 38 subjects (14.6%) experienced AEs. Subjects with 1 or 2 mismatched walls were more than twice as likely to have AEs compared to subjects with either 0 or 3–5 mismatch walls (24.0% vs. 10.8%, P = 0.006) (*Table 3*). *Figure 5B* shows the Kaplan–Meier curves of AEs by number of by dichotomized mismatched walls according to the new wall-based model. Cox regression analyses showed that that both the presence of visual mismatch in 1-2 walls [HR 2.412 (1.204–4.830), P = 0.010] and BNP (ng/L) [HR 1.001 (1.000–1.001), P = 0.001] were the only independent predictors of AEs (*Table 5*). None of the other innervation, perfusion and mismatch scores using standard 17 segments were associated with AEs.

Discussion

This study showed that a simple left ventricular wall-level based scoring method identified the highest AE risk in ischaemic HF subjects with intermediate levels of innervation/perfusion mismatches. Furthermore, innervation/perfusion mismatch seems a stronger predictor for arrhythmias compared to only innervation (i.e. ^{123}I-*m*IBG SDS) or perfusion (i.e. ^{99m}Tc-tetrofosmin SDS).

Most patients who die of ventricular arrhythmia have heart disease, predominately coronary artery disease. Although the exact pathophysiology of ventricular arrhythmias is still a matter of debate, it has been recognized that myocardial ischaemia and scar tissue may serve as substrate for ventricular arrhythmias. Areas with slow conduction may facilitate the development of re-entrant tachycardia.[22] Furthermore, cardiac sympathetic hyperactivity is also an important
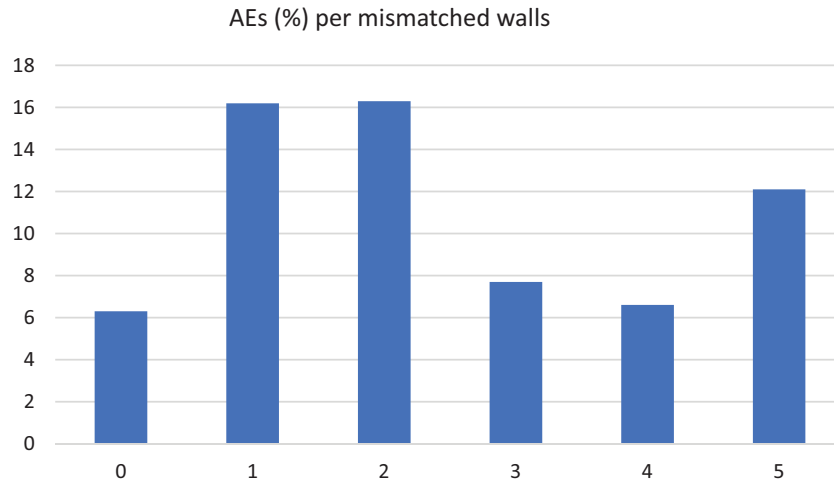
Figure 4 AEs per number of mismatched walls based on the wall-based model showing a 'bell-shaped' curve relation between AEs and number of mismatched walls.

Table 3 Patient characteristics of the total study population (left) and only subjects with LVEF ≤35% (right) with subgroups 1-2 mismatched walls and no 1-2 mismatched walls (i.e. 0, 3, 4, 5 segments) based on the wall-based model

	All subjects (n = 502)			Subjects with LVEF ≤35% (n = 261)		
	1-2 mismatched walls (n = 129)	No 1-2 mismatched walls (n = 373)	P-value	1-2 mismatched walls (n = 75)	No 1-2 mismatched walls (n = 186)	P-value
Age (years)	64.6 ± 11.2	65.0 ± 10.5	0.878	64.3 ± 11.4	64.7 ± 10.1	0.733
Male (%)	106 (82.2)	327 (87.7)	0.118	64 (85.3)	164 (88.2)	0.532
History of MI (%)	108 (83.7)	305 (81.8)	0.617	66 (88.0)	148 (79.5)	0.109
BMI (kg/m^2)	28.4 ± 6.0	28.4 ± 5.1	0.076	28.8 ± 5.7	28.9 ± 5.0	0.194
NYHA functional class 2/3 (%)	112 (86.8)/17 (13.2)	312 (83.6)/61 (16.4)	0.391	66 (88.0)/9 (12.0)	160 (86.0)/26 (14.0)	0.671
EDV (mL)	208 ± 52	211 ± 50	0.661	232 ± 45	237 ± 46	0.588
LVEF (%)	34.3 ± 6.5	34.5 ± 6.8	0.318	30.5 ± 3.6	29.6 ± 3.9	0.359
BNP (ng/L)	243 ± 401	241 ± 349	0.696	275 ± 486	268 ± 374	0.580
NE (pg/mL)	701 ± 417	669 ± 364	0.115	742 ± 456	675 ± 338	0.040
SPECT score						
[123]I-*m*IBG SDS	36.1 ± 13.2	42.9 ± 11.7	0.030	36.9 ± 12.9	45.9 ± 11.2	0.123
[99m]Tc-tetrofosmin SDS	23.4 ± 13.0	17.4 ± 10.4	0.001	25.2 ± 12.4	18.7 ± 10.3	0.035
Difference/mismatch score	12.6 ± 7.7	25.7 ± 12.7	<0.001	11.8 ± 7.0	26.6 ± 12.6	<0.001
Clinical events						
AEs (%)	21 (16.3)	31 (8.3)	0.010	18 (24.0)	20 (10.8)	0.006

AEs, arrhythmic events; BMI, body mass index; BNP, B-type natriuretic peptide; Difference/mismatch score, ^{123}I-mIBG SDS–[99m]Tc-tetrofosmin SDS; EDV, end-diastolic volume; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NE, norepinephrine; NYHA, New York Heart Association; SDS, summed defect score.

factor in the genesis of potential lethal ventricular arrhythmias in patients with impaired LVEF. In these patients, rhythm abnormalities are related to enhanced automaticity, triggered automaticity, and re-entrant mechanisms. These mechanisms are enhanced by release of NE. In addition, non-uniform denervated myocardium in infarct zones can be hypersensitive to NE. In particular, an infarct border zone containing a mixture of fibrotic and viable myocardial tissue is susceptible to development of re-entrant circuits. This mechanism is most likely
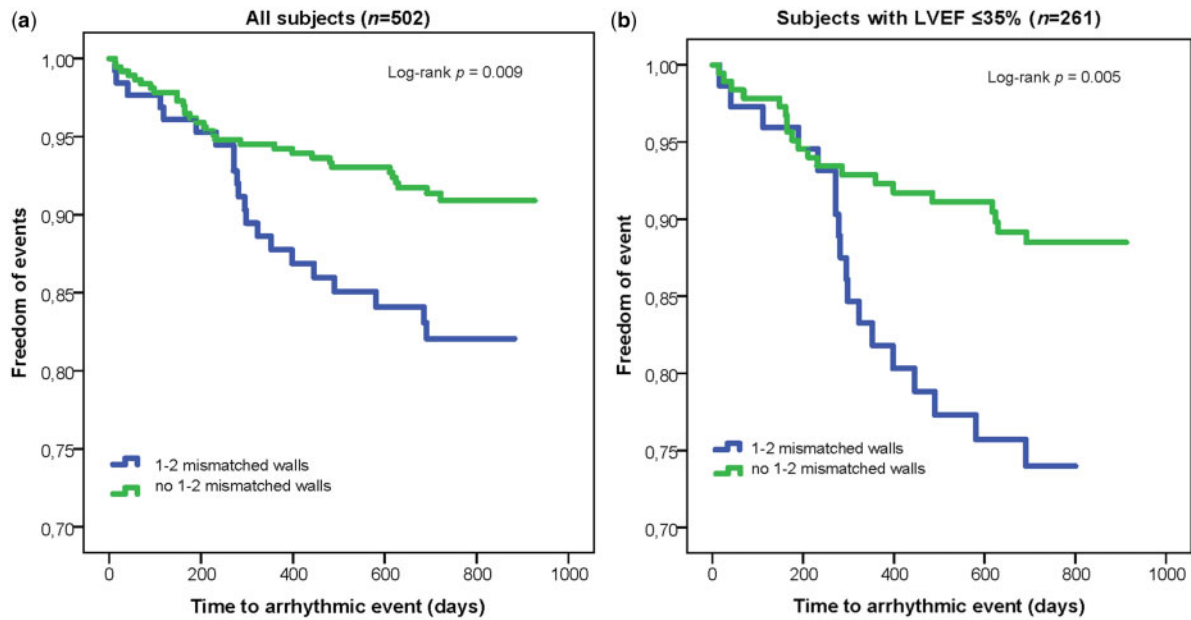
Figure 5 (*A*) Kaplan–Meier curves of all subjects showing AEs dichotomized for innervation/perfusion mismatch segments (1-2 segments vs. no 1-2 segments). (*B*) Kaplan–Meier curves of subjects with LVEF ≤35% showing AEs dichotomized for innervation/perfusion mismatch segments (1-2 segments vs. no 1-2 segments).

Table 4 Multivariate Cox regression analysis for AEs in total study population using variables: age, BMI, NYHA functional class, LVEF, BNP, NE, [123]I-*m*IBG SDS, ^{99m}Tc-tetrofosmin SDS, and innervation/perfusion mismatch SDS, new wall-based innervation/perfusion mismatch

	Variable	HR (95% CI)	χ^2	Change χ^2	*P*-value
AEs	BNP (ng/L)	1.001 (1.000–1.001)	7.940	4.591	0.005
	BNP (ng/L)	1.001 (1.000–1.001)	13.213	4.856	0.001
	1-2 mismatched walls	2.084 (1.109–3.914)			

Table 5 Multivariate Cox regression analysis for AEs in subject with LVEF ≤35% using variables: age, BMI, NYHA functional class, LVEF, BNP, NE, [123]I-*m*IBG SDS, ^{99m}Tc-tetrofosmin SDS, and innervation/perfusion mismatch SDS, new wall-based innervation/perfusion mismatch

	Variable	HR (95% CI)	χ^2	Change χ^2	*P*-value
AEs	1-2 mismatched walls	2.412 (1.204–4.830)	6.581	5.880	0.010
	BNP (ng/L)	1.001 (1.000–1.001)	13.434	4.129	0.001
	1-2 mismatched walls	2.538 (1.261–5.107)			

triggered by sympathetic nerve fibres being more susceptible to ischaemia than myocytes, thereby causing an imbalance between still viable but partly denervated and normal myocardium.[23,24] This imbalance in cardiac sympathetic innervation may create a myocardial substrate vulnerable to lethal arrhythmias.

Based on this hypothesis, it has been suggested that in addition to impaired [123]I-*m*IBG SDS an innervation/perfusion mismatch could be a predictor for AEs in CHF. However, the outcome of previous studies are not uniform. For example, Boogers *et al.*[10] evaluated [123]I-*m*IBG SDS and innervation/perfusion mismatch based on [123]I-*m*IBG SDS and [99m]Tc-

tetrofosmin SDS in 116 subjects with both ischaemic and non-ischaemic HF. The study showed that in univariate analysis innervation/perfusion mismatch based on [123]I-*m*IBG SDS and ^{99m}Tc-tetrofosmin SDS was a predictor for appropriate ICD therapy [HR 1.06 (1.02–1.09), *P* < 0.01]. However, multivariate analysis showed that only [123]I-*m*IBG SDS with a cut-off of 26 was an independent predictor for appropriated ICD therapy [HR 1.13 (1.05–1.21), *P* < 0.01]. This confirms that there is a relation between innervation/perfusion mismatch and ICD therapy, however, the impact of innervation abnormalities seems to be stronger. One of the explanations for the lack of predictive value for innervation/perfusion mismatch in multivariate analysis could be the heterogeneity in the study population (ischaemic vs. non-ischaemic HF and primary prevention ICD indication vs. secondary prevention ICD indication). Recently, Travin *et al.* showed in subjects with only ischaemic HF that [123]I-*m*IBG SDS was the only predictor for AEs [HR 0.975 (0.951–0.999), *P* = 0.042].[25] The HR <1, indicates that the risk of AEs decreases with increasing innervation defect scores. This observation is in part explained by the fact that subjects with intermediate abnormal SPECT studies had the highest risk for AEs compared to subjects with extensive or no abnormalities. In contrast to the strong linear relation between severity of cardiac sympathetic dysfunction and overall prognosis in CHF, the results of this study suggest that the relation between cardiac sympathetic dysfunction and arrhythmia is non-linear and support the previous mentioned hypothetical pathophysiological mechanism behind these fatal arrhythmias.

Our study shows that there also was a non-linear relation between wall-based innervation/perfusion mismatch and AEs. This 'bell-shape' relation between the number of innervation/perfusion mismatched walls and AEs, showed that the intermediate group (i.e. 1-2 mismatched walls) had the highest risk for developing AEs (*Figure 4*). These results are in line with the findings by Travin *et al.*[25] Similar results were shown in a multicentre study with 135 subjects with CHF referred for ICD implantation for primary prevention.[26] This study also showed a 'bell-shape' curve between the late H/M ratio in relation to appropriated ICD therapy, suggesting that subjects in the intermediate groups had the highest risk for fatal arrhythmia. However, in both these studies,[25,26] the predictive value of cardiac sympathetic dysfunction for arrhythmia or appropriate ICD therapy was lacking. An explanation for this lack of predictive value is that the models used assumed a linear relationship between variables. In our present study, we showed a non-linear relationship between the number of mismatched walls by the wall-based model and AEs. Consequently, the number of mismatched walls, used as a continue variable, was not a predictor for AEs (data not shown). However, when dichotomized (i.e. 1-2 vs. no 1-2 mismatched walls) the mismatched walls became an independent predictor for AEs. In line with previous studies[10,25] multivariate analysis shows that innervation/perfusion mismatch based on SDS had no predictive value in our study. This lack of predictive value could be related to the fact that innervation/perfusion mismatch based on SDS is used as a continuous variable. Furthermore, an innervation/perfusion mismatch based on innervation and perfusion SDS does not necessary reflect regional mismatch per segment, but only a mismatch of the total SDS. Finally, overall impaired myocardial [123]I-*m*IBG uptake, often present in HF subjects, makes distinction of the myocardium in 17 segments on SPECT difficult. Examining innervation and perfusion based on standard regional wall designation provides a simpler approach for risk stratification. This simplified wall-based method reduces the variation as introduced with the 17-segment model and the method thereby provides a look at the bigger picture.

Analyses showed that BNP and innervation/perfusion mismatch by the wall-based model were independent predictors for AEs in both the total study population and as well in those subjects with LVEF ≤35%. BNP has been proven to be a very good predictor for the overall prognosis in HF.[27] In our study, compared to the innervation/perfusion mismatch by the wall-based model [HR 2.084 (1.109–3.914)], the predictive value of BNP for AEs is relative low [HR 1.001 (1.000–1.001)]. However, this change in risk is per 1 ng/L change of BNP.

Finally, it seems that in subjects that fulfilled the current criteria for ICD implantation[6] (i.e. NYHA functional class 2 or 3 and LVEF ≤35%) the predictive value of innervation/perfusion mismatch by the wall-based model improves (i.e. HR increases). This underlines that the best risk assessment regarding the occurrence of AEs is a combination of clinical, echocardiographic and neurohormonal/perfusion parameters.

Limitations

The most important limitation is that some of the SPECT images were non-diagnostic as a result of insufficient [123]I-*m*IBG uptake. Although CZT detectors have an improved sensitivity over conventional anger cameras it still disputable if this improved sensitivity can overcome the lack of signal from subjects with a poorly innervated myocardium. Of the 635 ischaemic HF subjects only 502 had readable [123]I-*m*IBG and ^{99m}Tc-tetrofosmin SPECT images. This resulted in exclusion of 133 (20.9%) subjects. LVEF was significantly lower in subjects with a non-diagnostic [123]I-*m*IBG SPECT scan (data not shown). These significant lower values could indicate severe CHF. However, no significantly higher risk of AEs was observed compared to subjects with a diagnostic image (data not shown). Some SDS scores could not be assessed because they were classified as non-diagnostic (due to incomplete assessment of segments). This could have affected the outcomes of the analyses, but also underlines the shortcoming of the 17-segment model assessment. Furthermore, a quantitative approach based on the percentage [123]I-*m*IBG uptake per wall would be less subjective and maybe results in less variation. However, the current data did not permit for such a quantitative approach. Finally, the maximum follow-up time in this study was 30.4 months. A longer follow-up time would have probably resulted in more AEs and possible resulting in a stronger predictive model.

Conclusion

In subjects with ischaemic HF, there is a non-linear relation between innervation/perfusion mismatch assessed with a simplified wall-based model and AEs. This new and simple method to assess innervation/perfusion mismatch is feasible and may be helpful in risk assessment.

Conflict of interest: A.F.J. was an employee at GE Healthcare during the conduct of the original ADMIRE-HF study. The other authors declare that they have no conflict of interest.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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