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ORIGINAL RESEARCH

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Sex differences in ^{123}I-mIBG scintigraphy imaging techniques in patients with heart failure

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ABSTRACT

Background: ^{123}I-mIBG-scintigraphy could be a useful stratifying tool for patients with heart failure (HF). The purpose of this retrospective study is to evaluate whether there are differences between men and women with HF in terms of the prediction of cardiac arrhythmic events (AE).

Research and methods: A total of 306 patients, before implantable-cardioverter-defibrillator (ICD) implantation, were evaluated. They underwent ^{123}I-mIBG-scintigraphy and an evaluation of the results was performed after 85 months of follow-up. Early and late planar and SPECT cardiac images were acquired. Heart-to-mediastinum ratio (HM) for planar images and the sum of the segmental scores (SS) for SPECT were calculated.

Results: In the general population, age, early SS (ESS), late SS (LSS), and ejection fraction (EF) were statistically significant for the prediction of AE at Cox regression, while early and late HM (eHM,lHM) were not significative for the prediction of AE. Population was divided into females and males and univariate analysis was conducted separately for the two cohorts: no significant variables for prediction of AE were found in females. For males, ESS, LSS, EF, and late HM were statistically significant predictors of AE. The overall survival was similar in males and females, but the risk of AE is lower in males than in females.

Conclusions: ^{123}I-mIBG represents a more effective tool for the prediction of AE in male patients than in women.

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Cardiac innervation; cardiac arrhythmic events; ESS; heart failure; HM; mIBG; SPECT

1. Introduction

Meta-iodobenzylguanidine (mIBG), also known as Iobenguane, is a noradrenaline analog and it is considered a 'false' neurotransmitter since it is an aralkylguanidine derived from the combination of the benzyl group of bretylium, an antiarrhythmic drug, and the guanidine group of guanethidine, an adrenergic neuron blocker [1]. This molecule is taken up by presynaptic sympathetic nerve endings via sodium- and ATP-dependent 'uptake-1' mechanism and, differently from norepinephrine, it is not metabolized. It accumulates physiologically in neurosecretory vesicles of all tissues with adrenergic innervation such as the myocardium, salivary glands, and adrenal medulla. The possible applications of mIBG in nuclear medicine could range from oncological treatment and endocrinology to neurology and cardiology: mIBG labeled with ^{131}I is a radiotherapeutic metabolic agent in neuroectodermal malignancies [1,2]; when it is labeled with ^{123}I, it could be used to discriminate Parkinson's Disease (PD) and Multiple System Atrophy (MSA) through the identification of cardiac postganglionic autonomic involvement, since cardiac uptake is possible if only postganglionic sympathetic neurons are undamaged. This phenomenon is typical in MSA which has a preganglionic autonomic failure [3–5]; ^{123}I-mIBG finds application in the detection of phaeochromocytomas, paragangliomas, and neuroblastomas but could also be used in carcinoids, medullary thyroid carcinomas and nonfunctioning paragangliomas [6,7]. In cardiology, ^{123}I-mIBG main indication is for the evaluation of patients with a diagnosis of heart failure (HF) [8,9]. In this paper, the application of ^{123}I-mIBG in patients with HFrEF has been analyzed and viable solutions for the acquisition protocols have been proposed. Nowadays, no studies sex-based have been conducted to evaluate the difference between males and women with HF in terms of the prediction of cardiac arrhythmic events (AE). In the following paragraphs, a review of the possible role of mIBG in HF will be explained, and the study conducted will be presented.

1.1. Role of mIBG in heart failure

The scintigraphy with ^{123}I-mIBG could be a potentially useful tool to stratify patients with heart failure. It is possible to determine the density and the function (that is the turnover) of presynaptic norepinephrine (NE) receptors through the cardiac uptake on late ^{123}I-mIBG images. Since mIBG is an analog of the false neurotransmitter guanethidine, it is not degraded and catabolized back in the presynaptic terminals

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Article highlights

- ^{123}I- Meta-iodobenzylguanidine (mIBG) scintigraphy finds application in cardiology for the evaluation of patients with a diagnosis of heart failure (HF)
- This is the first study sex-based evaluating the difference between males and women with HF in terms of the prediction of cardiac arrhythmic events (AE) through ^{123}I-mIBG-scintigraphy
- 306 patients before implantable-cardioverter-defibrillator (ICD) implantation underwent ^{123}I-mIBG scan. Heart-to-mediastinum ratio (HM) for planar images and the sum of the segmental scores (SS) for SPECT were calculated.
- ^{123}I-mIBG represents a more effective tool for the prediction of AE in male patients than in women.

after the uptake in the presynaptic terminal by NET-1 (NE transporter 1 or also called uptake-1). It accumulates in presynaptic vesicles and gives information about the possible denervation grade in the myocardium [10] which is typical of chronic heart failure (CHF).

In fact, after the initial event which decreases the cardiac pump function, neurohormonal balance alterations and activation of the sympathetic nervous system occur to compensate for the pump function reduction [11]. The elevated circulating levels of NE determine a depletion of NE stored in the myocardium and this may be due to a protective mechanism, as demonstrated in a study by Bristow et al. They observed a decrease of 50% in alpha-adrenergic receptor density in IV class CHF [12].

Furthermore, another aspect we must consider for ^{123}I-mIBG scintigraphy: the images obtained 4 h after tracer administration (late) better predict the heart function and the patient outcome [13–15].

The parameters commonly used to define the innervation defeat are heart-to-mediastinum rate (HMR), washout rate (WR) between early and late planar images, and regional ^{123}I-mIBG uptake in Single-photon emission computerized tomography (SPECT) images. It was demonstrated that ^{123}I-mIBG cardiac uptake was depressed in patients suffering from idiopathic dilated cardiomyopathy and this correlates with left ventricular dysfunction [16]. In particular, HMR demonstrated to be a better poor prognosis predictor than LVEF < 20% (the sensitivity was 95% and 93% the specificity with HMR < 1.2) in a cohort of 90 patients with New York Heart Association (NYHA) Class II-IV HF and left ventricular ejection fraction (LVEF) <45% [17]. A meta-analysis by Verberne et al. demonstrated the decisive contribution of ^{123}I-mIBG imaging in heart failure with reduced ejection fraction (HFrEF), assessing that abnormal WR has a pooled hazard ratio (HR) of 1.72 for cardiac death and an HR of 1.08 for cardiac events [18]. Thanks to AdreView Myocardial Imaging for Risk Evaluation in Heart Failure [ADMIRE-HF] udy, it has been established the strong utility of HMR: a progressive decline in mortality was correlated with increasing HMR (from 20% for HMR <1.10 to 0% for HMR 1.80) while the low risk was present in patients with preserved HMR, that is major or equal to 1.60 [14].

The SPECT parameters were recently considered in a study by De Vincentis et al. [19]. They selected 170 patients with CHF eligible for implantable cardioverter-defibrillator (ICD) implantation which underwent planar and SPECT imaging. HMR (early, eHM, and late, lHM), ^{123}I-mIBG WR, early (ESS), and late (LSS) summed SPECT scores were obtained. Between them, 69 patients had an arrhythmic event (AE). They observed that the only predictor of AE was ESS, also in patients with ICD for primary prevention.

To date, no study has been done to verify whether there are gender differences in predicting arrhythmic events in patients with HF with ^{123}I-mIBG scintigraphy.

The purpose of this study, which collects the results of ^{123}I-mIBG cardiac scintigraphy, evaluating differences between males and females in patients with HFrEF in terms of prediction of AE, where for AE it was considered episodes of sustained ventricular tachycardia superior to 30 s, anti-tachycardiac pacing or defibrillation, resuscitated cardiac arrest or sudden cardiac death (SCD).

2. Patients and methods

2.1. Patient population

We retrospectively valued in our Institution 306 patients with HF who experienced or had not experienced AE, where AE was considered episodes of sustained ventricular tachycardia superior to 30 s, anti-tachycardiac pacing or defibrillation, resuscitated cardiac arrest or sudden cardiac death (SCD). Patients with NYHA class II or III, left ventricular ejection fraction (LVEF) <35%, the presence of indication for an ICD implantation as primary or secondary prevention, with an expected survival >1 year, an age major of 18 years old and which signed informed consent were included. All patients followed optimal medical therapy, as described in international current guidelines [20]. Patients with previous ICD implantation, cardiac resynchronization therapy (CRT) indication, oncological history, and severe valvopathy, which suffered acute coronary syndrome less than 3 months or had a contraindication to ICD implantation, were excluded. All patients underwent ^{123}I-mIBG scintigraphy 7–15 days before ICD implantation and evaluation of the results was performed after an 85-month follow-up. The study protocol obtained the approval of the institutional committee on human research and respected the ethical guidelines of the 1975 Helsinki Declaration.

2.2. Acquisition protocols

The patient preparation consisted of the administration of 5% Lugol solution to obtain the thyroid blockage before the injection of 150–185 MBq of ^{123}I-mIBG (AdreView, GE Healthcare). Planar anterior images of the thorax were acquired for 10 min with a zoom factor of 1 and a 128 × 128 matrix, respectively, 15 (early) and 240 (late) min after the tracer administration. A dual-head gamma camera (Infinia, GE Healthcare, Milwaukee, U.S.A.) equipped with a low-energy parallel-hole high-resolution collimator (LEHR) was used. After the planar images, at 25 min and 250 min post-injection, SPECT cardiac images were acquired using the same dual-headed gamma camera over 180° with a 90°-rotation, from 45° right-anterior oblique projection to the 45°

left-posterior oblique projection. The matrix used was 64 × 64 and a zoom factor was equal to 1. A step-and-shot technique was applied consisting of 64 projections that had gone on 30 s per frame in non-gated mode. The energy window for planar and SPECT images was equal to ±10% of the 159-KeV ^{123}I photopeak.

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

No standardization in calculating HMR has been reached since different criteria are present in the literature. For this reason, planar ^{123}I-mIBG images were analyzed and it was calculated HMR and WR for both early and late images as previously described by De Vincentis et al. [19]. The SPECT analysis has been conducted by only one researcher to lower interobserver variability. The SPECT analysis started with the reorientation of cardiac images, in short, vertical length, and horizontal long heart axes after filtered-back-projection (FBP) reconstruction with the support of Myovaton software implemented on a Xeleris Duo platform (GE Healthcare). Butterworth low-pass filter was used as a preprocessing filter (for early SPECT order: 10, cutoff frequency: 0.3 cycles/cm; for late SPECT order: 20, cutoff frequency: 0.3 cycles/cm). The heart images were analyzed with a standard 17-segment model, the same method of myocardial perfusion imaging (MPI) [21,22]. For all the segments, it was established that the score following a 5-point scale where a value major or equal to 70% was defined as normal and scored as 0, a value between 69 and 60% (mildly reduced uptake) was scored as 1, values between 59 and 50% (moderately reduced uptake) was scored 2. At least segments with a 49–40% defect (severely reduced uptake) were scored as 3, while absent uptake (i.e. ≤39%) was scored as 4. ESS and LSS were calculated as the sum of the segmental scores. The difference summed score (DSS) was gained through the subtraction between ESS and LSS.

2.4. Statistical analysis

All patients included in the study were considered for statistical analysis. Categorical variables were summarized using frequencies, and percentages, and compared using the $\chi 2$ test. Quantitative variables are expressed using median ± IQR and compared Wilcoxon rank-sum test. In addition to gender, we considered age, body mass index (BMI), males rate, comorbidities such as diabetes, dyslipidemia, chronic renal failure (CRF), chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), smoke habits, administered treatment as ACE-inhibitors, α and β-blockers, potassium-sparing diuretics, calcium antagonists, sartans, amiodarone and digitalis, the defect scores ESS, LSS, the planar parameters eHM, lHM, WR and ejection fraction (EF). Overall survival (OS) was calculated from ^{123}I-mIBG cardiac scintigraphy to death for any cause or AE. Patients without OS events were censored at the time of the last clinical follow-up. Quantiles of OS were estimated through Kaplan – Meier product-limit estimators and gender differences in survival rate were assessed using the log-rank test and stratified analyses. The effects of predictors were evaluated through univariate Cox regression. Hazard ratios (HRs) and their 95% confidence intervals (CI) were reported. A multivariate Cox regression analysis was also considered by including predictors in a stepwise fashion and minimizing the Akaike Information Criterion. The resulting best model included only one variable; therefore, we do not report multivariate analyses. All tests are two-tailed, a $p < 0.05$ was deemed as statistically significant. All analyses were conducted using R (R development core team, Vienna, Austria) version 4.2.0.

3. Results

3.1. Subjects

A total of 306 consecutive patients (247 males, 59 females) with HF before implantable cardioverter-defibrillator (ICD) implantation were enrolled, studied for arrhythmic events, followed for 85 months (See Figure 1) and the overall survival in males and females (see Figure 2) was described. A total of 115 patients had arrhythmic events during follow-up (89 males) and 191 (158 males) had not. Diabetes was present in 33% of patients, of which 38.3% experienced AE, and 40.9% had dyslipidemia. A 89.9% took beta-blockers while 82% diuretics. The characteristics of the population are better detailed in Table 1. The significant parameters were ESS with a $p < 0.001$, LSS with p equal to 0.013, and EF with p equal to 0.024. Planar parameters eH/M ($p = 0.234$), lH/M ($p = 0.309$), and WO ($p = 0.592$) were not significant.

3.2. Univariate analysis and OS estimation

At univariate analysis for the general population age, ESS, LSS, and EF were significant at Cox regression, while early and late HM were not significant. The HR of ESS was 1.021 [95% CI (1.005, 1.036), $p = 0.008$], while LSS had an HR of 1.017 [95% CI (1.002, 1.032), $p = 0.022$)]. Early H/M had an HR of 0.674 [95% CI (0.294, 1.545), $p = 0.351$)], late H/M of 0.504 [95%CI (0.218, 1.162)], the p-value was 0.108] and EF of 0.975 [95% CI (0.955, 0.996), the p-value was 0.019] (See Table 2). ESS and LSS demonstrated to be predictors of AE. After stratification, for females, we found no significant variable (see Table 3). For males, ESS, LSS, EF, and late H/M (but not early H/M) were significant. The HR of early H/M was 0.503 with CI (0.198,1.276), $p = 0.148$ while HR of late H/M was 0.339 with CI (0.132,0.874) and $p = 0.025$; HR for ESS was 1.029 with CI (1.011, 1.047), p was 0.001; HR of LSS was 1.025 with CI (1.008, 1.043), $p = 0.005$; HR of EF was 0.973 with CI (0.95, 0.997) and $p = 0.027$ (See Table 4).

Through the Kaplan–Meier curves it was seen that the overall survival was quite similar between women and men (Figure 2).

4. Discussion

Limited data are available to estimate the differences between females and males in outcomes of patients with HF and the major of them focus on ischemic disease. The gender impact on mortality in patients with HF is still controversial. Regarding the ischemic aspect, in a study by Dharma et al. [23] women and men with ST-segment elevation myocardial infarction and with

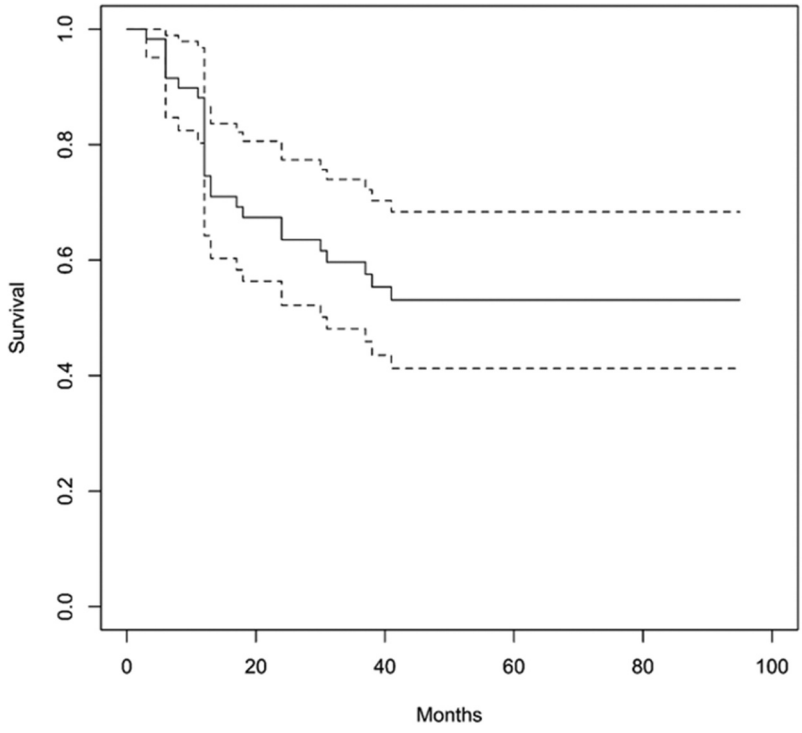

Figure 1. Kaplan–Meier curve for the general population displaying survival during the follow up. The survival curve includes AE and death. The dotted line indicates the confidence interval. The continuous line represents the survival trend versus time.

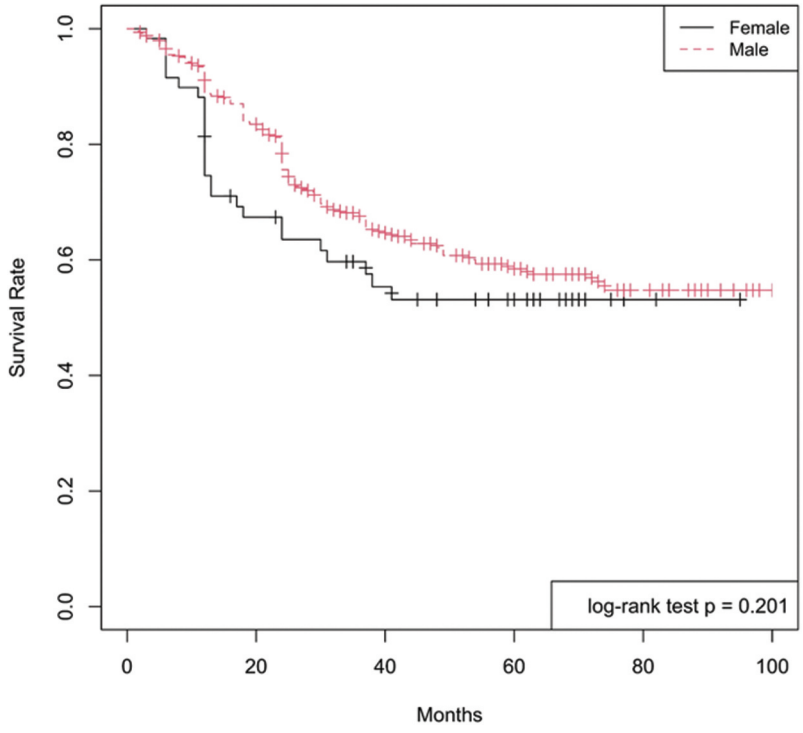

Figure 2. Kaplan–Meier curve displaying survival during the follow up for women and men separately. The survival curve includes AE and death. No gender difference in survival rate has been found.

a score ≥II in Killip classification had an equal risk of early mortality. In a study conducted on patients with HF, Biykem and Khalaf demonstrated that women with HF and a low left ventricular EF are more symptomatic and have poor outcomes compared to men. Nevertheless, the study had an underrepresented women population [24]. Recently Hyun-Jin et al. sought the gender differences in patients with HF and with HFrEF [25]. In women with HFrEF, they observed that ischemic disease is an independent risk factor for long-term mortality. On the opposite, for the survey of Gracia Gutiérrez et al., women presented a 33%

Table 1. Characteristics of general population. All patients have been divided per each variable represented in the first column in patients with AE and patients which did not experience AE. The *p* value of each variable has been reported.

Variables	All (*N* = 306)	With AE (*N* = 115)	Without AE (*N* = 191)	p value
Gender, male (%)	247 (80.7)	89 (77.4)	158 (82.7)	0.32
Age	64 [55-73]	65 [58-73]	63 [54-73]	0.097
Diabetes	101 (33.0)	44 (38.3)	57 (29.8)	0.164
Dyslipidaemia	128 (41.8)	47 (40.9)	81 (42.4)	0.885
COPD	57 (18.6)	27 (23.5)	30 (15.7)	0.124
CKD	51 (16.7)	20 (17.4)	31 (16.2)	0.916
Smoke	159 (51.9)	59 (51.3)	100 (52.4)	0.952
ACE-inhibitors	130 (42.5)	51 (44.3)	79 (41.4)	0.695
Beta-blockers	275 (89.9)	100 (87.0)	175 (91.6)	0.265
diuretics	251 (82.0)	99 (86.1)	152 (79.6)	0.199
Potassium- sparing diuretics	162 (52.9)	63 (54.8)	99 (51.8)	0.702
Calcium antagonists	17 (5.6)	8 (7.0)	9 (4.7)	0.567
Sartans	69 (22.5)	20 (17.4)	49 (25.6)	0.125
Ace_ARB	184 (60.1)	66 (57.4)	118 (61.8)	0.523
Digitalis	67 (21.9)	26 (22.6)	41 (21.5)	0.927
Amiodarone	54 (17.6)	24 (20.9)	30 (15.7)	0.321
Nitrates	93 (30.4)	37 (32.2)	56 (29.3)	0.691
alfa-blockers	11 (3.6)	5 (4.3)	6 (3.1)	0.753
Statin	185 (60.5)	69 (60.0)	116 (60.7)	0.995
ESS	29 [22-38]	27 [20-37]	33 [26-40]	**<0.001**
LSS	35 [26-43]	36 [28.5–45.5]	33 [24-41]	**0.013**
DSS	60 [19.6)	28 (24.3)	32 (16.7)	0.141
Early H/M	1.63 [1.50–1.78]	1.63 [1.48–1.73]	1.64 [1.51–1.79]	0.234
Late H/M	1.53 [1.39–1.71]	1.53 [1.38–1.66]	1.54 [1.40–1.73]	0.309
WR	30.1 [19.5–42.1]	30.7 [19.9–42.9]	29.8 [18.5–41.4]	0.592
EF	30 [25-35]	30. [24.5–35]	30 [25-35]	**0.024**
CAD	188 (61.4)	67 (58.3)	121 (63.3)	0.444

Table 2. The univariate analysis applied to the general population. For each variable, HR, the CI interval, and *p* value has been reported. Only age is a statistically significant variable for the prevision of arrhythmic event.

Variables	HR	Low CI	Up CI	p value
Gender, male	0.748	0.483	1.158	0.193
Age	1.017	1.001	1.032	0.033
BMI	0.49	0.189	1.271	0.143
SAH	1.236	0.846	1.807	0.274
Diabetes type II	1.362	0.934	1.984	0.108
Dyslipidemia	0.959	0.661	1.392	0.827
COPD	1.568	1.018	2.414	0.041
CRF	1.144	0.706	1.854	0.584
Smoke	0.977	0.78	1.223	0.837
ESS	1.021	1.005	1.036	0.008
LSS	1.017	1.002	1.032	0.022
Early H/M	0.674	0.294	1.545	0.351
Late H/M	0.504	0.218	1.162	0.108
EF	0.975	0.955	0.996	0.019
CAD	0.877	0.605	1.27	0.487

lower risk of 1-year mortality [26]. Women with advanced HF treated with palliative care seem to have a lower quality of life than men [27] even if the results seem not to be only sex-related. In a study by Hersi et al., sex was demonstrated to be an independent risk factor for in-hospital mortality for STEMI [28]. Comparable results were found by Lawesson et al. [29]. Several studies demonstrated that not only gender but also Killip class ≥II and age were independent predictors of in-hospital mortality in women and men [30–33]. There are also attractive differences between men and women in the biochemical aspect of ischemic disease. A novel review of the Suthahar group [34] reported several differences in biomarkers that reflect biological sex-related differences such as genetic differences, sex hormones influence, and different fat distribution [35,36]. Lower cardiac natriuretic peptide (NP) levels have been observed in males, while estrogen may increase the NP levels [37–42]. Higher levels of galectin-3 have been found in women and HF patients [43–46]. Men show a higher soluble form of ST2 (sST2) level, which acts as a decoy receptor of interleukin-33 (IL-33) which has cardioprotective effects [47]. Growth differentiation factor-15 is associated with a high risk to develop HF and it is lower in women [48–51] while osteopontin, a protein whose expression is up-regulated in HF [52], has lower levels in women [53,54]. The estrogen deficiency, which is typical of menopause, is associated with the increase in cardiac mass, and diastolic dysfunction and might have a central role in the genesis of HF with preserved EF (HFpEF) [55]. Women with breast cancer treated with aromatase inhibitors have an increased risk of HF [56]. Moreover, fetal HF is

Table 3. The univariate analysis applied to the females. For each variable, HR, the CI interval, and *p* value has been reported. No variable was statistically significant for the prevision of arrhythmic event.

Variables	HR	Low CI	Up CI	p value
Age	0.997	0.973	1.022	0.815
BMI	0.196	0.024	1.596	0.128
SAH	0.495	0.224	1.096	0.083
Diabetes type II	1.187	0.529	2.663	0.678
Dyslipidemia	0.861	0.384	1.934	0.718
COPD	1.945	0.73	5.188	0.184
CRF	0.227	0.031	1.677	0.146
Smoke	0.683	0.413	1.128	0.136
ESS	1.011	0.981	1.042	0.477
LSS	1.003	0.976	1.031	0.821
Early H/M	2.127	0.321	14.074	0.434
Late H/M	1.995	0.336	11.838	0.447
EF	0.982	0.943	1.024	0.402
CAD	0.567	0.246	1.305	0.182

Table 4. The univariate analysis conducted for men. For each variable, HR, the CI interval, and *p* value has been reported. Age, SPECT variables, EF and surprisingly late H/M were statistically significant variable for the prevision of arrhythmic events.

Variables	HR	Low CI	Up CI	p value
Age	1.028	1.008	1.048	0.006
BMI	0.858	0.265	2.777	0.799
SAH	1.699	1.076	2.684	0.023
Diabetes type II	1.411	0.922	2.16	0.113
Dyslipidemia	1.011	0.664	1.539	0.959
COPD	1.519	0.938	2.46	0.089
CRF	1.466	0.882	2.436	0.14
Smoke	1.091	0.845	1.408	0.505
ESS	1.029	1.011	1.047	0.001
LSS	1.025	1.008	1.043	0.005
Early H/M	0.503	0.198	1.276	0.148
Late H/M	0.339	0.132	0.874	0.025
EF	0.973	0.95	0.997	0.027
CAD	1.057	0.681	1.641	0.804

associated with maternal obesity and the expression of placental P-glycoprotein [57,58]. HFpEF has been highlighted in obese females [59–63] while the increased prevalence of HFpEF in older women seems to be due to the loss of ovarian hormones, in particular estrogens [64–69]. It is assumed that the G protein-coupled estrogen receptor (GPER) also known as GPR30 participates in the cardiac function and structure conservation after loss of estrogens. Estrogen loss causes dysfunction in cardiac relaxation, determines an increase of reactive oxygen species (ROS), and compromises the oxidant defenses, having a role in the hypertrophic and interstitial remodeling and aortic stiffening [70].

Although many gender difference studies on mortality risk have been conducted, no studies on the risk of having arrhythmic events have been conducted. We wondered if some differences in prognosis between male and female patients with HF could be evaluated with an ^{123}I-mIBG scan. In our study, the overall survival was similar in males and females, but the risk of cardiac events is lower in males than in females. Moreover, with increasing age, the risk in turn increases as expected. It could be deductible that males have fewer cardiac events than women and this is an important clinical aspect to consider if this preliminary results will be confirmed by further studies. This study observed how mIBG represents a valid tool for male patients in predicting AE: as lHM increases, cardiac events risk reduces behaving as a protective factor. On the opposite, SPECT parameters ESS and LSS represent risk factors. These results do not occur in women. The explanation could be found at first in the small number of women in the study population, so further evaluation with a larger female cohort is needed. However, the first evaluation of these results could also suggest that we must take carefully into account the results of an mIBG scan when the patient is a woman because mIBG seems not to be a good AE predictor tool in this category. On the opposite, in males, mIBG was confirmed to be a valid prognostic tool to stratify patients.

Moreover, an interesting result was that ESS was statistically significant in the univariate analysis conducted for the general population and men. This result could be interesting since, if it will be confirmed in further studies, it could be possible to obtain an evaluation of AE risk in a man only through a scan acquired 15 min after tracer injection. What is known so far is that the early HM ratio reflects the integrity of presynaptic nerve terminals and the function of the uptake-1 carrier protein. Late HM represents, instead, the neuronal function since gives information about the turnover of the noradrenaline analog, thus its uptake and storage when it is released [71]. It could be deduced that the counterpart SPECT values represent a receptor map when we referred to ESS, while LSS represents the cardiac function. In particular, when the sympathetic activity increases in the human body, which reflects a worsening of HF, the delayed images have diminished myocardial ^{123}I-mIBG uptake, and it is reflected in the increase of LSS

value which results in the worsening of ventricular function. This condition has been explained through the downregulation of NE receptors that occurs in response to an elevated myocardial interstitial NE concentration, this in turn is a consequence of hormone balance changes in CHF and rapid ventricular pacing [72]. Therefore, for the evaluation of the ventricular function, the acquisition of late images is necessary. Instead, to evaluate the AE risk, it could be reasonable to use only the early SPECT images since, according to these results, ESS is demonstrated to be a risk factor for AE in men.

Notably, HMR gives a valuation of the anterior-lateral and postural-septal walls together. Planar images represent an overlap of different cardiac segments, in particular the part from the anterior-lateral wall summed with the postural-septal wall part, including the superposition of different thoracic tissues characterized by ^{123}I-mIBG uptake such as lung and liver. Any detailed information about sept alone is so not possible to achieve with a planar scan. SPECT investigation can give a better assessment of regional denervation [11]. When a tomography scan is conducted, a valuation of the activity of each segment, and consequently of sept, can be obtained.

So, it is possible to be more accurate in the evaluation of the segmental deficit with SPECT images compared to planar images. Nonetheless, SPECT images are affected by partial volume effect (PVE), which occurs especially in structures smaller than two times the full width at half maximum (FWHM) of the spatial resolution. The cross-contamination effects caused by the spill-in and spill-out of the activity in the nearer voxels determine, respectively, an over and an underestimation which occurs also as a result of post-processing smoothing [73,74]. Moreover, the fixed voxel size in the reconstruction can lead to extra quantification problems since each voxel can be included in different types of tissue [75,76]. This may be the case in sept, where PVE can hamper the correct evaluation, especially in the case of thinning sept, although SPECT advantages are well known as a methodic which improves spatial resolution [77–80].

On the other hand, maybe a combination of different methodic could be useful for a better evaluation even if this requires supplementary research. Zelt et al. demonstrated how regional denervation volume has a better cause-specific mortality predictor for sudden cardiac arrest using [11C]meta-hydroxyephedrine (HED) PET [81]. This method has a superior spatiotemporal resolution and attenuation correction which permit a separate quantification of global denervation (uptake and retention of tracer) and regional heterogeneity (regional defect volume) of sympathetic myocardial innervation. They considered the tracer retention index (RI) and the volume of distribution (DV), two parameters that reflect global cardiac sympathetic innervation, and regional defect scores based on tracer normalized uptake (NUDS) and distribution volume (DVDS). The regional NUDS had the best SCA risk discrimination while global scale parameters are inferior SCA risk discriminators. Denervation could be a consequence of the stunning phenomenon of uptake 1 receptors due to high levels of NE even if denervation could also be due to the true denervation caused by ischemia and infarction. H/M is affected by neuronal stunning and denervation, but it is not possible to establish if the denervation is due to neuronal stunning or true loss of sympathetic nerves through a single tracer [82].

The overall survival of men and women was similar. This led us to suppose that it was probably associated with a lower rate of arrhythmic events in males compared to females. Therefore, men were less affected by arrhythmic events than women.

In conclusion, these preliminary results assessed the mIBG scan as a valid prognostic tool in males. Our results suggest that in women the use of this method for prognostic estimation should be taken carefully into account. The fact that ESS was significant in men suggests that, based on these preliminary results, the early images could be sufficient to obtain prognostic information about the risk of AE in men. This would reduce machine time, the duration of the exam and improve the patient's compliance.

5. Limitation of the study

This study is a retrospective evaluation of patients who underwent ^{123}I-mIBG scintigraphy in our Institution. Unfortunately, the female population was significantly inferior to its male counterpart since the research was based on the total number of subjects who underwent the exam in the past years.

As stated before, it was deduced that the risk of arrhythmic events was lower in men, and it can be partially explained by the hypothesis that men are less prone to arrhythmic events compared to females. However, the numerosity of women in the population leads to a cautions approach to these preliminary results. Further studies are underway with the intent to improve the female cohort. Moreover, it is a single-center study, and could be interesting to involve other centers to evaluate if these results will be confirmed.

Additionally, multivariate analysis has not been conducted. Further studies intend to enlarge the female population and conduct a multivariate analysis to obtain a more complete and definitive evaluation of independent predictors of AE.

6. Conclusions

Our results show ESS is a risk factor in the general population and especially it assumes more statistical weight when males are analyzed separately from women. After all these considerations, we can assume that the images obtained 15 min after tracer administration could be useful alone to stratify male AE risk. It could be reasonable to conduct the mIBG study by acquiring the images only at 15 min and, in particular, SPECT scan can give more information about the evaluation of AE risk. Making acquisition times faster could improve the patient compliance since it would avoid the long waiting times that late images require. Nevertheless, more prospective evaluations and the increase of the number of women in the study population are required to better understand if these preliminary results can be confirmed.

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Author contributions

M.C., V.F., G. D. V. conception and design, A.D.R., A.F. analysis and interpretation of the data; M.C., G.D.V. drafting of the paper, V.F., G.D.V. revising critically for intellectual content; G.D.V. final approval of the version to be published; and that all authors agree to be accountable for all aspects of the work.

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