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Original article

Impact of the number of comorbidities on cardiac sympathetic derangement in patients with reduced ejection fraction heart failure

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ABSTRACT

Introduction: Heart failure (HF) is frequently associated with comorbidities. ^{123}I-metaiodobenzylguanidine (^{123}I-mIBG) imaging constitutes an effective tool to measure cardiac adrenergic innervation and to improve prognostic stratification in HF patients, including the risk of major arrhythmic events. Although comorbidities have been individually associated with reduced cardiac adrenergic innervation, thus suggesting increased arrhythmic risk, very comorbid HF patients seem to be less likely to experience fatal arrhythmias. We evaluated the impact of the number of comorbidities on cardiac adrenergic innervation, assessed through ^{123}I-mIBG imaging, in patients with systolic HF.

Methods: Patients with systolic HF underwent clinical examination, transthoracic echocardiography and cardiac ^{123}I-mIBG scintigraphy. The presence of 7 comorbidities/conditions (smoking, chronic obstructive pulmonary disease, diabetes mellitus, peripheral artery disease, atrial fibrillation, chronic ischemic heart disease and chronic kidney disease) was documented in the overall study population.

Results: The study population consisted of 269 HF patients with a mean age of 66±11 years, a left ventricular ejection fraction (LVEF) of 31±7%, and 153 (57%) patients presented ≥3 comorbidities. Highly comorbid patients presented a reduced late heart to mediastinum (H/M) ratio, while no significant differences emerged in terms of early H/M ratio and washout rate. Multiple regression analysis revealed that the number of comorbidities was not associated with mIBG parameters of cardiac denervation, which were correlated with age, body mass index and LVEF.

Conclusion: In systolic HF patients, the number of comorbidities is not associated with alterations in cardiac adrenergic innervation. These results are consistent with the observation that very comorbid HF patients suffer lower risk of sudden cardiac death.

1. Introduction

Heart failure (HF) is a very prevalent condition associated with high morbidity and mortality rates, thus representing a relevant global health burden. It affects more than 26 million people worldwide [1], with overall prevalence in developed countries of 1-2% in continuous increase, and it is expected to rise up to 3% in U.S. by 2030 [2]. HF is particularly common in the elderly and it is considered one of the main

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geriatric syndromes, constituting the most frequent cause for hospitalization among older adults [3].

Cardiac sympathetic nervous system (SNS) derangement is a peculiar characteristic of HF and it plays a relevant role on HF incidence, progression and prognosis [4]. The failing heart undergoes a complex process of neuronal remodeling which is mainly characterized by the progressive loss of the adrenergic nerve endings. Determination of cardiac adrenergic status remains a challenging issue and, although several approaches have been employed, none of them is routinely used in the clinical practice due to several limitations/disadvantages of the various techniques. In the last decades, ^{123}I-meta-IodineBenzylGuanidine (^{123}I-mIBG) imaging came out as an effective tool to measure cardiac adrenergic innervation, with relevant potentialities in HF patients' risk stratification. Indeed, ^{123}I-mIBG imaging parameters have been reported as independent predictors of HF progression, major arrhythmic events and cardiac death [5–7]. HF patients with severe systolic dysfunction are at high arrhythmic risk, thus guidelines recommend implantable cardioverter defibrillators (ICD) therapy for primary prevention of sudden cardiac death (SCD) in this population [8]. In this scenario, ^{123}I-mIBG imaging has been shown to improve patient selection for ICD therapy, in terms of reduced inadequate device intervention and better impact on survival [9].

HF is frequently associated with comorbidities and chronic conditions, which negatively impact disease progression and outcome [10]. It has been widely recognized that concomitant conditions are often responsible for worsening of HF symptoms and limit the use of guidelines-guided therapies [11]. Of interest, comorbidities, including diabetes mellitus (DM) [12], chronic kidney disease (CKD) [13] and sleep-disordered breathing [14], are known to aggravate HF-related abnormalities in cardiac adrenergic innervation. Although SNS derangement has been associated with increased incidence of arrhythmic events, several comorbidity-based risk scores indicate that high-risk HF patients present an elevated probability of all-cause mortality but a low risk of arrhythmias or appropriate ICD shocks, an equivalent of SCD in the population undergoing device implantation. Consistently, a meta-analysis has evaluated the impact of comorbidities on the efficacy of primary prevention ICD therapy in patients with systolic HF, highlighting that the presence of more concomitant pathologies/conditions attenuates the benefit on survival of this therapeutic approach [15]. Accordingly, the stratification of systolic HF population, through a simple risk score based on 5 clinical items, revealed that ICD efficacy is limited in the high-risk groups in terms of survival [16].

Even though the negative impact of concomitant cardiovascular and non-cardiovascular diseases on the prognosis of HF patients is widely recognized, whether the number of associated comorbidities may influence cardiac adrenergic innervation in HF has not been adequately investigated. Following these premises, the aim of the present study was to evaluate the impact of the number of comorbidities on cardiac adrenergic innervation, assessed through ^{123}I-mIBG imaging, in patients with systolic HF.

2. Materials and Methods

2.1. Study Population

Participants have been enrolled at the Departments of Translational Medical Sciences and Advanced Biomedical Sciences of the University of Naples "Federico II". Inclusion criteria were: patients aged ≥18 years; diagnosis of HF with altered left ventricle ejection fraction (LVEF <50%) from at least 6 months from study enrollment; stable clinical conditions during the month prior to inclusion; optimal pharmacotherapy according to European Society of Cardiology (ESC) Guidelines [8]. Acute coronary syndromes and/or cardiac revascularization in the previous 6 months represented exclusion criteria, together with dialysis-dependent kidney failure and inability to understand and/or consent to study participation.

Enrolled patients underwent medical history collection, accurate clinical examination and evaluation of the main demographic/clinical factors, including body mass index (BMI) and cardiovascular risk factors. Furthermore, transthoracic echocardiography and assessment of the cardiac adrenergic innervation through myocardial scintigraphy with ^{123}I-mIBG were performed in all patients. In order to test the impact of comorbidities on cardiac adrenergic innervation, the presence of 7 comorbidities/risk factors, considered in the metanalysis by Steinberg and collaborators [15], has been documented in the study population (smoking, COPD, DM, peripheral artery disease, AF, ischemic heart disease [IHD], CKD). Kidney disfunction was defined by a glomerular filtration rate <60 mL/min, according to CKD-EPI equation. Based on the median number of associated comorbidities, the study population was subsequently divided into two groups: 3 or more comorbidities identified the high-risk group while 2 or less comorbidities the low-risk group.

Furthermore, an additional model was performed including 12 comorbidities. To this aim, 5 additional conditions have been considered: arterial hypertension, pulmonary hypertension, dyslipidemia, polypharmacotherapy (treatment with 5 or more drugs), anemia (serum hemoglobin < 12 g/dL). The study population was again divided into a high- (≥6 comorbidities) and a low-risk (<6 comorbidities) groups.

The protocol has been approved by the Local Ethical Committee of University of Naples "Federico II". All participants were carefully informed and signed a written consent to participate to this study. Data from the study population were partially reported in a previous study [17].

2.2. Echocardiography

All participants underwent a 2-dimensional echocardiography with Doppler ultrasound examination and tissue Doppler Imaging, using a VIVID E9 ultrasound system. All measurements were performed in accordance with the recommendations provided by American Society of Echocardiography and the European Association of Cardiovascular Imaging [18]. The diameters of the left ventricle were obtained in the M-mode, whereas the global and regional function of the left ventricle was calculated from the apical four- and two-chamber projection, using the Simpson biplane method, as previously described [19].

2.3. ^{123}I-mIBG imaging

To determine cardiac adrenergic innervation, a ^{123}I-mIBG cardiac scintigraphy was performed in all study participants as previously described [19,20] and in accordance with the European Association of Nuclear Medicine Cardiovascular Committee and the European Council of Nuclear Cardiology recommendations [21]. Heart to mediastinum (H/M) ratios were computed for early and late planar imaging through division of the mean counts per pixel within the myocardium by the mean counts per pixel within the mediastinum. The mIBG washout rate was obtained using the following calculation: ([early heart counts per pixel−early mediastinum counts per pixel]−[late heart counts per pixel decay-corrected−late mediastinum counts per pixel decay corrected])/(early heart counts per pixel−early mediastinum counts per pixel) × 100 [22]. Both intra- and inter-observer reproducibility were excellent and the quality of the acquisitions was adequate for all patients.

2.4. Statistical Analysis

Continuous variables were expressed as mean±standard deviation (SD) and compared using Student's t-test. The categorical variables were expressed as a percentage and compared using the $\chi 2$ test. Multivariate regression analysis was used to identify factors associated with early and late H/M ratios and washout rates obtained through ^{123}I-mIBG scintigraphy. The analysis included age, LVEF and BMI, which are factors known to impact cardiac innervation, in addition to gender and number

of concomitant comorbidities. In the first model the comorbidities/conditions included were 7: smoking, COPD, DM, peripheral artery disease, atrial fibrillation, IHD and CKD. In the second model based on 12 comorbidities, arterial hypertension, pulmonary hypertension, dyslipidemia, polypharmacotherapy and anemia were also considered. All analyses were performed using the STATA 11.2 software (Stata Corp. LP Collage Station, Texas USA) considering as statistically significant a p value <0.05.

3. Results

Characteristics of the overall study population, consisting of 269 HF patients, 227 males (84%), with a mean age of 66±11 years, a mean BMI of 28±4 kg/m^2 and a mean LVEF of 31±7% are reported in Table 1.

Regarding the distribution of the number of comorbidities in the study population, 11 patients (4%) showed no comorbidity, 47 patients (18%) presented a single comorbidity, 58 (22%) two comorbidities, 87 (32%) three comorbidities, 46 (17%) four comorbidities, 17 (6%) five comorbidities and 3 (1%) six comorbidities. Of note, no patient presented all the seven comorbidities considered.

Data on the population stratified by the median value of 3 comorbidities are reported in Table 2. More comorbid patients (≥ 3 comorbidities; n= 153; 57%) were older, with a higher NYHA functional class and were less likely to receive beta-blockers compared to patients with less than 3 comorbidities, whereas no statistically significant differences emerged in terms of gender, BMI, LVEF and other HF therapies. At univariate analysis, the high comorbidity group presented lower late H/M ratio values compared to low comorbidity group (p=0.04), while no differences were evident in early H/M ratio (1.70± 0.24 vs. 1,73 ± 0.24; p=0.40) and washout rate (35.60 ± 18.53 vs. 36.14 ± 21.54) between the two groups. Of note, all comorbidities/risk factors considered were significantly more prevalent in the high comorbidity group compared to the low comorbidity one (Supplemental Table 1).

At multivariable regression analysis, age, BMI and LVEF came out to be significantly and independently associated with both early and late H/M ratios, while age and LVEF were also corelated to washout rate (Table 3). Importantly, the number of comorbidities did not influence cardiac sympathetic innervation, as it did not show any significant correlation with all the mIBG parameters (Table 3).

These results were also confirmed in the model including 12 comorbidities/conditions. Indeed, dividing the study population of 238 patients by the median value of six comorbidities, patients in the low comorbidity group (<6 conditions, n= 100; 42%) were younger, with higher NYHA functional class and values of late H/M ratio (1.57±0.29 vs. 1.50±0.20, p<0.02) as compared to the high comorbidity groups (≥6 comorbidities, n= 138; 58%). No statistically significant differences emerged for gender, BMI, LVEF and the other mIBG parameters between the two groups (Supplemental Table 2). The multivariable regression confirmed that the number of comorbidities did not impact the mIBG parameters of cardiac adrenergic innervation (Supplemental Table 3).

Table 1
Characteristics of the overall population.

Characteristics	Overall Population (n=269)
Age mean, ± SD	66.2 ± 10.8
Gender (male), n (%)	227 (84.4)
BMI (Kg/m^2), ± SD	28.4 ± 4.2
LVEF mean, ± SD	31.1 ± 7.0
Early H/M mean, ± SD	1.71 ± 0.24
Late H/M mean, ± SD	1.53 ± 0.25
Washout rate mean, ± SD	35.83 ± 19.85
NYHA II, n (%)	186 (69.1)
NYHA III, n (%)	80 (29.7)
NYHA IV, n (%)	3 (1.1)
β-blockers, n (%)	198 (73.6)
RAAS, n (%)	209 (70.7)
MRA, n (%)	110 (40.9)
Smoking, n (%)	156 (58)
COPD, n (%)	81 (30.1)
PAD, n (%)	41 (15.2)
AF, n (%)	56 (20.8)
IHD, n (%)	187 (69.5)
CKD, n (%)	80 (29.7)
Diabetes, n (%)	110 (40.9)
Arterial Hypertension, n (%)	197 (73.2)
Dyslipidemia, n (%)	168 (62.5)
Pulmonary Hypertension, n (%)	198 (73.6)
Polipharmacotherapy, n (%)	181 (67.3)
Anemia, n (%)	50 (18.6)

AF, Atrial Fibrillation; BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; CKD, Chronic Kidney Disease; H/M, heart to mediastinum ratio; IHD, Ischemic Heart Disease; LVEF, Left Ventricular Ejection Fraction; MRA, Mineralocorticoid Receptor Antagonist; NYHA, New York Heart Association; PAD, Peripheral Artery Disease; RAAS, Renin-Angiotensin-Aldosterone-System; SD, Standard Deviation.

Table 2
Characteristics of the study population stratified by number of comorbidities.

Characteristics	≥ 3 Comorbidities *(n=153)*	< 3 Comorbidites *(n=116)*	p-value
Age, mean ± SD	68.3 ± 9.4	63.4 ± 11.7	≤ 0.001
Gender (male), n (%)	130 (85)	97 (83.6)	0.446
BMI (Kg/m^2), mean ± SD	28.5 (4.7)	28.2 (3.6)	0.544
LVEF (%), mean ± SD	30.7 (6.7)	31.6 (7.3)	0.311
Early H/M, mean ± SD	1.70 ± 0.24	1.73 ± 0.24	0.402
Late H/M, mean ± SD	1.51 ± 0.21	1.57 ± 0.29	0.047
Washout rate (%)	35.60 ± 18.53	36.14 ± 21.54	0.829
NYHA II, n (%)	93 (60.8)	93 (80.2)	0.020
NYHA III, n (%)	57 (37.2)	23 (19.9)	
NYHA IV, n (%)	3 (2)	0	
β-blockers, n (%)	104 (68)	94 (81)	0.011
RAAS, n (%)	114 (74.5)	95 (81.9)	0.097
MRA, n (%)	91 (59.5)	48 (41.4)	0.493

BMI, Body Mass Index; H/M, Heart to Mediastinum ratio; IHD, Ischemic Heart Disease; LVEF, Left Ventricular Ejection Fraction; MRA, Mineralocorticoid Receptor Antagonist; NYHA, New York Heart Association; RAAS, Renin-Angiotensin-Aldosterone-System; SD, Standard Deviation.
The p value derives from Student's t test for continues variables, and chi square test for categorical data

4. Discussion

The most important finding of the present investigation is that, although several comorbidities have been previously associated with reduced cardiac sympathetic innervation, the absolute number of comorbidities does not impact mIBG parameters of cardiac innervation in systolic HF patients. Moreover, our study confirms that age, BMI and LVEF are independent predictors of cardiac adrenergic derangement.

One of the pillars of chronic HF is constituted by SNS hyperactivity/derangement which plays a pivotal role in HF onset and progression [4]. It is mainly characterized by a progressive reduction in the number of cardiac sympathetic nerve fibers paralleled by the desensitization/downregulation of adrenergic receptors on plasma membrane of cardiomyocytes [23].

^{123}I-mIBG cardiac imaging has been successfully employed to assess the status of myocardial adrenergic innervation and to obtain prognostic information in patients with systolic HF. Indeed, the above-mentioned HF-dependent abnormalities in cardiac innervation are associated with increased risk of cardiovascular mortality, HF hospitalization and major arrhythmic events, as demonstrated in several study including the ADMIRE-HF [24]. One of the main predictors of cardiac denervation is represented by the reduction in LVEF, which represents the principal factor driving primary prevention ICD candidacy of HF patients, based on current guidelines [8]. Consistently, our results confirm the association between LVEF and mIBG parameters of cardiac innervation.

Based on current guidelines recommendation, a relevant number of

Table 3
Regression analysis for ^{123}I-mIBG cardiac scintigraphy parameters.

	Late H/M R^{2a}: 0.235			Early H/M R^{2a}: 0.125			Washout Rate R^{2a}: 0.047		
Variables	*B*	*SE*	*Sig.*	*B*	*SE*	*Sig.*	*B*	*SE*	*Sig.*
Gender	-0.054	0.037	0.147	-0.026	0.038	0.496	1.970	3.265	0.547
Age	-0.006	0.001	≤ 0.0001	-0.003	0.001	0.013	0.244	0.117	0.038
BMI	-0.013	0.003	≤ 0.0001	-0.016	0.003	≤ 0.0001	-0.188	0.281	0.505
LVEF	0.013	0.002	≤ 0.0001	0.008	0.002	≤ 0.0001	-0.602	0.173	≤ 0.001
Comorbidities*	-0.010	0.011	0.373	0.004	0.011	0.691	-0.317	0.973	0.745

BMI, Body Mass Index; LVEF, Left Ventricle Ejection Fraction; R^{2a}, Adjusted R^2; SE, Standard Error; *Comorbidities included: Smoking, Chronic Obstructive Pulmonary Disease, Diabetes Mellitus, Peripheral Artery Disease, Atrial Fibrillation, Ischemic Heart Disease and Chronic Kidney Disease

ICD recipients never receive benefit from device therapy, and are exposed to a series of device-related complications and/or adverse events, including inappropriate shocks (20%), lead failure (17%) and infections (6%) [25]. Thus, in the last decades, considerable efforts have focused on the identification of novel factors influencing the risk of SCD in HF patients.

Ageing [19] and several comorbidities, including DM [12], CKD [13] and sleep-disordered breathing [14], are independently associated with reduced cardiac adrenergic innervation. Since cardiac ^{123}I-mIBG uptake has been shown to ameliorate the cost-effectiveness screening of ICD guideline-eligible HF patients [9,26], ageing and comorbidities are variables that may potentially identify those HF patients at highest risk of ventricular arrhythmias.

However, several lines of evidence indicate that elderly multimorbid HF patients are at high risk of all-cause mortality but are less likely to die for SCD and/or to receive benefits form ICD therapy [27]. A meta-analysis published few years ago, including 3348 patients with severe systolic HF, reported that therapy with implantable devices as ICD is less effective in terms of survival in patients suffering from higher number of comorbidities. The authors considered seven comorbidities (smoking, COPD, DM, peripheral artery disease, AF, IHD and CKD) that should be carefully evaluated in HF candidates to ICD therapy, since they limit the benefit of device implantation [15]. Based on the results of the metanalysis by Steinberg and collaborators, in the present study we have evaluated the impact of the number of comorbidities on cardiac adrenergic innervation, assessed through myocardial scintigraphy with ^{123}I-mIBG, in a population of patients with chronic systolic HF. Considering the same seven comorbidities, we have herein reported the lack of any significant relationship between number of comorbidities and cardiac innervation status, whereas age, BMI and LVEF came out as significantly associated with mIBG parameters as previously shown by us and others [17,19]. At univariate analysis, we have observed a significant difference in late H/M ratio between the low and high comorbidity groups, which were not homogeneous for age, NYHA functional class and beta-blocker use. Of note, no differences emerged in early H/M ratio and washout rate between the two groups. However, the number of concomitant pathologies does not influence mIBG parameters of cardiac innervation, including late H/M ratio, as it is evident from the results of the regression analysis, which also included age, gender, BMI and LVEF as independent variables.

As emerged by The Swedish Heart Failure Registry [28], which included more than 10000 patients, comorbidities are very frequent in patients with HF and are associated with worse outcome. Among cardiovascular comorbidities, the most frequent were AF, arterial hypertension and myocardial ischemia, whereas the most relevant non-cardiovascular ones included COPD, DM and renal impairment [28]. Moreover, mainly non-cardiovascular comorbidities significantly limit the prescription of guideline-recommended pharmacological therapies due to drug interactions or specific contraindications. Thus, we have also performed a second regression analysis by including 5 additional conditions (arterial hypertension, pulmonary hypertension, dyslipidemia, polypharmacotherapy and anemia) to those considered by Steinberg and colleagues. Similar results have been obtained, confirming that the number of comorbidities does not influence cardiac sympathetic innervation in HF (Supplemental Table 3).

Furthermore, our findings are also in line with another previous evidence reported by Goldenberg and colleagues, which developed a risk stratification score for primary prevention ICD implantation in systolic HF patients. Also in this case, high risk patients, identified on the basis of five clinical items (age> 70 years, advanced NYHA functional class, blood urea nitrogen> 26 mg/dl, QRS duration> 120 millisecond and presence of AF), showed less benefit from ICD therapy [16].

Therefore, since myocardial denervation is known to increase the arrhythmic risk in HF patients, our results may be consistent with the observation that an elevated number of comorbidities attenuates the benefit of ICD therapy in HF patients. Indeed, very comorbid HF patients display a high risk of all-cause death but may not present an elevated risk of SCD, since, as we have here demonstrated, comorbidities do not confer an additional contribute to the denervation of the failing heart.

4.1. Study limitations

Our results derived from a monocentric study on a limited number of patients, thus larger multicentric investigations may be needed to confirm our findings. All the study participants had the diagnosis of HF, thus the lack of control group of healthy subjects could represent a limitation. Although gender was not associated with parameters of cardiac innervation, the disproportion between males and females in our study population does not allow to draw definitive conclusions. Furthermore, patients with very high and very low number of comorbidities were underrepresented in our study population. Finally, we do not have follow-up data to verify the impact of our results on cardiovascular outcomes.

5. Conclusions

The present study shows that the number of comorbidities does not influence cardiac adrenergic innervation assessed through ^{123}I-mIBG scintigraphy, which is in turn affected by age, BMI and LVEF. Our data may explain, at least in part, the previous observation that very comorbid HF patients present a lower arrhythmic risk and receive less benefit from ICD therapy compared to HF patients with a low number of concomitant associated pathologies.

Declaration of Competing Interest

The authors declare they have no conflict of interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2021.01.010.

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