Insulin resistance is associated with impaired cardiac sympathetic innervation in patients with heart failure

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Aims
Insulin resistance (IR) represents, at the same time, cause and consequence of heart failure (HF) and affects prognosis in HF patients, but pathophysiological mechanisms remain unclear. Hyperinsulinemia, which characterizes IR, enhances sympathetic drive, and it can be hypothesized that IR is associated with impaired cardiac sympathetic innervation in HF. Yet, this hypothesis has never been investigated. Aim of the present observational study was to assess the relationship between IR and cardiac sympathetic innervation in non-diabetic HF patients.

Methods and results
One hundred and fifteen patients (87% males; 65 ± 11.3 years) with severe-to-moderate HF (ejection fraction 32.5 ± 9.1%) underwent iodine-123 meta-iodobenzylguanidine (123I-MIBG) myocardial scintigraphy to assess sympathetic innervation and Homeostasis Model Assessment Insulin Resistance (HOMA-IR) evaluation to determine the presence of IR. From 123I-MIBG imaging, early and late heart to mediastinum (H/M) ratios and washout rate were calculated. Seventy-two (63%) patients showed IR and 43 (37%) were non-IR. Early [1.68 (IQR 1.53–1.85) vs. 1.79 (IQR 1.66–1.95); P = 0.05] and late H/M ratio [1.50 (IQR 1.35–1.69) vs. 1.65 (IQR 1.40–1.85); P = 0.020] were significantly reduced in IR compared with non-IR patients. Early and late H/M ratio showed significant inverse correlation with fasting insulinemia and HOMA-IR.

Conclusion
Cardiac sympathetic innervation is more impaired in patients with IR and HF compared with matched non-IR patients. These findings shed light on the relationship among IR, HF, and cardiac sympathetic nervous system. Additional studies are needed to clarify the pathogenetic relationship between IR and HF.

Keywords
heart failure • insulin resistance • 123I-MIBG • cardiac sympathetic innervation

Introduction
Insulin resistance (IR) is common in non-diabetic patients with heart failure (HF) and has been associated with adverse prognosis. However, pathogenetic mechanisms that link IR to unfavourable clinical outcome in non-diabetic HF patients are not completely understood. Hyperinsulinemia, which characterizes IR, promotes sympathetic activation,2 and impaired cardiac sympathetic innervation has been showed in insulin-resistant hypertensive patients with normal left ventricular (LV) function. In addition, reduction of glycated haemoglobin in patients affected by diabetes mellitus (DM) with normal cardiac function has been correlated with
of cardiac sympathetic innervation. In fact, significantly more impaired cardiac sympathetic innervation has been recently reported in diabetic HF patients compared with non-diabetic subjects and associated with unfavourable clinical outcome. Yet, there are no studies that investigated the status of cardiac sympathetic innervation in non-diabetic HF patients also affected by IR. Therefore, in the present study, we tested the hypothesis that IR is associated with more impaired cardiac sympathetic innervation in non-diabetic HF patients compared with patients with HF but not IR.

Methods

Study population

One hundred and fifteen consecutive patients (87% males; median age 65 ± 11.3 years) with severe-to-moderate systolic HF (mean LV ejection fraction (EF) 32.5 ± 9.1%) referring to the HF Unit at Federico II University of Naples, Italy, were enrolled. To be included in the study, patients needed to fulfil the following criteria: LVEF ≤ 45% in at least two consecutive transthoracic echocardiograms, diagnosis of HF since at least 6 months, stable clinical conditions (NYHA class I-III), coronary angiography within 1 year from enrolment, and no acute coronary syndrome or angina in the 6 months before inclusion in the study. At the time of enrolment, all patients were on optimized medical therapy for HF including angiotensin-converting enzyme inhibitors or AT1-antagonists, beta-blockers, loop diuretics, anti-aldosterone, and digitals when necessary, in addition to conventional drugs used for treatment of cardiovascular risk factors and for secondary prevention of ischaemic heart disease. Based on IR index, patients were divided into two groups, with and without IR. All patients gave written informed consent and local ethic committee approved the protocol. Thirty-eight of 115 patients belong to the group of non-diabetic HF patients reported in previous study.

Study protocol and procedures

On the first study day, patients underwent clinical examination, venous blood sample collection, and transthoracic echocardiography. The following day, iodine-123 meta-iodobenzylguanidine (123I-MIBG) myocardial scintigraphy was performed. At clinical examination, demographic data and medical history were recorded. In particular, age, sex, height and body weight, HF medications, tobacco use, hypertension, dyslipidaemia, family history of coronary events, and presence of co-morbidities were assessed. NYHA class was estimated from patients’ symptoms, family history of coronary events, and presence of co-morbidities. Venous blood sample collection and assessment of IR

Venous blood sampling was obtained in all patients to assess biochemical data, including fasting glucose and insulin. IR was assessed through the evaluation of Homeostasis Model Assessment Insulin Resistance (HOMA-IR). In particular, HOMA-IR was calculated using the formula fasting Glucose (mmol/L) × fasting Insulin (mIU/L)/22.5, and the presence of IR was defined as HOMA-IR value > 2.5.

Transthoracic echocardiography

A standard transthoracic echocardiography was performed in all patients using a VIVID E9 ultrasound system (GE Healthcare) with second-harmonic capability and a 3.5 MHz probe. All measurements were performed according to the European Society of Cardiology Recommendations for Chamber Quantification. LV diameters were obtained in the M-mode view. Global and regional LV function was evaluated and LVEF was calculated from apical four- and two-chamber views using the Simpson’s biplane method.

123I-MIBG imaging procedures

After blockage of the thyroid gland with 300 mg of perchlorate, an activity of 111 MBq 123I-MIBG (Covidien, Mallinckrodt) was intravenously administered over 1–2 min. A 10-min planar image was acquired from an anterior thoracic view (256 × 256 matrix) 15 min (early image) and 3 and 50 min (late image) after tracer administration, as previously reported. Imaging was performed using a dual-head camera system (Skylight, Philips) equipped with low-energy, parallel-hole, high-resolution collimator and peaked at 159 keV with a symmetrical 20% energy window. Two observers, blinded about patients’ status, analysed 123I-MIBG studies. MIBG uptake was semi-quantified by calculating a heart-to-mediastinum (H/M) ratio after drawing regions of interest (ROI) over the heart and mediastinum. This approach provides a highly reproducible index of cardiac sympathetic activity. Briefly, H/M ratio was computed from the early and late images by dividing the mean counts per pixel within the myocardium by the mean counts per pixel within the mediastinum. Using dedicated post-processing software on a dedicated workstation (Philips), the cardiac ROI was assessed using a manually drawn polygonal ROI placed over the myocardium including the LV cavity on the MIBG images. Care was taken to exclude lung or liver from the myocardial ROI. The mediastinal ROI with a square shape was placed on the upper half of the mediastinum and had a size of 7 × 7 pixels. The location of mediastinal ROI was determined using as landmarks the lung apex, the upper cardiac border, and the medial contours of the lungs. H/M ratio was computed for early and late imaging. By comparing early and late activities, the MIBG washout rate from the myocardium was derived, providing a parameter that reflects retention of nor- epinephrine by sympathetic neurons. MIBG washout rate was calculated using the following formula: (early heart counts/pixel − early mediasti- num counts/pixel) − (late heart counts/pixel decay-corrected − late mediastinum counts/pixel decay-corrected)/(early heart counts/pixel − early mediastinum counts/pixel). Reproducibility of 123I-MIBG analysis in our laboratory has been recently reported. The absorbed dose per unit of activity of 123I-MIBG was 0.018 mGy/MBq.

Statistical analysis

Numerical variables that showed normal distribution were expressed as mean ± SD; otherwise, variables non-normally distributed were expressed as medians and inter-quartile range. Unpaired t-test or non-parametric Mann–Whitney test was used when appropriate for between-group comparison. Categorical variables were analysed by chi² test. Correlation between variables was assessed by linear regression analysis. Multivariable regression analysis was performed in different steps to overcome collinearity between covariates included in the model as insulinemia and HOMA-IR. All data were collected in an Excel database and analysed by SPSS 20.0. Statistical significance was accepted at P ≤ 0.05.

Results

Of 115 patients, 15 (13%) were in NYHA class I, 66 (57%) in NYHA class II, and 34 (30%) in NYHA class III. In 73 patients (63%) HF was of ischaemic origin and in 42 (37%) patients aetiology of HF was an idiopathic dilated cardiomyopathy. Seventy-six per cent of patients were on treatment with inhibitors of renin–angiotensin system (ACE inhibitors or ARBs) and 72% took beta-blockers (77% on carvedilol, 14% on bisoprolol, and 8% other beta-blockers), whereas 37% of patients were on mineralocorticoid receptor antagonists. Median early H/M
ratio was 1.80 (IQR 1.60–1.88) and median value of late H/M ratio was 1.76 (IQR 1.36–1.70); mean washout rate was 10.08 ± 9.50.

**Characteristics of IR and non-IR patients**

Seventy-two (63%) patients showed IR (HOMA-IR > 2.5) and 43 (37%) were non-IR (HOMA-IR ≤ 2.5). No significant differences between IR and non-IR patients were observed for age, LVEF, NYHA class, HF aetiology, and HF treatments (Table 1). IR patients showed significantly higher fasting insulinemia and fasting glucose levels compared with non-IR patients (P < 0.001) (Table 1).

**MIBG uptake in IR and non-IR patients**

IR patients, compared with non-IR patients, showed significantly reduced early H/M ratio [1.68 (IQR 1.53–1.85) vs. 1.79 (IQR 1.66–1.95); P = 0.05] and significantly reduced late H/M ratio [1.50 (IQR 1.35–1.69) vs. 1.65 (IQR 1.40–1.85); P = 0.020] (Figure 1A).
and B). Washout rate did not differ between IR and non-IR patients (10.46 ± 8.79 vs. 9.45 ± 10.63; P = 0.578).

**Determinants of I^{123}MIBG uptake**

In the whole population, early and late H/M ratio showed a significant inverse correlation with age, fasting insulinemia (Figure 2A and B), HOMA-IR (Figure 2C and D), and NYHA class and a significant direct correlation with LVEF and HF aetiology. These variables were included in a multivariable model to assess the independent predictors of I^{123}MIBG uptake. At multivariate regression analysis, LVEF (β = 0.230; P = 0.017), fasting insulinemia (β = −0.223; P = 0.016), and HOMA-IR (β = −0.264; P = 0.004) remained independent predictors of early H/M ratio, whereas independent predictors of late H/M ratio were HF aetiology (β = 0.203; P = 0.039) and LVEF (β = 0.243; P = 0.014).

**Discussion**

The findings of the present study demonstrate that MIBG uptake is significantly reduced in non-diabetic HF patients with IR compared with matched non-diabetic HF patients without IR. Since reduced MIBG uptake reflects reduced pre-synaptic norepinephrine uptake due to cardiac sympathetic nervous system overactivity, this observation might contribute to elucidate the interaction between IR and prognosis in patients with HF.1

**IR and cardiac sympathetic innervation in HF**

The pathogenetic relationship between cardiac sympathetic innervation and IR is quite complex, since IR represents, at the same time, cause and consequence of HF. In fact, hyperinsulinemia, which characterizes IR, has been reported to increase neural sympathetic activation,2 which, in turn, may exert deleterious effects on cardiac structure and function, leading to impaired cardiac innervation.11 Very consistent with our observations, a previous study by Mongillo et al.12 reported, in a small group of patients, a direct correlation between pre-synaptic noradrenaline re-uptake, evaluated by positron emission tomography using the noradrenaline analogue [11C]meta-hydroxy-ephedrine, and insulin sensitivity in patients with LV dysfunction. In addition, impaired cardiac sympathetic innervation has been reported in type 2 diabetic patients with normal cardiac function compared with matched non-diabetic patients,13,14 whereas Takahashi et al.15 demonstrated a synergistic detrimental effect of hypertension and type 2 DM on cardiac innervation in patients with IR and cardiac sympathetic innervation.
patients with normal cardiac function that did not correlate with glycated haemoglobin and fasting glucose plasma levels.

Conversely, IR may be consequence of HF. In fact, it has been demonstrated that overstimulation of beta-adrenergic receptors impairs insulin sensitivity through an Akt-mediated effect. More recently, Ciccarelli et al. using a transgenic mice model, showed that ischaemia-induced up-regulation of G protein-coupled receptor kinase 2 promotes IR by interfering with insulin signalling. As it has been demonstrated that insulin signalling exerts protective effects in the heart through inhibition of apoptosis and oxidative stress and enhances cardiomyocyte survival upon ischaemic injury, development of IR may set a vicious pathogenic circle along which IR begets IR through exacerbation of HF. Consistent with this hypothesis, it has been recently reported that improvement of loading ventricular conditions, induced by mechanical ventricular assistance, restores insulin sensitivity in patients with advanced HF.

Current study provides further novel insights on the association between IR and HF. In our study, IR was 63% prevalent in HF patients, quite consistent with the 61% prevalence reported by Alizadjali et al. in a population of 129 HF patients. In addition, impaired myocardial glucose uptake has been shown in DM patients with coronary artery disease and reduced EF as well as in HF patients without DM using positron emission tomography. In the current study, patients with HF and IR showed significantly reduced MIBG uptake, reflecting sympathetic nervous system overactivity, compared with insulin-sensitive patients, despite no differences in clinical status, LVEF, and HF treatments. The finding of impaired values of both early and late H/M ratios strengthens the conception that a complex and strict relationship exists between IR and cardiac sympathetic nervous system. Conversely, no differences in MIBG washout rate were found between patients with and without IR. This result might depend on the great variability of washout rate values observed in clinical practice, and the limited number of patients enrolled in the current analysis could have been not sufficient to demonstrate significant differences. In addition, to further support the interaction between IR and adrenergic system, a significant inverse correlation was found between HOMA-IR and both early and late H/M, and between fasting insulin plasma levels and early and late H/M. Since reduction of H/M ratios are independent prognostic predictors in HF patients, these data are consistent and further support the adverse prognostic impact of IR in patients with HF. The finding of independent role of HF aetiology in the prediction of late H/M might depend on the higher prevalence of HF of ischaemic aetiology and related to a more clear and defined interaction between ischaemia and sympathetic nervous system compared with adrenergic impairment observed in idiopathic dilated cardiomyopathy.

Limitations
Lack of assessment of the effects of therapeutic interventions on IR and on MIBG uptake may represent a limitation of the study and deserves further investigation. Second, lack of follow-up does not allow to establish the independent prognostic value of IR in non-DM patients with HF. Finally, the limited number of patients might have underestimated differences in washout rate between groups, and studies on larger populations could be useful to clarify the value of this parameter in clinical practice.

Conclusions
Patients with HF and IR demonstrate significantly reduced MIBG uptake compared with matched non-IR patients. Thus, the findings contribute to shed light on the relationship among IR, HF, and cardiac sympathetic nervous innervation. Additional studies are needed to elucidate the pathogenetic basis of this complex interaction.

Conflict of interest: None declared.

References
Disintegration of polyvinyl alcohol membrane covering atrial septal defect device

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A 69-year-old man with a history of cryptogenic stroke at the age of 50 and subsequent multiple transient ischaemic attacks presented with inferior myocardial infarction. Coronary angiography revealed heavy thrombotic burden in right coronary artery with unobstructed left coronary system. He was later diagnosed with a small secundum atrial septal defect (ASD) and underwent percutaneous ASD closure with a 28-mm Cardia Ultra-sept septal occluder. The device is composed of polyvinyl alcohol (PVA) membrane covering a nitinol frame (Panel A). Peri-procedure transoesophageal echocardiography (TEE) showed a well-seated device and contrast enhanced transcranial Doppler (TCD) at 3-month follow-up were negative. Ten months later he had several transient neurological events. TCD demonstrated multiple high-intensity signals suggesting re-occurrence of a large inter-atrial shunt (Panel B). A repeat TEE showed the PVA coating had disintegrated (dashed arrow, Panel C) although the frame was intact (solid arrow, Panel C, see Supplementary data online, Movie I). Colour Doppler and continuous wave Doppler showed that there was continuous shunting across the device (Panel D and E, see Supplementary data online, Movie II). A 30-mm Cribriform Amplatzer closure device was anchored on top of the previous device to seal the holes (Panel F). No residual shunt was detected, and the patient remains asymptomatic. Disintegration of the PVA membrane is rare and usually requires surgical intervention. To our knowledge, this is the first case demonstrating feasibility of covering the damaged membrane with another occlusion device via percutaneous route.

Supplementary data are available at European Heart Journal – Cardiovascular Imaging online.

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