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BRIEF REPORT

Meta-Iodobenzylguanidine Iodine-123 and Cardiac Adrenergic Activity in Familial Dilated Cardiomyopathy

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Familial dilated cardiomyopathy (FDCM) is characterized by genetic heterogeneity, incomplete age-dependent penetrance, and a multifactorial pathogenesis (1). Diagnosis is still dependent on clinical criteria and familial investigation (2). On the other hand, several abnormalities have been described among asymptomatic relatives, such as isolated left ventricle (LV) enlargement (3). These abnormalities could assist in identifying affected relatives, who are potential candidates for early therapeutic interventions. However, currently not even the presence of such abnormalities allows inferring carrier state or future progression of the disease. We hypothesized that

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meta-iodobenzylguanidine iodine-123 (^{123}I-*m*IBG) imaging, a tool for monitoring sympathetic activity, could be useful in the evaluation of family members, as it reflects pathophysiologic mechanisms involved in disease progression (4). This evaluation could provide prognostic data useful in this clinical setting.

We evaluated 45 FDCM members from 23 families defined by the European Society of Cardiology criteria (2); 25 patients (56%) were male, with a median age of 43 years (interquartile range, 36 to 51 years). One of the families has the disease locus located in chromosome 7q22.3-31.1 (5). All participants underwent 12-lead electrocardiogram and 2-dimensional echocardiogram. Measurements were done according to the American Society of Echocardiography. Forty members also underwent cardiac magnetic resonance (CMR) on a 3-Tesla scanner (Magneton trio, Siemens AG, Erlangen, Germany). The protocol included contrast-enhanced images, acquired 10 to 15 min after intravenous administration of gadobutrol (Gadovist [Schering AG, Berlin, Germany]; 0.2 mmol/kg). The ^{123}I-*m*IBG imaging was performed after intravenous administration of 370 MBq (10 mCi) of ^{123}I-*m*IBG (4). We used a dual-headed gamma camera (GE Millennium MG, Haifa, Israel), equipped with low-energy, high-resolution, parallel-hole collimators, using a 20% window centered at the 159-keV photo peak. Images were processed with dedicated software (QGS/QPS [Cedars-Sinai Medical Center, Los Angeles, California] on a Xeleris [Paris, France] workstation). No attenuation correction was performed. Anterior projection planar thoracic images were obtained 20 min and 4 h after tracer injection, and heart/mediastinal (H/M) ratio and myocardial washout rate (WR) calculated twice by 2 independent blinded observers. The final results were obtained by the mean of the average of each operator. A blood sample was obtained for B-type natriuretic peptide (BNP) quantification (Architect system, Abbott, Abbott Park, Illinois) just before ^{123}I-*m*IBG administration. Heart rate variability parameters were calculated, using a DigiTrack-Plus Recorder (Philips Medical Systems, Andover,

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ABBREVIATIONS AND ACRONYMS

BNP = B-type natriuretic peptide

CMR = cardiac magnetic resonance

EF = ejection fraction

FDCM = familial dilated cardiomyopathy

H/M = heart/mediastinal

LV = left ventricular

WR = washout rate

Massachusetts) and a Philips Zymed Holter, Model 1810 Plus Software (Philips Medical Systems). All statistical analyses were performed with SPSS for Windows (version 16.0; SPSS Inc, Chicago, Illinois). Categorical data were compared using Fisher exact test. Student *t* and Mann-Whitney *U* tests were used to compare continuous variables. The Spearman correlation was used to evaluate associations in continuous variables with asymmetric distribution, such as LV mass index and LV ejection fraction (EF).

Twenty-nine familial members (64%) had EF <50% (DCM patients), and 16 had EF ≥50%, including 6 with reverse remodeling (previous LV systolic dysfunction) and 10 asymptomatic relatives. An expected difference between both groups was observed in CMR-indexed LV end-diastolic volumes (134 ml/m^2 [range 100 to 161] vs. 85 ml/m^2 [range 73 to 95]; $p < 0.001$), LVEF (30% [range 25% to 45%] vs. 55% [range 55% to 64%]; $p < 0.001$), right ventricular EF (48 ± 10% vs. 55 ± 7%; $p = 0.017$), late hyperenhancement (8 patients vs. none; $p = 0.035$), plasma BNP (104 pg/ml [range 18 to 354 pg/ml] vs. 10 pg/ml [range 10 to 16 pg/ml]; $p < 0.001$], myocardial WR (43 ± 11% vs. 34 ± 9%; $p = 0.011$), and late H/M ratio (1.73 ± 0.26 vs. 1.89 ± 0.14; $p = 0.027$) (Fig. 1). No heart variability parameter value was distinct between both groups. We did not find significant differences in WR value and late H/M ratio between members with (47.2 ± 11.3% and 1.6 [range 1.4 to 1.8], respectively) and without (40.2 ± 11.3% and 1.7 [range 1.6 to 1.9], respectively) delayed hyperenhancement on CMR ($p = 0.16$ and $p = 0.22$, respectively). The majority (55%) of DCM patients were in New York Heart Association functional class I, and 90% were treated with beta-blockers. In this group, WR was higher than 30% (≥2 SDs) in 24 (83%), and late H/M was inferior to 1.7 in 11 patients (38%). Myocardial WR and late H/M ratio were both correlated with BNP ($r = 0.595$, $p = 0.01$; $r = -0.622$, $p = 0.01$) (Fig. 2), LVEF ($r = -0.668$, $p = 0.01$; $r = 0.685$, $p = 0.01$), LV diastolic ($r = 0.677$, $p = 0.01$; $r = -0.584$, $p = 0.01$), and systolic ($r = 0.743$, $p = 0.01$; $r = -0.660$, $p = 0.01$) indexed volumes and LV indexed mass ($r = 0.638$, $p = 0.01$; $r = -0.471$, $p = 0.05$) on CMR imaging. In the group with normal LV systolic function, we found an abnormally high myocardial WR (>30%) in 11

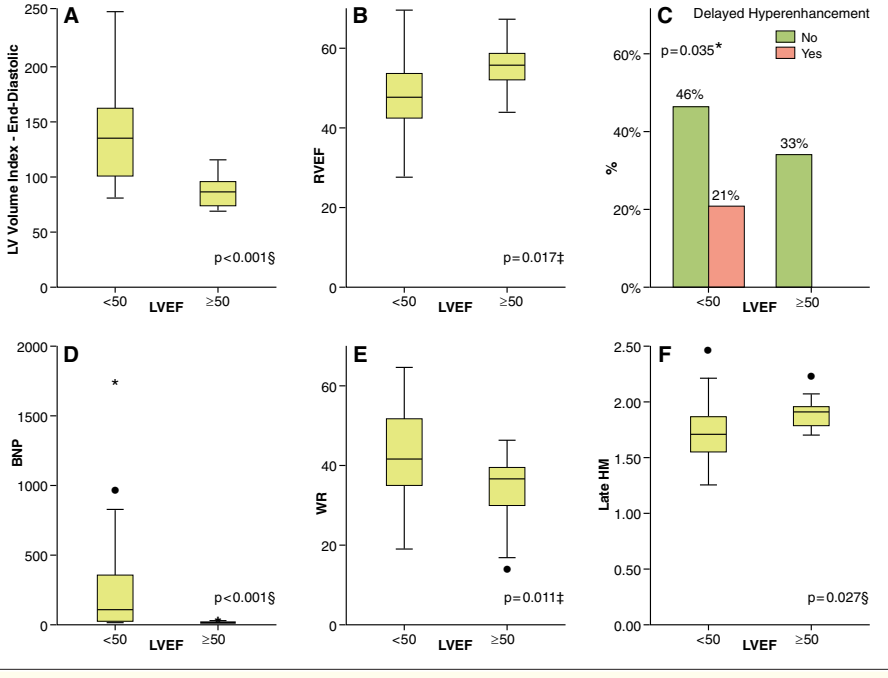

Figure 1. Comparison Between FDCM Patients and Relatives According to LVEF

(A) Cardiac magnetic resonance (CMR) left ventricular (LV) end-diastolic volume, **(B)** CMR right ventricular ejection fraction (RVEF), **(C)** delayed hyperenhancement, **(D)** plasma B-type natriuretic peptide (BNP), **(E)** myocardial *meta*-iodobenzylguanidine iodine-123 (^{123}I-*m*IBG) washout rate (WR), **(F)** ^{123}I-*m*IBG late heart to mediastinum activity ratio (H/M). *Chi-square test, ‡Student *t* test for independent groups; §Mann-Whitney *U* test. FDCM = familial dilated cardiomyopathy; LVEF = left ventricular ejection fraction.

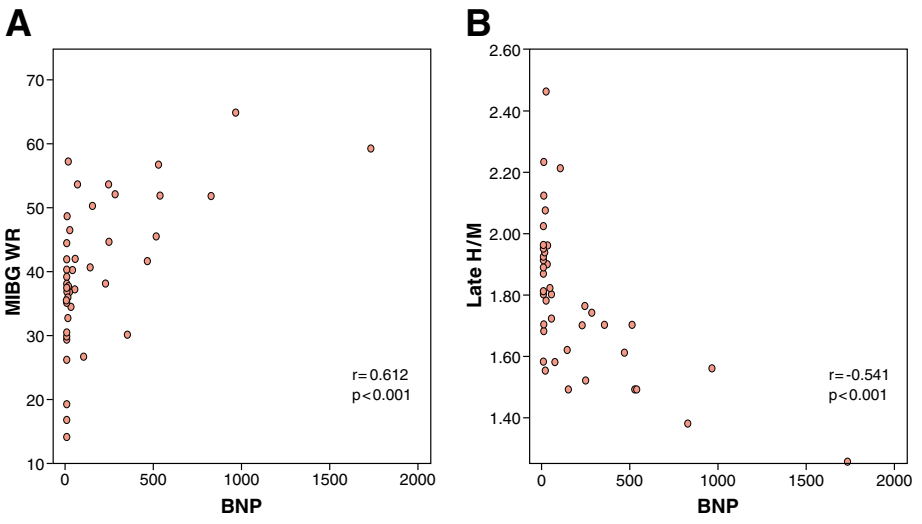

Figure 2. Relationship of Plasma BNP to Cardiac ^{123}I-*m*IBG Scintigraphy Data

Correlations between plasma BNP levels and **(A)** myocardial ^{123}I-*m*IBG WR and **(B)** late H/M. Abbreviations as in Figure 1.

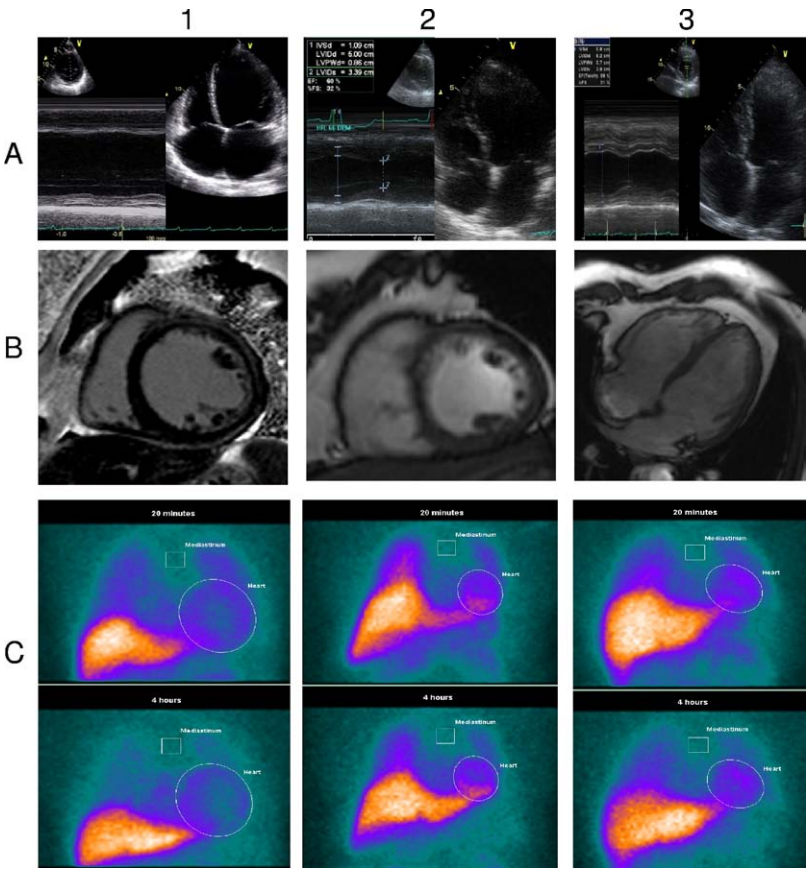

Figure 3. Characterization of Familial DCM Members Using Different Imaging Methods

Illustrative examples of **(A)** 2-dimensional echocardiogram, **(B)** cardiac magnetic resonance, and **(C)** ^{123}I-*m*IBG scan images of: 1) a patient with dilated cardiomyopathy (DCM) and late hyperenhancement; 2) a patient with reverse remodeling and left bundle branch block; and 3) an identified carrier with preserved left ventricular ejection fraction. ^{123}I-*m*IBG parameters: 1) late H/M = 1.6, WR = 41.6%; 2) late H/M = 1.9, WR = 36%; 3) late H/M = 1.8, WR = 40.2%. Abbreviations as in Figure 1.

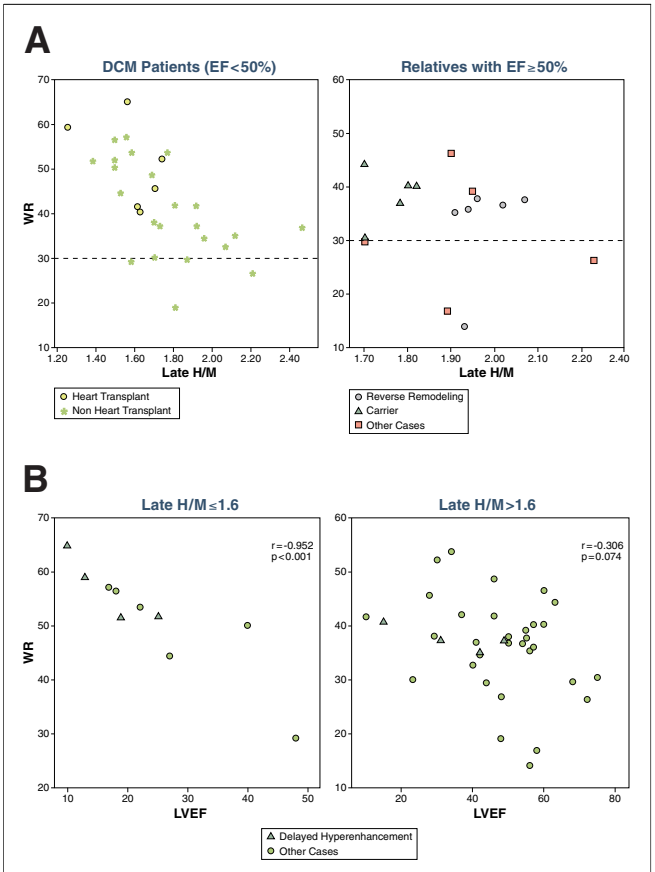

Figure 4. Cardiac ^{123}I-*m*IBG Scintigraphy Parameters in FDCM Members

(A) Distribution of scintigraphic parameters according to left ventricular ejection fraction (EF) of family members. Dilated cardiomyopathy (DCM) patients: relation with occurrence of heart transplantation during follow-up. Relatives with EF ≥50%: relation with carrier state of asymptomatic members and evidence of reverse remodeling among patients. **(B)** Distribution of WR and LVEF according to late H/M; relation with the presence of delayed hyperenhancement in cardiac magnetic resonance. Abbreviations as in Figure 1.

participants (69%), including 5 with reverse remodeling, 4 of 5 identified carriers, and 2 relatives with normal echocardiograms and unknown carrier state (Fig. 3). We did not find correlations between myocardial ^{123}I-*m*IBG WR and LVEF or indexed volumes or mass. However, ^{123}I-*m*IBG WR was correlated with normalized low-frequency power ($r = 0.691$, $p = 0.01$) and low-frequency/high-frequency ratio ($r = 0.702$, $p = 0.01$) heart rate variability parameters. During 558 days (range 432 to 863 days) of follow-up, 6 patients (21%) were submitted to heart transplantation. WR was significantly different between DCM patients who did (51 ± 10%) and did not (41 ± 11%) undergo transplantation ($p = 0.05$), as was the presence of late hyperenhancement on CMR ($p = 0.02$) (Fig. 4). None of those with EF >50% developed or had worsening of heart failure symptoms in this time interval.

Our study provides evidence of the heterogeneity of ^{123}I-*m*IBG findings between FDCM members (with known and unknown disease). We did find rapid WR in a high percentage of individuals with normal EF, and this may reflect the increased adrenergic drive related to the cardiac remodeling process. This hypothesis was somewhat corroborated by the presence of an elevated WR in individuals with reverse remodeling and in 4 locus disease carriers who, theoretically, have higher risk for DCM development. In relatives with EF >50%, a rapid WR could reflect specific histopathologic base or particular gene/protein involvement that causes major interference with cardiac sympathetic nerve metabolism; alternatively, it could reflect the decreased contractility of cardiac myocytes, eventually detected by other diagnostic tools. Late H/M ratio, an index of sympathetic denervation, is usually altered with more severe heart failure, so it is not expected to be significantly changed at early stages of FDCM. In the preserved systolic function group, we did not obtain correlations between WR and LV volumes. This result could be dependent on sample size or just reflecting the great heterogeneity of sympathetic drive between individuals, even with identical LV dimensions and systolic function. We found a positive correlation between WR and 2 heart variability indexes related to sympathetic activity only in the group of patients with EF >50%; this could reflect changes of the sympathovagal balance throughout different stages of disease, as already pointed out by other investigators.

Because of the small number of patients in this study and the short-term follow-up, we cannot evaluate the prognostic value of the ^{123}I-*m*IBG scintigraphy parameters. These parameters could add complementary information to other morpho-functional imaging studies, guiding the start of early medical treatment or the clinical follow-up schedule of asymptomatic relatives.

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Key Words: dilated cardiomyopathy ■ familial ■ genetic ■ *m*IBG.