burden (2.25 coronary arteries with ≥50% stenosis for HIV+, 2.27 for uninfected patients), CAD distribution, and indications for angiography and CMR.

Despite these similarities, HIV+ patients had twice the extent of myocardial scar compared with uninfected control patients (22.8% vs. 11.3%; $p = 0.01$) (**Figure 1**). After accounting for CAD extent by dividing total myocardial scar burden by number of arteries with ≥50% stenosis, this difference between HIV+ patients and uninfected control patients remained highly significant (10.7% vs. 5.0%; $p < 0.001$). Parallel analyses of only patients with EHR-documented, adjudicated MI yielded similar results; HIV+ control patients with adjudicated MI ($n = 7$), compared with uninfected controls patients with adjudicated MI ($n = 13$), had roughly double the mean scar burden (26.5% vs. 14.5%; $p = 0.07$) and scar per coronary arteries with ≥50% stenosis (12.3% vs. 6.3%; $p = 0.01$). Location and severity of scar corresponded closely for all patients, suggesting that myocardial scar analyzed tended to be vascular in nature; the mean % of scar in myocardial segments corresponding to coronary arteries with versus without severe CAD (≥70% stenosis) was 33.9% versus 12.5% ($p = 0.03$).

Our finding that HIV+ persons have more extensive myocardial scar than uninfected persons in the setting of CAD and MI warrants further study. Despite the small size of this study, the effect size of our findings and degree of statistical significance generate novel hypotheses regarding HIV and vascular scar burden that merit examination in larger cohorts. If our findings are confirmed and HIV+ persons have larger areas of necrosis and scar following MI, this may ultimately help inform HIV-related mechanisms implicated in heart failure and sudden cardiac death.

*Matthew J. Feinstein, MD
Sumeet S. Mitter, MD
Ajay Yadlapati, MD
Chad J. Achenbach, MD, MPH
Frank J. Palella, Jr., MD
Pedro E. Gonzalez, MD
Sheridan Meyers, MD
Jeremy D. Collins, MD
Sanjiv J. Shah, MD
Donald M. Lloyd-Jones, MD ScM

*Division of Cardiology
Department of Medicine
Department of Preventive Medicine
Northwestern University Feinberg School of Medicine
680 North Lake Shore Drive, Suite 1400
Chicago, Illinois 60611
E-mail: matthewjfeinstein@northwestern.edu

http://dx.doi.org/10.1016/j.jacc.2016.07.771

Please note: Dr. Palella Jr. is on the speakers bureau and is a consultant for Janssen Pharmaceuticals, Merck & Co, and Bristol-Myers Squibb. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

REFERENCES

1. Paisible AL, Chang CC, So-Armah KA, et al. HIV infection, cardiovascular disease risk factor profile, and risk for acute myocardial infarction. J Acquir Immune Defic Syndr 2015;68:209–16.

2. Remick J, Georgiopoulou V, Marti C, et al. Heart failure in patients with human immunodeficiency virus infection: epidemiology, pathophysiology, treatment, and future research. Circulation 2014;129:1781–9.

3. Tseng ZH, Secemsky EA, Dowdy D, et al. Sudden cardiac death in patients with human immunodeficiency virus infection. J Am Coll Cardiol 2012;59:1891–6.

4. Hofmann U, Frantz S. Role of lymphocytes in myocardial injury, healing, and remodeling after myocardial infarction. Circ Res 2015;116:354–67.

6-Month Effects of Fingolimod on Indexes of Cardiovascular Autonomic Control in Multiple Sclerosis

Fingolimod, the first oral agent for treatment of multiple sclerosis (MS), exerts its main action through the engagement of sfingosine-1-phosphate receptors (S1Pr) (1) at the lymphocyte level. However, S1Pr are also expressed in the atrial myocytes and endothelial cells, and their activation may frequently cause a nonharmful bradycardia following the first dose. The drug is generally well tolerated, although some cardiovascular adverse effects have been reported, including first- or second-degree atrioventricular blocks (1) and a moderate reduction in the left ventricular systolic function (2). In a very limited number of patients, major cardiovascular events also have been signaled (1). The influence of fingolimod treatment on the autonomic cardiac control over time is still not fully clarified. In this observational longitudinal study, we investigated the effect of fingolimod on the sympathetic and parasympathetic heart control and on the arterial baroreflex function after 6 months of treatment.

We consecutively recruited 21 subjects, 11 men and 10 women, affected by the relapsing remitting form of MS and beginning the treatment with fingolimod (single daily oral dose of 0.5 mg) in compliance with the Helsinki Declaration. Patient characteristics were: age 41.9 ± 7.8 years, body mass index 23.3 ± 2.9 kg/m^2, time from MS onset 12.4 ± 7.2 years. The Expanded Disability Status Scale median score was

JACC VOL. 68, NO. 18, 2016
NOVEMBER 1, 2016:2026–32

TABLE 1 Effects of Fingolimod on BP, Cardiac Rhythm, Indexes of Cardiovascular Autonomic Control and Baroreflex Function at T_{6m}

	T_0	T_{6m}	$T_{6m} - T_0$	p Value
Systolic BP mean, mm Hg	99 ± 10	104 ± 13	5.5 ± 13	0.08
Systolic BP SD, mm Hg	4.1 ± 1.6	5.3 ± 2.7	1.1 ± 3.2	0.14
Diastolic BP mean, mm Hg	68.1 ± 8.6	68 ± 10	0.8 ± 13.2	0.79
Diastolic BP SD, mm Hg	1.9 ± 0.6	2.6 ± 1.3	0.7 ± 1.5	0.06
PI mean, ms	867 ± 129	875 ± 106	8.4 ± 73.6	0.62
PI SD, ms	52.6 ± 18.8	36.3 ± 14.2	−15.7 ± 14.2	<0.01
PNN50, %	14 ± 16	5 ± 9	−9 ± 15	<0.01
RMSSD, ms	33.19 ± 17.15	22.6 ± 11.2	−10.6 ± 16.5	<0.01
LF, ms^2	977.5 ± 722.9	330.5 ± 272.1	−647 ± 652.1	<0.01
HF, ms^2	404.5 ± 402.4	128.2 ± 102.6	−276.3 ± 373.3	<0.01
LF/HF	3.5 ± 2.2	3 ± 1.6	−0.45 ± 2	0.33
BRSsq, ms/mm Hg	17.4 ± 8.3	9.8 ± 4.2	−7.6 ± 6.3	<0.01
BRSα, ms/mm Hg	24.9 ± 20.1	11.7 ± 6.1	−13.2 ± 11.9	<0.01

Values are mean ± SD. The $T_{6m} - T_0$ column represents the mean ± SD of the individual differences.

BP = blood pressure; BRSα = spontaneous baroreflex sensitivity by alpha coefficient technique; BRSsq = spontaneous baroreflex sensitivity by sequence technique; HF = high-frequency; LF = low-frequency; PI = pulse interval; PNN50 = the percentage of normal beats differing for >50 ms from the preceding normal beat; RMSSD = the root mean square of successive pulse interval differences; T_0 = after first dose of treatment; T_{6m} = after 6 months of treatment.

5.0 (range 1.0 to 6.5). Exclusion criteria were history of cardiac, renal, and respiratory diseases, and use of drugs interacting with cardiac function within the last 4 weeks.

Continuous finger arterial blood pressure (BP) was recorded for 10 min before the first dose (T_0) and after 6 months of treatment (T_{6m}) in supine position. Systolic and diastolic BP were measured in each beat, and the beat length was estimated by the pulse interval (PI) (i.e., the time period between consecutive systolic peaks). Heart rate (HR) was derived by the formula HR = (1,000/PI) · 60.

From the analysis of the PI beat-to-beat series, the percentage of normal beats differing for >50 ms from the preceding normal beat (PNN50) and the root mean square of successive PI differences (RMSSD) were computed. The fast Fourier transform estimated the PI spectral characteristics. From each spectrum, the power density was integrated over the low-frequency (LF) (0.04 to 0.15 Hz) and the high-frequency (HF) (0.15 to 0.4 Hz) bands. The LF/HF power ratio was also calculated. PNN50, RMSSD, and the HF power have been associated with the parasympathetic control of the heart, the LF power with the sympathetic control and the LF/HF ratio with the sympathovagal balance (3). The sequence and the alpha coefficient techniques estimated the spontaneous baroreflex sensitivity (BRS) (4).

The results of the analysis are reported in **Table 1**. With reference to T_0, after 6 months of treatments, the PI mean value was unchanged, whereas the PI SD decreased (−30%). All the PI-derived indexes of parasympathetic heart control significantly lowered: pNN50 (−64%), RMSSD (−32%), and power in the HF band (−68%). The PI power in the LF band also decreased (−66%).

Concerning the baroreflex function, the gain of the baroreflex markedly decreased either when estimated by the sequence technique (−7.8 ms/mm Hg, with a drop of −43.7%) or the alpha coefficient technique (−13.2 ms/mm Hg, with a drop of −65%).

Thus, at T_{6m}, we observed a consistent reduction in the baroreflex sensitivity and in all indexes of the sympathetic and parasympathetic heart control. A reduction in the vagal drive to the heart was already reported after 3 months of fingolimod treatment (5). In our study, we show that this reduction is still present after 6 months and, importantly, for the first time, we document a concomitant impairment of the baroreflex function and of the sympathetic drive to the heart over this time window.

To discriminate whether this midterm autonomic dysfunction might either depend on the drug treatment or on the progression of the disease, we evaluated in a matched group of 17 MS patients under another drug treatment (natalizumab), the same autonomic variables 6 months apart. In this control group, no significant change was observed in any autonomic parameter. This finding supports the hypothesis that the changes in the autonomic indexes observed in the fingolimod-treated patients over the 6-month timespan might mostly depend on the drug effect and not be a consequence of the disease evolution during this time frame.

From the clinical perspective, our study suggests that a periodic surveillance of the autonomic heart control may be appropriate in MS patients treated long term with fingolimod.

*Vittorio Racca, MD
Marco Rovaris, MD
Emanuele Vaini, MSc
Rosella Cavarretta, MD
Maurizio Ferratini, MD
Anastasia Toccafondi, BMSc
Marco Di Rienzo, MSc

*Cardiology Rehabilitation Centre
Santa Maria Nascente Institute IRCCS
Fondazione Don Carlo Gnocchi
Via Capecelatro 66
20148 Milan
Italy
E-mail: vracca@dongnocchi.it

http://dx.doi.org/10.1016/j.jacc.2016.08.032

Please note: The study was funded by a "Ricerca Corrente 2014-2015" grant from the Italian Ministry of Health and the Don Gnocchi Foundation. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

REFERENCES

1. La Mantia L, Tramacere I, Firwana B, et al. Fingolimod for relapsing-remitting multiple sclerosis. Cochrane Database Syst Rev 2016;4:CD009371.

2. Racca V, Di Rienzo M, Cavarretta R, et al. Fingolimod effects on left ventricular function in Multiple Sclerosis. Mult Scler 2016;22:201–11.

3. Task Force of the ESC and the NASPE. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Circulation 1996; 93:1043–65.

4. Parati G, Di Rienzo M, Mancia G. How to measure baroreflex sensitivity: from the cardiovascular laboratory to daily life. J Hypertens 2000;18:7–19.

5. Simula S, Laitinen T, Laitinen TM, et al. Effect of fingolimod on cardiac autonomic regulation in patients with multiple sclerosis. Mult Scler 2016;22: 1080–5.

Is Histamine H_2 Receptor a Real Promising Target for Prevention or Treatment of Heart Failure?

The recently published research by Leary et al. (1) in the *Journal* provided novel clinical evidence regarding the benefit effect of histamine H_2 receptor antagonists (H2RAs) on heart failure (HF). We appreciate the long and hard effort the authors performed in this work, which, however, also brings up the following clinical issues.

The most concerned issue is the missing information regarding whether H2RA exhibits superior effect than β-blockers. Properly addressing this issue will help readers recognize the position of H2RA among the well-established anti-HF drugs. Much like β_1 receptor, H2R is also a Gs-protein coupled receptor sharing a common downstream pathway. But the affinity of catecholamines for human β_1 receptor (p*K*i value: 6.0) is more than a hundred times higher than that of histamine for human H2R (p*K*i value: 3.8) according to information from the International Union of Pharmacology database (2). Therefore, histamine might not achieve comparative receptor activation effect as catecholamines do unless its concentration reaches over 2 orders of magnitude greater than catecholamines. During HF development, persistent activation of sympathetic nerves continuously maintains a relatively high level of noradrenaline. Nevertheless, discontinuous degranulation of cardiac mast cells, the acknowledged main source of cardiac histamine, is unlikely to continuously maintain a high histamine level. Although we previously pointed out that histamine was a newly recognized sympathetic neurotransmitter coexisting with noradrenaline, the simultaneously released histamine on sympathetic activity did not exceed noradrenaline (3). Because the antagonism of a neutral antagonist depends mainly on the agonism of its target receptor, one may speculate that the effects of H2RA on HF should be no better than the antagonism of β_1 receptor. If this is correct, H2R might not be a promising drug target for HF, which may also be 1 of the important reasons for certain pharmaceutical companies not willing to move forward as mentioned in the editorial comment of this study (4).

An additional issue is the drug interaction. In this regard, important missing information is the specific ligands of H2RA used among the 313 users. Certain H2RAs, such as cimetidine, are strong cytochrome P-450 (CYP450) enzyme inhibitors. Combination use, especially long-term, of cimetidine with other anti-HF drugs was very likely to result in their decreased metabolism and increased plasma concentration, which would eventually contribute to the final HF incidence. Therefore, if cimetidine was used in some of the 313 H2RA users, these cases should be excluded or at least stratified in the study.

***Gong-Hao He, MD, PhD**
Gui-Li Xu, PhD
Wen-Ke Cai, MD, PhD
Juan Zhang, MSc

*Department of Pharmacy
Kunming General Hospital of Chengdu Military Region
212 Daguan Road
Kunming 650032
China
E-mail: gonghow@hotmail.com

http://dx.doi.org/10.1016/j.jacc.2016.06.078

Please note: All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

REFERENCES

1. Leary PJ, Tedford RJ, Bluemke DA, et al. Histamine H2 receptor antagonists, left ventricular morphology, and heart failure risk: the MESA study. J Am Coll Cardiol 2016;67:1544–52.

2. IUPHAR/BPS Guide to Pharmacology. Available at: http://www.guidetopharmacology.org/GRAC/searchPage.jsp. Accessed September 6, 2016.

3. He G, Hu J, Li T, et al. The arrhythmogenic effect of sympathetic histamine in mouse hearts subjected to acute ischemia. Mol Med 2012;18:1–9.

4. Kitakaze M. Clinical evidence of the role of histamine in heart failure. J Am Coll Cardiol 2016;67:1553–5.

REPLY: Is Histamine H_2 Receptor a Real Promising Target for Prevention or Treatment of Heart Failure?

We appreciate the thoughtful review of our work (1) by Dr. He and colleagues. Although salient, the lack of