

Disclaimer: The manuscript and its contents are confidential, intended for journal review purposes only, and not to be further disclosed.

URL: <http://circ-submit.aha-journals.org>

Title: Response to Letter from Pal and colleagues

Manuscript number: CIRCULATIONAHA/2016/021488

Author(s): Houman Ashrafian, John Radcliffe Hospital, Oxford, United Kingdom

Nikhil Pal, University of Oxford

Nadiya Sivaswamy, University of Aberdeen

Masliza Mahmood, John Radcliffe Hospital, Oxford, United Kingdom

Arash Yavari, University of Oxford

Amelia Rudd, University of Aberdeen

Satnam Singh, University of Aberdeen

Dana Dawson, University of Aberdeen

Jane Francis, oxford

Jeremy Dwight, Oxford Heart Centre, John Radcliffe Hospital

Hugh Watkins, University of Oxford

Stefan Neubauer, John Radcliffe Hospital, Oxford, United Kingdom

Michael Frenneaux, University of East Anglia

Disclaimer: The manuscript and its contents are confidential, intended for journal review purposes only, and not to be further disclosed.

# **Response to letter regarding article, 'The Effect of Selective Heart Rate Slowing in Heart Failure with Preserved Ejection Fraction'.**

Nikhil Pal, MBBS, MRCP<sup>1</sup>; Nadiya Sivaswamy<sup>2</sup>, MD; Masliza Mahmod, MRCP, DPhil<sup>1</sup>; Arash Yavari, MRCP, DPhil<sup>1</sup>; Amelia Rudd, HND<sup>2</sup>; Satnam Singh MBBS, MRCP<sup>2</sup>; Dana K. Dawson, DM, DPhil<sup>2</sup>; Jane M. Francis, DCR(R)<sup>1</sup>; Jeremy S Dwight, MD, FRCP<sup>1</sup>; Hugh Watkins, MD, PhD, FRCP, FMedSci<sup>1</sup>; Stefan Neubauer, MD, FRCP, FACC, FMedSci<sup>1</sup>; Michael Frenneaux, PhD, FRCP, FMedSci<sup>3</sup>; Houman Ashrafian, MA, DPhil, MRCP<sup>1</sup>.

<sup>1</sup>Division of Cardiovascular Medicine, Radcliffe Department of Medicine, John Radcliffe Hospital, Oxford, OX3 9DU, UK

<sup>2</sup>School of Medicine and Dentistry, University of Aberdeen, Aberdeen AB25 2ZD, UK

<sup>3</sup>Norwich Medical School, University of East Anglia, Bob Champion Research and Educational Building, James Watson Road, Norwich Research Park, Norwich, NR4 7UQ

**First author:** Pal N

**Corresponding author:**

Professor Houman Ashrafian  
Experimental Therapeutics  
Radcliffe Department of Medicine  
University of Oxford  
John Radcliffe Hospital  
Oxford, OX3 9DU, UK  
Telephone: 0044 1865 234 670

Fax: 0044 1865 234658

Email: [houman.ashrafian@cardiov.ox.ac.uk](mailto:houman.ashrafian@cardiov.ox.ac.uk)

**Word Count: 274**

**Disclosure statement:** No potential conflict of interests to declare by any of the authors.

Disclaimer: The manuscript and its contents are confidential, intended for journal review purposes only, and not to be further disclosed.

Dear Editor

We thank Dios *et al*/ for their comments related to differences in outcomes noted between our observations and in previously published work exploring the role of Ivabradine in patients with Heart Failure with Preserved Ejection Fraction (HFpEF).<sup>1</sup>

We acknowledge the central issue; namely the heterogeneity of patients recruited related to the lack of clear consensus regarding the pathophysiology of HFpEF and the inability of traditional diagnostic techniques such as resting echocardiography (ECHO) to diagnose this condition.

We used similar inclusion criteria to previously published work such as the aldosterone trial, which included not only resting ECHO parameters to diagnose diastolic dysfunction, but also cardiopulmonary exercise (CPEX) testing.<sup>2</sup> This was employed to include patients who demonstrated objective evidence of limitation in exercise capacity (peak oxygen consumption at maximal exercise,  $VO_{2\text{ peak}}$ , <80% predicted for age and sex), with a pattern of gas exchange indicating that this limitation was cardiac in origin. Furthermore we included a separate group of asymptomatic hypertensives. The latter nevertheless had reduced exercise capacity. The purpose of this group was to assess the effects of heart rate reduction in hypertensives without symptoms of heart failure. Borlaug *et al* have highlighted the importance of such chronotropic incompetence in impairing exercise capacity in the HFpEF population.<sup>3</sup>

Others too have observed value in the application of exercise echocardiography in diagnosing patients with HFpEF with adverse outcomes.<sup>4</sup> With further advancement in our understanding of the underlying pathophysiology of HFpEF, diagnostic techniques such as exercise ECHO and CPEX may gain prominence. Refining comprehensive assessment during exercise will likely identify a cohort of patients with clear-cut HFpEF and facilitating clinical trials and clinical practice.<sup>5</sup>

## References

1. Pal N, Sivaswamy N, Mahmood M, et al. Effect of Selective Heart Rate Slowing in Heart Failure With Preserved Ejection Fraction. *Circulation* 2015;132:1719-25.
2. Edelmann F, Wachter R, Schmidt AG, et al. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: The ald-dhf randomized controlled trial. *JAMA* 2013;309:781-91.
3. Borlaug BA, Reddy YNV. Determinants and Correlates of Exercise Capacity in Heart Failure\*. *JACC: Heart Failure* 2015;3:815-7.
4. Donal E, Lund LH, Oger E, et al. Value of exercise echocardiography in heart failure with preserved ejection fraction: a substudy from the KaRen study. *European Heart Journal - Cardiovascular Imaging* 2015.
5. Abudiab MM, Redfield MM, Melenovsky V, et al. Cardiac output response to exercise in relation to metabolic demand in heart failure with preserved ejection fraction. *European journal of heart failure* 2013;15:776-85.

Disclaimer: The manuscript and its contents are confidential, intended for journal review purposes only, and not to be further disclosed.

Disclaimer: The manuscript and its contents are confidential, intended for journal review purposes only, and not to be further disclosed.

URL: <http://circ-submit.aha-journals.org>

Title: The controversial role of Ivabradine in HFpEF. Fixing the pieces

Manuscript number: CIRCULATIONAHA/2015/020561

Author(s): Santiago de Dios, University Hospital La Zarzuela

The controversial role of Ivabradine in HFpEF. Fixing the pieces

De Dios, Ivabradine in HFpEF

Santiago de Dios, MD

Department of Cardiology

University Hospital La Zarzuela

Calle Pleyades 25, 28023 Madrid, Spain

0034650336439 Fax: 913570501

Drdedios@gmail.com

Disclaimer: The manuscript and its contents are confidential, intended for journal review purposes only, and not to be further disclosed.



Dear editor

Recently it has been published the article "The Effect of Selective Heart Rate Slowing in Heart Failure with Preserved Ejection Fraction"<sup>1</sup> signed by Ashrafian H, Pal N et cols, a prospective randomized double blind placebo-controlled trial developed to test the utility of Ivabradine (Iva) in Heart Failure with preserved Ejection Fraction(HFpEF). It was designed as a crossover study comparing Iva versus placebo to test its value to improve effort capacity measured as the peak O<sub>2</sub> uptake in the ergospirometry. The conclusion was that Iva not only did not improve the capacity but diminished the patients outcomes.

Previous studies made in this field, which tried to answer the same question,( whether Iva improves effort capacity in HFpEF), such as the developed by Kosmala <sup>2</sup>, De Luca <sup>3</sup> even the one by Simantirakis <sup>4</sup>, which tested it in long term, concluded just the opposite, that Iva improves effort capacity measured as well as the O<sub>2</sub> uptake.

How could this be possible? The answer probably stays at the patient selection and the vast variety of clinical situations included in the entity we call HFpEF

If we understand the definition of HF as the incapacity of the Heart to answer the blood flow demand of the tissues, the patients included in the article of Ashrafian perfectly fit this definition, as they were in class II and they have an impaired O<sub>2</sub> uptake, a widely proven parameter of HF.

However, these patients did not have affected the echocardiographic diastolic function. Precisely, the diastolic dysfunction in the echocardiogram were part of the inclusion criteria in the studies developed by Simantirakis and Kosmala, which also match with HFpEF.

As the paper of Iva in HF is based on its effect on an impaired diastole, it is even logic that the only patients who will benefit from its use are those who present diastolic dysfunction.

In the patients of the Ashrafian trial, the authors postulate that one of the mechanism responsible of the reduced cardiac output during exercise could be chronotropic incompetence. A drug that reduces capacity of tachycardia will probably worsen the outcomes in these patients.

Moreover, in the hypertensive patients used as matches in the study who did not have diastolic dysfunction, neither chronotropic incompetence, the effect of Iva was neutral.

The result of this trials and its analysis are just another proof of the poor knowledge we have of HFpEF and our therapeutic and management options.

Individual selection of different therapies, even Iva in HFpEF, is as always needed

Disclosures: None

1. Pal N, Sivaswamy N, Mahmood M, Yavari a, Rudd A, Singh S, Dawson DK, Francis JM, Dwight JS, Watkins H, Neubauer S, Frenneaux M, Ashrafian H. Effect of selective Heart Rate Slowing in Heart Failure With Preserved Ejection Fraction. *Circulation*. 2015;132(18):1719-1725
2. W. Kosmala, D.J. Holland, A. Rojek, L.Wright, M. Przewlocka-Kosmala, T.H. Marwick, Effect of If-channel inhibition on hemodynamic status and exercise tolerance in heart failure with preserved ejection fraction: a randomized trial, *J. Am. Coll. Cardiol*. 2013;62:1330–1338.
3. Gabriele De Masi De Luca, Ivabradine and diastolic heart failure, *J. Am. Coll. Cardiol*. 2012;59(13s1):E1009-E1009.
4. Simantirakis EN,. Nakou E.S,. Kallergis E.M,. Arkolaki E.G. Patrianakos, A.P,. Papakonstantinou P.E, Chlouverakis G.I. Vardas., P.E. Long-term effect of If-channel inhibition on diastolic function and exercise capacity in heart failure patients with preserved ejection fraction *International Journal of Cardiology* 2015;187:9–11