

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The Heart Failure with Preserved Ejection Fraction (HFpEF) Pathophysiology, observational Study (IDENTIFY-HF): does increased arterial stiffness associate with HFpEF, in addition to ageing and vascular effects of co-morbidities? - rationale and design.
AUTHORS	Ali, Danish; Callan, Nualla; Ennis, Stuart; Powell, Richard; McGuire, Scott; McGregor, Gordon; Weickert, Martin; Miller, Michelle; Cappuccio, Francesco; Banerjee, Prithwish

VERSION 1 – REVIEW

REVIEWER	michael macdonald changi general hospital singapore
REVIEW RETURNED	06-Dec-2018

GENERAL COMMENTS	This is an interesting study. My only comment would be regarding the selection of the HF-PEF group. In order to ensure that you truly have a HF-PEF group you should consider using age related cut offs of NTproBNP. By using a level of 125 I think you are reducing your specificity. It is incredibly important that you select patients with real HF, and not allow dilution, particularly given your numbers of patients are so small.
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REVIEWER	Stefano Ghio Fondazione IRCCS Policlinico S Matteo Pavia Italy
REVIEW RETURNED	23-Dec-2018

GENERAL COMMENTS	<p>The authors describe the protocol of an observational study, IDENTIFY-HF, that will investigate whether increasing arterial stiffness as a result of increasing common comorbidities is associated with HFpEF.</p> <p>The reviewer agrees with the authors that in order to develop evidence-based treatments in patients with a syndrome which lacks evidence based treatments such as HFpEF, further investigation is mandatory to better understand its pathophysiology.</p> <p>Therefore, the study protocol of IDENTIFY-HF could be of interest to the readers of the journal.</p> <p>I would only suggest to make a small change in the abstract: IDENTIFY-HF will investigate whether ... rather than "investigates".</p>
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	<p>If it is possible to comment the protocol, I find rather strange that the echocardiographic examination does not include parameters of pulmonary pressure and of right ventricular function. Pulmonary hypertension and right ventricular dysfunction are quite common in HFpEF patients.</p> <p>If the authors aim at correlating clinical phenotypes with plasma concentration of several biomarkers, then the presence / absence of PH and/or RV dysfunction may make a huge difference. By the way, pulmonary stiffness is also certainly different in HFpEF vs HFrfEF patients (see for example Am Heart J 2017;192:120-7).</p>
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REVIEWER	Noel Bairey Merz MD Cedars-Sinai Medical Center
REVIEW RETURNED	27-Dec-2018

GENERAL COMMENTS	<p>A study design paper for a cross-sectional study of pre-defined groups using an outcome of arterial function to further understand HFpEF. Several issues to address to strengthen the work:</p> <ol style="list-style-type: none"> 1. Avoid terms in the abstract, text and conclusions such as "increasing arterial stiffness" - this is misleading and suggests you are doing repeated measures in the same cohort prospectively. 2. Cite prior datasets that have looked at PWV both cross-sectionally, and prospectively over time with aging (Framingham, etc) 3. Cite the cross-sectional design as a limitation 4. The Introduction and Hypothesis sections are overlapping and redundant
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

Many thanks for the useful comments and recommendations and we appreciate the concern regarding the cut off for the NT-proBNP. We have adopted the definition of HFpEF from the guidelines 2016 of the European Society of Cardiology. All our HFpEF patients have documented signs and symptoms of heart failure, as well of its associated echocardiographical abnormalities, and hence confident our HFpEF are true HFpEF patients.

Reviewer 2. We are grateful for these helpful comments and have made the recommended changes, as highlighted in manuscript. All the transthoracic echocardiograms done include pulmonary pressures and right ventricular structural and functional assessment done.

Reviewer 3: Again, we are much obliged for the constructive comments and we have adjusted accordingly.

- The term "increasing arterial stiffness" has been replaced with increased arterial stiffness to avoid confusion
- A citation of previous datasets has been added to look at PWV both cross-sectionally and prospectively over time.
- We have added the cross-sectional design as a limitation
- We have adjusted the removed the overlap between the Introduction and Hypothesis section.

VERSION 2 – REVIEW

REVIEWER	Stefano Ghio Fondazione IRCCS Policlinico S Mateo 27100 Pavia Italy
REVIEW RETURNED	05-Sep-2019
GENERAL COMMENTS	The authors have accepted the suggestions of the reviewer. I have no further request. The manuscript can be accepted.