Author's response to reviews

Title: Utility of NT-proBNP as a rule-out test for left ventricular dysfunction in very old people with limiting dyspnoea: the Newcastle 85+ Study

Authors:

Joanna Collerton (joanna.collerton@ncl.ac.uk)
Andrew Kingston (andrew.kingston@ncl.ac.uk)
Fahad Yousaf (drfyousaf@gmail.com)
Karen Davies (karen.davies@ncl.ac.uk)
Antoinette Kenny (antoinette.kenny@nuth.nhs.uk)
Dermot Neely (dermot.neely@nuth.nhs.uk)
Carmen Martin-Ruiz (carmen.martin-ruiz@ncl.ac.uk)
Guy MacGowan (guy.macgowan@ncl.ac.uk)
Louise Robinson (a.l.robinson@ncl.ac.uk)
Thomas BL Kirkwood (tom.kirkwood@ncl.ac.uk)
Bernard Keavney (bernard.keavney@manchester.ac.uk)

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Author's response to reviews: see over
Dear Dr Manginas

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Utility of NT-proBNP as a rule-out test for left ventricular dysfunction in very old people with limiting dyspnoea: the Newcastle 85+ Study.

Thank you for your e-mail of 28th August 2014 in relation to the above manuscript. We are most grateful for the helpful comments from the reviewers and we have revised our manuscript in the light of these. We detail our responses to the specific comments below; our responses are presented in bold type.

Reviewer: 1
In the key words, they should alter 80 years and over to become 85 years and over.
We selected the key word ‘Aged, 80 and over’ rather than ‘Aged, 85 and over’ as the former is a recognised MeSH term. We would therefore prefer to retain ‘Aged, 80 and over’.

Reviewer: 2
Taking into account the difficulty in the recruitment and evaluation of very elderly patients, this is a
meritorious study indeed. However, in my opinion, there are serious questions that should be commented.

I do not exactly how these findings are applied into clinical practice. Patients were selected according to the presence of limiting dyspnoea, independently of any other semiology. Can we consider this as a good way to select patients in order to evaluate the utility of natriuretic peptides? The gold standard is really LVD diagnosed by echo, not heart failure (HF). So what important is limiting dyspnoea in the selection of elderly patients.

In my opinion, authors should have evaluated previous history and HF semiology more systematically to select patients with HF. The study is really focused in the value of peptides in detecting LVD, not in helping physicians to rule out HF in elderly patients. Sample to this outcome (LVD) is very small, particularly to detect diastolic dysfunction, which is very frequent in elderly patients, independently of clinical manifestations.

On the other hand, I think the echocardiographic criteria to diagnosis severe diastolic dysfunction are questionable (E/e’ > 10 ?)

In summary, I think it is a valuable study but without a clear application in the clinical practice.

We thank the reviewer for his positive comments as to the merit and value of this study.

We acknowledge that the use of LV dysfunction as the target condition is a limitation (Discussion: page 13, paragraph 2 – strengths and limitations section). We agree that the use of clinical heart failure as the target condition would have made for a superior investigation. However, clinical assessment for HF was not possible within the scope of the Newcastle 85+ Study. Nevertheless, our focus on the use of natriuretic peptides to rule out LV dysfunction in a sample with a clinical suspicion of HF is in accordance with other important work in the field[1-7]; we have now added references to such studies (Discussion: page 13, paragraph 2 – strengths and limitations section).

We acknowledge that the use of limiting dyspnoea to define a sample with a suspicion of HF without clinical examination is a potential limitation; clinical examination was not possible within this study. However, the classical physical signs of HF are known to lack both sensitivity and specificity in this age group.[8] Dyspnoea has a high sensitivity (89%) for chronic HF, although low specificity (51%).[8]

We did not exclude participants with other potential causes of dyspnoea as we were interested in NT-proBNP’s performance in a ‘real life’ unselected sample of dyspnoeic very old people.
Furthermore, the co-existence of multiple morbidities is common in this age group. We address these issues in the revised discussion (page 13, paragraph 2 – strengths and limitations section). We accept that our sample size is modest in absolute terms, but it compares well with existing studies in this ‘difficult to study’ age group; to our knowledge it is the largest population-based study of the utility of natriuretic peptides in very old people with a clinical suspicion of chronic HF. The prevalence of systolic dysfunction and isolated moderate/severe diastolic dysfunction were high in this very elderly cohort; 34% and 19% respectively.

The echocardiographic criteria used to assign diastolic dysfunction were reported in our earlier work with this cohort and were in accordance with the British Society of Echocardiography guidelines.[9] We acknowledge that, whilst the general approach to assessing diastolic dysfunction is similar across studies, specific criteria and cut-points vary widely. We addressed this issue in our earlier work[9] by analysing our diastolic function data using the scheme implemented by Bursi et al. in the Olmsted County study.[10] Although a smaller number of participants could be classified using the approach of Bursi et al., the proportion of classifiable participants with moderate or severe diastolic dysfunction was very similar to that yielded by our approach (30.9% vs 31.0%).[9] The methodological challenges of accurate measurement of left atrial volume, Valsalva manoeuvres and pulmonary venous flow (variably incorporated in diastolic function classification schemes in previous studies), precluded their use in this domiciliary study of very old people.

We believe that our results have the potential to be applied in clinical practice (as highlighted by reviewer 3 in his suggested amendment to the abstract). We believe that when assessing very old people with limiting dyspnoea, in whom HF is a potential diagnosis, optimal evaluation may require direct access to echocardiography without preliminary natriuretic peptide measurement (stated in Discussion, page 14 – conclusions section).

Reviewer: 3

Discretionary revisions

Abstract Line 33: I would suggest adding a final more explicit sentence (if word limit allows) suggesting that clinicians consider proceeding direct to echocardiography in the very old in the investigation of limiting dyspnoea though to potentially be HF.
We agree that such a sentence would improve the abstract but are already up to the word limit. If it were possible to replace the text ‘less than or equal to’ with the symbol ‘≤’ throughout the abstract this would allow insertion of the following sentence: ‘Optimal evaluation of the dyspnoeic very old may require direct access to echocardiography, without preliminary peptide measurement.’ We have not made this change in the revised manuscript as the online submission system was not able to accept the ‘≤’ symbol in the abstract our original submission. However we would be keen to make this amendment if possible.

Line 56: Suggest amend to ‘……50% of HF in people over the age....’

DONE. We have replaced the original text of ‘around 50% of HF over the age of 70’ with ‘around 50% of HF in people over the age of 70’.

Line 277: Suggest delete the repeated ‘in the old’ at the end of this sentence.

DONE. We have replaced the original text ‘Atypical HF presentations in the very old, coupled with high levels of non-specific ECG findings and co-morbidity, may limit the utility of such approaches in the very old’ with ‘Atypical HF presentations in the very old, coupled with high levels of non-specific ECG findings and co-morbidity, may limit the utility of such approaches in this age group.’

We have submitted a ‘good’ copy of the revised manuscript together with a version tracking the changes made.

We thank you for considering this revised manuscript.

Yours sincerely

Dr Joanna Collerton      Professor Bernard Keavney
References


Prevalence of left ventricular dysfunction in a UK community sample of very old people: the 


Systolic and Diastolic Heart Failure in the Community. *JAMA* 2006, 296(18):2209-2216.