Author’s response to reviews

Title: Prenatal hypoxia induces increases in cardiac contractility on a background of decreased capillary density

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Author’s response to reviews: see over
23 December 2008

Mr. J. Dunckley
Assistant Editor
BMC Cardiovascular Disorders
BMC-Series Journals
www.biomedcentral.com

Dear Sir,

RE: Resubmission of manuscript Nos:5048302982187002 - BMC Cardiovascular Disorders

Please find enclosed a copy of the resubmitted manuscript that we wish to submit to BMC Cardiovascular Disorders for consideration at the next most convenient opportunity. This manuscript is titled ‘Prenatal hypoxia induces increases in cardiac contractility on a background of decreased capillary density’ and details novel work establishing the importance of the fetal environment in the development of the coronary circulation in the rat and how changes during this period are manifest in adult animals. The manuscript consists of the text, with an accompanying table and six figures.

We have received comments from three referees and we are very pleased with the positive reviews we have received. We are also grateful to the third reviewer for the care with which the manuscript was read and the helpful suggestions that have been enclosed, we hope that the new manuscript satisfactorily addresses these concerns and they are attached at the base of this letter. We admit that the succinct writing style chosen initially is probably the cause for misunderstandings in the text, for which we apologise. Given below is a summary of the combined changes that have been made to the manuscript in an attempt to clarify the changes:

Changes to Manuscript:
1) Title: This is unchanged

2) Abstract: Details regarding results from both eNOS and iNOS western blots has been added to the text

3) Background: This is unchanged

3) Methods: Methods remain largely unchanged. An extra detail regarding Masson’s Trichrome staining was added (Page 7, Paragraph 2)
4) Results: These are largely unchanged, a Figure label has been changed to better reflect the data present and rate-pressure product has been defined in the text. A further note has been added regarding Masson’s Trichrome staining to clarify the decision to leave the data out – it seems inappropriate to include yet further negative data that does not really contribute to the interpretation.

5) Discussion: The discussion has been re-written with particular attention paid to details covering ‘impaired relaxation’ (Page 13 Paragraph 2). Comment is made as to alternate mechanisms controlling relaxation. The section covering ‘capillary density’ has been extensively re-written to hopefully address more completely the concerns of the reviewer (Page 13 Paragraph 3 to Page 14 Paragraph 2). This detail has been simplified and is less speculative.

6) References: These have been amended to more accurately reflect the details outlined in the discussion. Some references have been removed.

7) Table 1: This is unchanged

8) Figure Legends: These are unchanged

9) Figures: These are unchanged

To the best of our knowledge this document now addresses the concerns laid out by the individual referees as detailed below. We have also tried as closely as possible to format the document correctly to the journal style.

The authors have particularly chosen to submit to BioMed Central due to the rapid response time, of particular significance for this rapidly developing field of work. In addition, the University of Birmingham is a member of BioMed Central and we are keen to support this venture. Please do not hesitate to contact me should you require any further details regarding the manuscript. Thank you for your time.

Yours faithfully,
Response to Reviewer’s Comments:
Manuscript Number: 5048302982187002
Reviewer: Loren P. Thompson

The authors wish to thank the reviewer for the helpful comments regarding the manuscript. We have re-written the discussion section of manuscript in an attempt to address these comments and hope that this now better reflects the data illustrated. We have simplified the discussion in the hope that this clarifies the reasons behind the investigations undertaken. We highlight below the major amendments made to the manuscript.

MAJOR COMMENTS:
1) Cardiac hypertrophy – We have removed the speculative discussion regarding the impact of chronic hypoxia in utero (CHU) on development of hypertrophy that may occur as a result of the apparent obesity. Instead we have addressed hypertrophy in the context of normal physiological growth from a young age. Given that hyperplasia of the myocardium is essentially absent we feel the term ‘hypertrophy’ in this context is appropriate – however, have supplemented the term ‘allometric growth’ where appropriate in order to prevent any confusion. None was intended and we hope the lack of clarity is addressed in the new text. We make one passing reference to ‘pathological hypertrophy’ with regard to examples for reduced coronary flow reserve but feel that this is implicit in the text and should not lead to confusion.

2) Role of endothelial nitric oxide synthase (eNOS): We have re-addressed the rationale for measuring the expression of eNOS in light of the results we present. Multiple mechanisms are available for the control of coronary flow and the NOS isoforms are obvious candidates and we hope the explanation given will present a reader unfamiliar with the subject a framework to understand the experiment. If we were to detail explicitly the mechanism contributing to the maintenance of coronary flow a better experimental protocol would be chosen. We hope that these experiments establish a ‘basal reference point’ from which future experiments can examine these specific questions in more detail.

MINOR COMMENTS:
1) Masson’s Trichrome staining: a difficult question to get right – this was a lot of data but essentially all negative. We took the decision not to present the data as yet more negative data would not support the conclusions made in the text. However, we did feel that the technique needed to be mentioned as it would be an obvious question for a potential reader to ask.

2) Rate-pressure product has been defined in the text – (Page 10, paragraph 2). An oversight on our part.

3) ‘Adult’ has been added to clarify the details regarding iNOS.