Author's response to reviews

Title: Influence of oxygen tension on myocardial performance. Evaluation by tissue Doppler imaging

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Author’s response to reviews: see over
Dear Sir,

please find enclosed the revised manuscript entitled "Influence of oxygen tension on myocardial performance. Evaluation by tissue Doppler imaging" which we hope now meets the criteria for publication in Cardiovascular Ultrasound. We are pleased with the comments from the three reviewers and we have considered all issues raised in a point-to-point fashion.

All authors have read and approved submission of the manuscript and the manuscript has not been published and is not being considered for publication elsewhere in whole or part in any language except as an abstract. There are no financial or other relations that could lead to a conflict of interest.

Yours sincerely,

Ole Frøbert, MD, ph.d.

**Reviewer 1**

We thank the reviewer for constructive criticism.

**Major concerns**

1. The reviewer points to the possibility that heart rate could affect Tissue Doppler derived parameters of diastolic function. We agree in this concern and we have included a paragraph in the discussion on the issue:

**Addition p. 8, l. 6:**

_We found that heart rate increased with hypoxia and decreased with hyperoxia. This might have affected our measures of LV systolic and diastolic function but we consider this unlikely on the basis of our previous studies (ref, ref) demonstrating that TEI index, strain rate and the tissue tracking was unrelated to heart rate._

2. We agree with the reviewer that the increase in TEI index with hyperoxia with no corresponding change in E/E’ ratio merits caution in interpretation. We have added the following in the discussion:

**Addition p. 8, l. 13:**

_During hypoxia as well as hyperoxia no change in LV filling pressure was noted as the E/E’ ratio was unchanged. The individual parameters in the E/E’ ratio are known to be influenced by heart rate but as a ratio it seems independent of heart rate and load conditions (ref). Therefore, we did not perform any adjustments for heart rate in the evaluation of LV diastolic function._

**Minor concerns**

1 and 2. We have added the relevant reference (Isaaz-K, Current Opin Cardiol 2002, 17: 431-442) in the introduction and methods as suggested.
Reviewer 2
We thank the reviewer for constructive criticism.

1. The reviewer points to the possibility that changes in sympathetic tone influence heart rate which again could affect myocardial performance. We agree in this concern and we have included a paragraph in the discussion on the issue:

Addition p. 8, l. 6:

*We found that heart rate increased with hypoxia and decreased with hyperoxia. This might have affected our measures of LV systolic and diastolic function but we consider this unlikely on the basis of our previous studies (ref, ref) demonstrating that TEI index, strain rate and the tissue tracking to be unrelated to heart rate.*

2. The reviewer points to the fact that changes in RV tissue tracking indicate substantial change in pulmonary hemodynamics. We have included a paragraph on this in the discussion:

Addition p. 7, end of second paragraph:

*On the other hand, RV-systolic function decreased which is likely to be correlated to the increased systolic pulmonary pressure reflecting the increased pulmonary vascular resistance during hypoxia.*

3. The reviewer asks for more illustrations. We have included illustrations of heart rate, tricuspid regurgitation and right ventricular function.

4. The reviewer suggests two recent references to further help interpreting data. The corresponding author has read the references with great interest. However, it is not our impression that the two excellent papers (the one by Cherniack primarily deals with respiratory changes while the other Prabharakar and Peng is dedicated to chemoreceptor function) fit into the present study.
Reviewer 3
We thank the reviewer for constructive criticism.

Constructive comments in the abstract:
1. LV is now spelled out when used the first time in the abstract and in the text.
2. It is now specified that measurements were carried out at respiratory equilibrium:

Old version p2, l 5:
Seven male volunteers (mean age 38±3 years) were examined with echocardiography at:
1) normoxia..

Revised:
Seven male volunteers (mean age 38±3 years) were examined with echocardiography at
respiratory equilibrium during: 1) normoxia..

3. We have changed tricuspid regurgitation to systolic tricuspid regurgitation in results (p. 6
l. 14 and l.21). The consequences for pulmonary hemodynamics are discussed:

Addition p. 7, end of second paragraph:
On the other, hand RV-systolic function decreased which is likely to be correlated to the
increased systolic pulmonary pressure reflecting the increased pulmonary vascular
resistance during hypoxia.

4. TEI index and E/E´ are now explained in the methods section. Unfortunately the word
count does not allow this in the abstract.

Addition p. 4, l. 18:
The peak E velocity was obtained by pulsed Doppler measurements of the mitral inflow at
the tip of the mitral leaflets.

Addition p. 4, l. 20:
The tissue E´ velocity was obtained by Tissue Doppler at the lateral mitral annulus. The
TEI index (spectral or TDI) was assessed by Doppler time intervals from the mitral inflow
and LV outflow tract or the time intervals were obtained by TDI at the lateral mitral
annulus. The TEI index was calculated by a-b/b where the time interval “a” was measured
from cessation to onset of mitral inflow and the time interval “b” was the duration of the LV
outflow velocity profile.

5. This was an error. During hyperoxia global systolic contraction amplitude decreased.
This has been corrected in the revised abstract.

Methods
1. We have changed “.. participated in the study” to “completed the study” in order to
underline that all subjects underwent all examinations (p. 4, top).
2. Explanation of TEI and E/E’.

Addition p4, l. 24:

*The TEI index (spectral or TDI), a combined measure of systolic and diastolic function, was assessed by…*

Addition p4, l. 26:

*E/E’ has been proposed as a tool for assessing LV filling pressures that combines the influence of transmitral driving pressure and myocardial relaxation (ref).*

3. ECHO is now in capital letters.

4. In the study protocol (p.6 l. 4) the following has been added:

*Blood pressure was measured once during each of the three respiratory steady state situations by an automatic blood pressure measuring device based on the oscillometric method.*

Collection of respiratory parameters is already described under “ventilation system” p.4 second paragraph.

The spelling error in “statistical” has been corrected.

Results

1. Blood pressure results are now given:

*Old version p6, l. 8:*
Neither systolic nor diastolic blood pressure changed with test situation.

*Revised:*  
Neither systolic (126±6, 123±8, 122±12 mmHg, respectively, P=ns) nor diastolic blood pressure (80±5, 78±8, 81±6 mmHg, respectively, P=ns) changed significantly with test situation.

2. The sentence has been changed:

*Old version p6, l. 22:*
Hyperoxia worsened left ventricular function. Strain rate was reduced in 10 segments (figure 2) with preponderance in the..  

*Revised:*  
Hyperoxia reduced strain rate in 10 segments (figure 2) with preponderance in the..
3. To equal tricuspid regurgitation and pulmonary systolic pressure requires knowledge about right ventricular and atrial pressures which was not obtained. We therefore believe that tricuspid regurgitation is the correct term here.

4. The spelling error has been corrected.

The abbreviations in table 1 are now explained.

The capital letter problem of some author names has been corrected.