PEER REVIEW HISTORY

This paper was submitted to the ADC but declined for publication following peer review. The authors revised the paper and re-submitted to BMJ Open where it was re-reviewed and then accepted.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Myocardial performance assessment in neonates by strain and strain rate by tissue Doppler is improved by one-segment analysis – a quality improvement cohort study
AUTHORS	Nestaas, Eirik ; Støylen, Asbjørn; Fugelseth, Drude

VERSION 1 - REVIEW

REVIEWER	Mertens, Luc Hospital for Sick Children, Cardiology
REVIEW RETURNED	10-Apr-2012

GENERAL COMMENTS	General remarks. 1. This paper looks at myocardial performance using tissue-Doppler derived strain measurements. The authors seem to have two different aims for this study, 1. The first aim is to compare two different methods: one dividing the myocardial walls into two different segments and a second method treating the wall as a single myocardial segment. They were able to show that the first method was more reproducible compared to the second method. 2. The second aims, not explicitly stated, were to compare infants who were ‘asphyxiated’ at birth versus non-asphyxiated infants. Only the first aim is explicitly mentioned which weakens the paper as the study is presented as a methodological paper about different echocardiographic measurement techniques. This is probably interesting for echocardiographers but the clinical relevance is less clear. So if the paper is a technical paper then the relevance of including two different cohorts of patients needs to be explained. If the purpose of the paper is more clinical and is aimed at trying to look for regional myocardial dysfunction in asphyxiated infants this should be explicitly stated as an aim of the study. For a clinical journal adding a clinical aim and message would add relevance for the reader. Regarding the methodological aim, the authors limited the echocardiographic analysis to tissue Doppler-derived strain measurements, which are indeed very cumbersome and time-consuming while this technique has largely been replaced in clinical practice by speckle-tracking technology. I wondered why the authors

	decided to continue to use tissue-Doppler derived strain that is angle-dependent, has a lower signal-to-noise ratio and has a higher variability in neonates as demonstrated by previous studies. So they would need to build a case why tissue-Doppler derived strain measurements would be advantageous to speckle tracking techniques which are less angle-dependent and less influenced by noise. Even in the discussion, no mention is made of other echocardiographic techniques currently available. So the paper would benefit from better defining the aims and clearly state that there was methodological as well as a clinical question. Regarding the clinical question, it seems really crucial to better define the 'asphyxiated' neonatal group. On which criteria was this based? Providing the clinical characteristics of the two groups would really be beneficial and helpful for the reader. 2. The one-segment versus the two-segment method is not very well explained in the paper. The one-segment method is explained in the methods section with technical details but I am not sure how the authors split up the wall into two segments. This should be explained in detail as well and an image would really help to explain this to the reader who is less informed on echocardiographic technology. I suppose he authors measured a basal and more apical segment and averaged the measurements for the wall. It could be that most of the variability comes from the more apical segment which is generally less well aligned and more noisy. 3. For the clinical data, it would be interesting to know whether the infants who were more significantly affected by perinatal asphyxia had lower longitudinal strain measurements and whether the strain measurements predicted clinical outcomes. 4. For the logic of the paper, it would seem more relevant to start the result section with the reproducibility data before providing the clinical results.

REVIEWER	Bijnens, Bart ICREA - Universitat Pompeu Fabra
REVIEW RETURNED	30-Apr-2012

GENERAL COMMENTS	This paper describes the assessment of 1-segment tissue Doppler-based deformation quantification in neonates, comparing normal and asphyxiated individuals. The authors show that 1-segment analysis is more robust compared to using more segments. This is a rather obvious conclusion since, as they state themselves, more smoothing is done when using more tissue, thus signal to noise ratio improves. Therefor, this is neither a new finding, nor do the authors show that this provides novel insight into myocardial performance in neonates. Additionally, the authors suggest that mitral ring motion might be an alternative, which could be expected to behave indeed similarly to using larger segments and more robust measurements.

	Therefor, this paper adds very little compared to the previous publications of the authors. Additionally, the argument that 1-segment analysis only provides advantages, since myocardial damage would be global, is rather weak. Very few cardiac disease show real global changes in myocardial deformation. Most often there are regional changes in deformation with specific spatial distribution depending on the insult to the tissue. For example, pressure overload leads to specific (septal) basal changes while abnormalities related to genetic cardiomyopathies mostly lead to basal lateral changes. In case of asphyxia, one could expect reduced perfusion and additionally volume overload together with pressure overload due to hypoxia. Besides ischemic damage to the tissue, this will also lead to differential increased loading in different segments. The volume overload will also lead to additional increase in RV pressures (as was shown in athletes) which affects the basal RV much more compared to the apex. This can e.g. be seen in the previous paper (cardiol young) of the authors, where RV basal deformation decreases more compared to apical. Therefor, even in asphyxia, it might not be the best idea to average all segments when physiological/clinical questions need to be addressed. So, unless the authors show that to answer a specific clinical question, the 1-segment analysis performs better, the fact that it would be more reproducible is not a convincing argument to promote it. Some additional comments: - In the introduction, the authors state that deformation analysis is most suitable for comparing hearts of different size and during growth. However, this statement might not be the best choice to argument for the use of deformation, since it is both dependent on the size and does changes importantly during growth, with larger deformation for smaller/younger hearts. In itself, this doesn't have to be a problem, but this clearly has to be taken into account when interpreting results. - a figure would be needed to show the image together with the ROI for analysis - the size of the ROI should be discussed in relation to length and width of the wall in these individuals - where was the onset of the strain calculations ? onset of QRS ? R-wave ? - on the figure of the traces, the timing of events should be indicated and strain traces should be provided next to the SR - was there any post-systolic strain ?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

General remarks.

1. This paper looks at myocardial performance using tissue-Doppler derived strain measurements. The authors seem to have two different aims for this study,

1. The first aim is to compare two different methods: one dividing the myocardial walls into two different segments and a second method treating the wall as a single myocardial segment. They were able to show that the first method was more reproducible compared to the second method.

2. The second aims, not explicitly stated, were to compare infants who were 'asphyxiated' at birth versus non-asphyxiated infants.

Only the first aim is explicitly mentioned which weakens the paper as the study is presented as a methodological paper about different echocardiographic measurement techniques. This is probably interesting for echocardiographers but the clinical relevance is less clear. So if the paper is a technical paper then the relevance of including two different cohorts of patients needs to be explained. If the purpose of the paper is more clinical and is aimed at trying to look for regional myocardial dysfunction in asphyxiated infants this should be explicitly stated as an aim of the study. For a clinical journal adding a clinical aim and message would add relevance for the reader.

Q1: There were two aims of this study. One was to compare the repeatability in the one-segment analyses against repeatability in the two-segment analyses previously performed. The second aim was to see if the one-segment analyses were able to assess the differences in myocardial performance between the asphyxiated and non-asphyxiated neonates. We have now updated the last part of the introduction section regarding this issue, as well as the limitations section of the Discussion.

Regarding the methodological aim, the authors limited the echocardiographic analysis to tissue Doppler-derived strain measurements, which are indeed very cumbersome and time-consuming while this technique has largely been replaced in clinical practice by speckle-tracking technology. I wondered why the authors decided to continue to use tissue-Doppler derived strain that is angle-dependent, has a lower signal-to-noise ratio and has a higher variability in neonates as demonstrated by previous studies. So they would need to build a case why tissue-Doppler derived strain measurements would be advantageous to speckle tracking techniques which are less angle-dependent and less influenced by noise.

Even in the discussion, no mention is made of other echocardiographic techniques currently available.

Q2: The main limitation for the speckle-tracking techniques is the poor temporal resolution of the B-mode. Speckle-tracking depends for quality of tracking on limited change from frame to frame, which would be a major problem in children, especially in neonates, with high heart rates. As already stated in the manuscript (Measurement section of Materials and Methods), the frame rates in most tissue Doppler images in our study ranged 170-220/second. The typical grey-scale frame rates in our images were 75-90/sec. At a heart rate of 150 there will then be 30-36 grey scale images in each heart cycle, while there will be typically 70-90 tissue Doppler frames per heart cycle. Especially for strain rate indices, assessing the peak values by the speckle tracking techniques carry a high risk for missing the true peak values due to the low frame rate.

We have added a section in the introduction regarding the use of speckle-tracking techniques, and we have added a paragraph to the Discussion section regarding the use of speckle-tracking and other modalities for assessment of deformation.

So the paper would benefit from better defining the aims and clearly state that there was methodological as well as a clinical question.

Q3: As stated in Q1, we have now redefined the aims of this study.

Regarding the clinical question, it seems really crucial to better define the 'asphyxiated' neonatal group. On which criteria was this based? Providing the clinical characteristics of the two groups would really be beneficial and helpful for the reader.

Q4. We have now described in more detail the inclusion criteria for the asphyxiated group, in the materials and methods section.

2. The one-segment versus the two-segment method is not very well explained in the paper. The one-segment method is explained in the methods section with technical details but I am not sure how the authors split up the wall into two segments. This should be explained in detail as well and an image would really help to explain this to the reader who is less informed on echocardiographic technology. I suppose he authors measured a basal and more apical segment and averaged the measurements for the wall. It could be that most of the variability comes from the more apical segment which is generally less well aligned and more noisy.

Q5. The length of each wall eligible for analysis was typically 25 mm, and the most curved part of the wall close to the apex were not within this length, i.e. the most curved part of the myocardial walls were not included in the one-segment nor the two-segment analyses. The same part of the myocardial wall was used in both analyses. In a previous paper *(Nestaas, E, Stoylen, A, Sandvik, L, Brunvand, L, Fugelseth, D. Feasibility and reliability of strain and strain rate measurement in neonates by optimizing the analysis parameters settings. Ultrasound Med Biol 2007 Feb;33(2):270-8)* we have compared the noise in the apical and the basal segments in two-segment analysis and actually shown that the noise in the apical segments were less than in the basal segments, probably due to a higher beam density close to the probe.

We have now described in more detail the two-segment analyses procedure, in the materials and methods section, and we have updated fig 1 now illustrating in more detail the one-segment and two-segment analysis procedure.

3. For the clinical data, it would be interesting to know whether the infants who were more significantly affected by perinatal asphyxia had lower longitudinal strain measurements and whether the strain measurements predicted clinical outcomes.

Q6. We now have compared the myocardial deformation against the biochemically injury of the heart, assessed by troponin T values.

4. For the logic of the paper, it would seem more relevant to start the result section with the reproducibility data before providing the clinical results.

Q7. We now start the result section (and the Discuscion section) with the reproducibility data.

Reviewer: 2

Comments to the Author

This paper describes the assessment of 1-segment tissue Doppler-based deformation quantification in neonates, comparing normal and asphyxiated individuals.

The authors show that 1-segment analysis is more robust compared to using more segments. This is a rather obvious conclusion since, as they state themselves, more smoothing is done when using more tissue, thus signal to noise ratio improves. Therefor, this is neither a new finding, nor do the authors show that this provides novel insight into myocardial performance in neonates. Additionally, the authors suggest that mitral ring motion might be an alternative, which could be expected to behave indeed similarly to using larger segments and more robust measurements.

Therefor, this paper adds very little compared to the previous publications of the authors.

Q8. One-segment analysis is not equivalent to "smoothing". Strain rate is the difference between velocities of two points divided by the distance between them. Noise is the sum of the noise of the two velocity measurements. This means, however, that increased strain length will increase the signal-to-noise ratio, and decrease the spatial resolution. The one-segment analysis procedure has (the expected) advantages of ease and reproducibility compared to the two-segment analysis procedure. However, before our study was conducted, it was not known if the decreased spatial resolution obtained by analyzing fewer and larger segments could even out the differences found between the groups using two-segment analysis. We now have emphasized this point, in the "Should one-segment or two-segment analyses be used in neonates?" section of the Discussion.

Assessment of mitral ring motion in general is less noisy than deformation analyses by tissue Doppler, as the measurements are based on velocity measurements and not on difference in velocity between points. However, we show that by using a large sample area for the deformation analyses the repeatability indices were similar to the repeatability indices in atrioventricular plane motion analyses in adults (ref no 42 in the manuscript) and in fact better than in neonates (ref no 29 in the manuscript). We now state in the "further studies" section of the Discussion that AV-plane motion indices (both velocities and excursions/displacement of the AV-plane) should be compared against the deformation indices in neonates.

Additionally, the argument that 1-segment analysis only provides advantages, since myocardial damage would be global, is rather weak. Very few cardiac disease show real global changes in myocardial deformation. Most often there are regional changes in deformation with specific spatial distribution depending on the insult to the tissue. For example, pressure overload leads to specific (septal) basal changes while abnormalities related to genetic cardiomyopathies mostly lead to basal lateral changes.

In case of asphyxia, one could expect reduced perfusion and additionally volume overload together with pressure overload due to hypoxia. Besides ischemic damage to the tissue, this will also lead to differential increased loading in different segments. The volume overload will also lead to additional increase in RV pressures (as was shown in athletes) which affects the basal RV much more compared to the apex. This can e.g. be seen in the previous paper (cardiol young) of the authors, where RV basal deformation decreases more compared to apical. Therefor, even in asphyxia, it might not be the best idea to average all segments when physiological/clinical questions need to be addressed. So, unless the authors show that to answer a specific clinical question, the 1-segment analysis performs better, the fact that it would be more reproducible is not a convincing argument to promote it.

Q9: The main point is that the fundamental insult (asphyxia) is global. It may be true that the resulting dysfunction can be unevenly distributed between regions. However, even so, using a

method with more noise may mask this, so it will be a balance between the lack of regional information and the improved accuracy of a less noisy dataset. We have now emphasised in the Limitations section that one-segment analysis cannot assess differences between the apical and basal parts of each wall, of group of walls or of the whole heart. We report that such differences were found between the apical and basal segment in the right walls by the two-segment analyses and that detecting such differences would not be possible using the one-segment analysis procedure.

We have added a section to the introduction section regarding the distribution of myocardial injury following birth asphyxia.

Some additional comments:

- In the introduction, the authors state that deformation analysis is most suitable for comparing hearts of different size and during growth. However, this statement might not be the best choice to argument for the use of deformation, since it is both dependent on the size and does changes importantly during growth, with larger deformation for smaller/younger hearts. In itself, this doesn't have to be a problem, but this clearly has to be taken into account when interpreting results.

Q10 We now have moderated this statement and now write that these indices <u>may</u> be more suitable for comparing hearts of different sizes.

- a figure would be needed to show the image together with the ROI for analysis

Q11: We now have expanded fig 1 to show in more detail the one- and two-segment analysis procedure.

- the size of the ROI should be discussed in relation to length and width of the wall in these individuals

Q12: The rationale for choosing the strain length and size of the ROI in relation to the length and width of the walls is now explained in the Data analysis section of the Materials and methods.

- where was the onset of the strain calculations ? onset of QRS ? R-wave ?

Q13: We now describe in the Data analysis section of the materials and methods the starting point for the strain calculation

- on the figure of the traces, the timing of events should be indicated and strain traces should be provided next to the SR

Q14: See Q11. We now have expanded fig 1, now showing the timing of the events by placing the strain and strain rate curves underneath each other.

- was there any post-systolic strain ?

Q15: We now state that there was little or no post-systolic strain in the measurements.

VERSION 2 – REVIEW

REVIEWER	Mertens, Luc The Hospital for Sick Children
REVIEW RETURNED	12-Jul-2012

- The reviewer completed the checklist but made no further comments.