Author's response to reviews

Title: Microvolt T wave alternans in adults with congenital heart diseases characterized by right ventricle pathology or single ventricle physiology: a case control study

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Author's response to reviews: see over
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Point-by-point response to reviewer’s comments on the manuscript

"Microvolt T wave alternans in adults with congenital heart diseases characterized by right ventricle pathology or single ventricle physiology: a case control study"

The authors would like to thank Reviewers for their thorough review of our manuscript and valuable suggestions that help improve the quality of the paper. The following responses have been prepared to address all Reviewers’ comments in a point-by-point fashion.

To Reviewer 1: Ami Bhatt

Minor essential revisions:

1. Pulmonary hypertension in individuals with potential shunt lesions may not be accurate at a PAP > 37 mmHg based on echo. Please add a sentence explaining your rationale, or a quote of another research article which uses such a cutoff in ACHD.

   Indeed, the gold standard in pulmonary arterial hypertension (PAH) diagnostic algorithm is cardiac catheterization. However due to its invasive character the authors (alike other investigators, e.g. Diller et al. Circulation 2005;112:828-835) decided to use echocardiography which renders the diagnosis of PAH highly probable. According to current guidelines on PAH management, “tricuspid regurgitation velocity 2.9-3.4 m/s, pulmonary artery systolic pressure 37-50 mmHg with/without additional echocardiographic variables suggestive of PH” (class IIaC) was considered a sufficient criterion. Above that, patients with this diagnosis manifested additional clinical and echocardiographic features characteristic for PAH what also increased its probability.

   Text is revised – we added a sentence explaining our rationale.

2. In the ToF population, were there any QRS > 180 ms and did these correlate with non-neg MTWA? Mentioning this in the discussion may strengthen your conclusions and add validity for the predictive value of this testing.

   Widening of QRS remains an acknowledged risk factor of VA among patients after ToF repair, but only unoperated individuals with this anomaly were included into the study group. Therefore, despite being acquainted with M. Gatzoulis articles the authors have not performed the proposed analysis.
Discretionary revisions:

1. It is surprising that your population had so many NYHA Class I patients. In general, in moderate to severe CHD in adults, true NYHA Class I are rare. The pVO2 in the range 50%, speaks again such high NYHA classes and perhaps patient self misinterpretation/lack of awareness. You may want to address this in the discussion or a study limitations with a sentence.

Despite some methodological objections (lack of objective assessment), NYHA classification is still most widely used tool, including adults with CHD presenting a distinct pathophysiology of heart failure. It has been also proven that the deterioration of patients’ functional status assessed with this classification has an adverse prognostic value with regard to SCD in this population [Khairy et al. *Circulation* 2008, 117:85-92, Diller et al. *Eur Heart J* 2006, 27:1737-1742]. Although our study group consisted of patients with complex forms of CHD, over half of them (51.1%) presented as NYHA class 1. Similar results were obtained by other investigators – NYHA class 1 was reported by Piran et al. [*Circulation* 2002;105:1189-1194] in 40% of subjects with single or systemic right ventricles (mean age 28.6±7.8 years), whereas Diller et al. [*Circulation* 2005, 112:828-835] classified 49% of patients with different complex forms of CHD (mean age 33±13 years) as being asymptomatic. Common underestimation of patients’ self-reported functional status is mostly caused by lifelong adaptations to their heart disease and not being aware of slowly progressing exercise intolerance. Additionally, relatively young mean age of our study group (34.2±13.6 years) makes NYHA Class 1 truly more possible as the symptoms of heart failure have not emerged yet. In contrast, the study conducted by Bolger et al. [*Circulation* 2002;106:92-99] among adults with complex CHD aged 33.5±1.5 years revealed NYHA class 1 and 2 in, respectively, 21% and 59% of subjects. An explanation of such difference comparing to our results may be the fact that study group enrolled by us in almost one third consisted of patients with Ebstein syndrome, who are considered as being asymptomatic over decades [ESC guidelines for the management of grown-up congenital heart disease. *Eur Heart J* 2010, 31:2915-57], whereas this defect was not included into the study protocol by Bolger. Nevertheless, in such a heterogenous and not numerous population generalization and unequivocal conclusions are hardly possible.

Text is revised - the Discussion section has been extended to clarify this issue.
2. Was there a pVO2 or VE/VCO2 cutoff of significance which correlated with positive MTWA? This would be interesting to the ACHD population.

The study aimed at assessing the potential value of MTWA with regard to SCD risk stratification among ACHD. Therefore the authors sought to determine whether there is any relationship between incidence of abnormal MTWA and other clinical features acknowledged as SCD risk factors. Heart failure being among them was quantified with NYHA classification and objective cardiopulmonary test. We did not intend to assess the diagnostic value of particular parameters. Nevertheless, the data obtained by our team constitute a very good starting point for another analysis that would address more thoroughly the problem you raised.

3. All periods have come across as commas in the tables and numbers listed.

   Text is corrected for typographical error.

4. Please use terms univariate and multivariate.

   Text is corrected as directed.

**To Reviewer 2: Sean Wu**

*Minor essential revisions:*

1. Numerous sentences need to be proof-read by a native English speaker.

   Text is corrected according to a native English speaker remarks.

2. The authors should make clearer distinction, in the Results and Discussion section, their discussion on factor that increases odds for having positive MTWA from the discussion on the likelihood of a positive MTWA on developing SCD/VA. Presumably, the interest in measuring MTWA is to predict whether someone is at a greater likelihood of having VA if they have abnormal MTWA on screening. This aspect was not well explored.

   The remark addresses probably the greatest limitation of the study which is lack of prospective evaluation of MTWA prognostic value with regard to SCD/VA risk among adult patients with congenital heart disease (ACHD). This noninvasive test has been incorporated into current guidelines concerning SCD prevention (class IIa). However, no prospective analysis regarding significance of MTWA in this particular population has been published so far. Taking into account a small number of patients combined with a low expected number of SCD per year, a statistically well-designed study would require to last at least 10 years. Therefore, at this stage of the project the authors decided to publish analysis which only indirectly enables them to prove the role of MTWA in SCD/VA stratification among ACHD.
The authors attempted to evaluate whether abnormal MTWA coincides with different acknowledged SCD risk factors in this population such as episodes of VA in ambulatory ecg monitoring, heart failure, cyanosis, etc. This analysis constituted an introduction to ongoing follow-up of hard endpoints. On the basis of the results presented in the study one may also make an attempt to narrow down the group of ACHD patients who should have a detailed assessment of indications for ICD therapy, including MTWA.

Text is revised – we extended the Limitations section to clarify this aspect.

With kind regards,

Aleksandra Cieplucha