Author’s response to reviews

Title: Non-diagnostic autopsy findings in sudden unexplained death victims

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Rebuttal Letter (also attached as a separate file)

Yazdanfard et al. describe the autopsy findings of 99 sudden unexplained death patients and report that 2/3 of the victims had non-normal but non-diagnostic autopsy findings and suggest that these findings could be early markers of structural heart disease. The manuscript is definitely interesting but requires some further specifications to improve the accessibility of the data and strengthen the conclusions.

Dear editor/reviewer. We thank you for your time to review our paper and the comments given. We also thank you for giving us the opportunity to resend our paper. We have answered all comments below. Please also see our revised paper with track changes marked in red.

1) In the definitions section you report that congenital heart defects are defined as presence of "congenital defects, including but not limited to persistent foramen ovale and septal defects, but not considered a likely substrate for ventricular arrhythmias or heart failure-related death": patent (not persistent) foramen ovale is considered a normal finding in children under 6 years of age and this should be specified in the definition.
Rebuttal: You are correct in the need for clarification on this matter.

Action: We have now specified that patent foramen ovale is considered an abnormal finding in victims over 5 years of age. We have also changed the term from persistent to the more correct patent. In addition, we have added ages to our victims with congenital malformations. None of them are younger than 6 years.

Please see the definitions section under methods (p6), which now reads:

“Congenital heart defects: Presence of congenital defects, including but not limited to patent foramen ovale (in victims older than 5 years of age) and septal defects, but not considered a likely substrate for ventricular arrhythmias or heart failure-related death.”

2) In the results -&gt; previous health status section the percentage as given are deceptive. You correctly describe your population as having had cardiac assessment in 21% of cases but when you describe the exams performed you should give the percentage related to the cardiac assessment population and not the whole, as you say "... of these victims..." implying referral only to those 21.

Rebuttal: We agree. Thank you for pointing this out.

Action: The percentages given for the exams performed are now corrected accordingly.

Please see the Previous health status section under Results (p8).

3) In the results -&gt; autopsy findings section you describe a relation between age and cardiac mass. Comparing data about a body measure and age in a population comprising paediatric patients requires correction for some measures of body size (in this case BSA would be the best choice). It's unclear if you compared cardiac mass or cardiac mass corrected for BSA in the text. Should you have performed the analysis on the raw data it would be advisable to repeat it with the corrected ones.
Rebuttal: We agree the analysis should be with BSA corrected cardiac mass.

Action: We have now done the correlation analysis correctly. Please see the Autopsy findings section under Results (p9), which now reads:

“Cardiac mass was significantly larger for men compared to women after correction for body surface area (BSA); 217g/m² vs 173g/m², p=0.0026). We observed a relationship between age and BSA corrected cardiac mass (r=0.57, p<0.001).”

4) In the results autopsy findings section you describe the presence of minor congenital defects in 5 victims and state that 3/5 had patent (not persistent) foramen ovale (PFO). You should specify the age of those patients because PFO is considered a normal finding in patients under the age of 6. If some of those 3 patients is <6 years old should be considered a normal finding in my opinion.

Rebuttal: Thank you for your comment. We have no victims that were under the age of 6, but naturally this needs to be specified.

Action: We have now specified the age of the victims. Additionally, we added the age of the victims with the other congenital defects too. The youngest victim was 17 years old.

Please see the revised Autopsy findings section under Results (p9), which now reads:

“Minor congenital defects were seen in 5 victims with non-diagnostic findings (8%) and included three victims with patent foramen ovale (aged 18, 28, 42 years), one victim had an atrial septal defect (age 17 years), finally in one victim no specific information was available other than it was ‘minor’ (age 32 years).”

Additionally, we were asked to discuss genetics testing in autopsies.
Rebuttal: We did not perform molecular autopsy (genetic testing) of the victims in our population. According to ESC guidelines there is recommendation for doing molecular autopsy on victims where one suspects cardiomyopathies/channelopathies (Class IIa, Level of evidence C). Molecular autopsy can be difficult to interpret due to variants of unknown significance (VUS), and the lack of genotype-phenotype correlation.

Action: We have added to the discussion regarding molecular autopsy. Also see our limitations. The added part of Discussion now reads:

“At our institution we do not routinely perform genetic testing in unexplained SCD cases. While a molecular autopsy could be used in autopsied cases which fulfills diagnostic criteria for certain cardiomyopathies (e.g. HCM, DCM, and ARVC). Variants of unknown significance (VUS) as well as the lack of genotype-phenotype correlation can make interpretation difficult, especially in unexplained SCD cases. Current guidelines state that targeted post-mortem genetic analysis of potentially disease-causing genes should be considered in all sudden death victims in whom a specific inheritable channelopathy or cardiomyopathy is suspected (class IIa, level of evidence C)[42].”