What is the cause of QTc prolongation in patients with alcohol withdrawal syndromes?

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We have read with interest the paper of Cuculi et al. in a recent issue of the Swiss Medical Weekly [1]. Clearly, one plausible explanation for the high mortality of patients with alcohol withdrawal syndromes may be the occurrence of malignant cardiac arrhythmias. Prolonged QT interval is considered as one marker for such life threatening rhythm disturbances and indeed, in the studied group of Cuculi et al. 18 patients had a normal QTc interval (<440 ms in males, <460 ms in females) and 31 patients had a prolonged interval. Patients with prolonged QTc were older (51.3 ± 10.7 yrs vs. 43.8 ± 7.7 yrs), and presented more delirium tremens and seizures (n = 20 vs. n = 13 and n = 11 vs. n = 5). Other reported clinical and laboratory parameters did not differ substantially.

The mean QTc in the study group was 458 ± 42 ms, but the difference in means between subgroups with and without QT prolongation was not reported. We suppose, that the two subgroups differed significantly with regard of QT interval duration, otherwise the distinction of these groups would make no sense. The minor difference in age could not account for significant QT differences [2], so the authors were probably correct when they suggested that the number of patients with “central nervous stress possibly explained the disturbance of these groups.” The minor difference in age could not account for significant QT differences [2], so the authors were probably correct when they suggested that the number of patients with “central nervous stress possibly explained the disturbance of these groups.”

However, this explanation is uncertain. The utility of any “universal” formulas for QT rate adjustment have been severely criticized. A major methodological problem with the study of Cuculi et al. is their use of the Bazett formula, which greatly over-adjusts QT interval at high heart rates and under-adjusts it at low heart rates. Any comparison of Bazett-corrected QT values can only be justified at equal (or near equal) heart rates [3] but the authors did not report on heart rate data! We assume, that morbidity in the subgroup with QT prolongation was more severe as suggested by the higher number of seizures and delirium. Indeed, such conditions may have resulted in higher heart rates. The application of “study specific” QT interval correction [4] would have been suitable in the study of Cuculi et al. in order avoid the methodological problem inherent in the use of Bazett’s method and to evaluate the association between “central nervous system stress” and QT interval prolongation. We also suggest that in their response (if applicable) the authors report the means and standard deviations for the various ECG measure for their subgroups.

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References

Authors’ reply
We would like to thank Dr Andrassy and Dr Szabo for their critical comments.

The mean QTc was 480 (± 32) ms in the group with QTc prolongation and 417 (± 26) ms in the group with normal QTc (p <0.0001). In our paper we proposed cerebral stress as one possible explanation for QTc prolongation during alcohol withdrawal [1]. High catecholamine levels induced by cerebral stress have been shown to cause electrophysiological changes [2] and experimentally induced myocardial damage [3] after subarachnoid haemorrhage. The hypothesis that cerebrally induced catecholamine influence is indeed responsible for this phenomenon is further supported by the finding of marked QTc prolongation in patients with tako-tsubo cardiomyopathy [4], who are known to have high catecholamine levels.

Dr Andrassy and Dr Szabo suggested that the difference of the QTc intervals between the two groups might be partly explained by different heart rates. An analysis of the mean heart rates (which were not reported in the paper) showed a slight, but non-significant difference (100/min in the group with prolonged QTc vs. 93/min in the group with normal QTc; p = 0.2) most likely not responsible for the observed difference in QTc duration. There are various approaches to assess the duration of QT-interval and all of them have strengths and weaknesses. The Bazett formula already corrects for heart rate and remains a valuable tool to identify patients at risk for developing cardiac arrhythmias.

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