Ischemic Burden in ST Elevation Myocardial Infarction and Circadian Rhythms

To the Editor:

We read the recent publication by Ammirati et al with interest. It analyzed a cohort of 1099 patients in Italy, Scotland, and China to confirm results of Suárez-Barrientos et al, Reiter et al, and our own study. The authors of these 3 recent publications showed statistically significant relationships between the time of symptom onset and the size of ST-segment–elevation myocardial infarction in terms of peak creatine kinase.

Both Reiter et al and our team found a higher vulnerability to ischemia in patients with symptom onset occurring at night (between midnight and 6:00 AM). In their study, Ammirati et al concluded that they were unable to reproduce our results or draw similar conclusions. However, we feel that their methodology failed to adequately investigate the time-of-day effect on myocardial infarct size, and we have several comments.

First, Ammirati et al did not compare significant clinical characteristics among the 4 time groups, including whether prehospital treatment was different—specifically in terms of antplatelet therapy; whether the rate of anterior wall infarction was the same between the different time groups; and whether the primary percutaneous coronary intervention was successfully performed. Furthermore, there was no information on the success of thrombolysis. In the second analysis, on the basis of the Italian population artificially grown by bootstrapping, other more important factors are not given, including whether the ischemic time and the rate of primary percutaneous coronary intervention were the same between the different time groups. All these factors directly influence peak creatine kinase.

Second, experimental models of myocardial infarction, showing an important time-of-day effect on infarct size, have suggested that part of the explanation for these differences may be genetic. The time-of-day effect has been confirmed after the deletion of the clock gene. The existence of such mechanisms and observations among humans are yet not known, but differences in the frequency distribution of genes do exist between ethnic groups. This is the case for clock gene alleles, as published recently. Therefore, with the current state of knowledge, we suggest a prudent analysis of multiethnic cohorts when investigating circadian rhythms.

Interestingly, the 3 figures of Ammirati et al show trends similar to the observations made by both Reiter et al and our team; even if the difference was not statistically significant in their results, patients with symptom onset occurring at night had a higher peak creatine kinase. In our opinion, the significance of variation is of the utmost importance, and we feel it would be a mistake to look only for large variations. Circadian rhythms only exert a moderate influence on biological and hemodynamic values; blood pressure, for example, is only 15% lower at night. Thus, we believe that the observations of Ammirati et al are actually in line with previous results and enhance the link between circadian rhythms and vulnerability to ischemia.

In addition, we would like to point out that statistically nonsignificant trigonometric regression analysis results of Ammirati et al may be because of the use of an overly simple trigonometric transformation, that is, the use of a simple sinus function, instead of more detailed transformations involving sin(x) and cos(x) terms, as supported by the significant results provided by the Kruskal–Wallis test procedure.

We agree with Ammirati et al on the importance of further studies to explore the link between circadian rhythm and vulnerability to ischemia among patients with ST-segment–elevation myocardial infarction, but basic crucial information is necessary to answer this intriguing question.

Disclosures

None.

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