LETTERS TO THE EDITOR

doi:10.1093/ehjci/jet155
Online publish-ahead-of-print 1 September 2013

Normal apical myocardial perfusion in the rat model with Takotsubo syndrome: is subsequent microvascular dysfunction and hypoperfusion an epiphenomenon?

The pathophysiology of Takotsubo syndrome (TTS) continues to be elusive, but important recent contributions, like the one published on line on 5 July 2013 in the Journal, will pave the way for the eventual unravelling of the mysteries surrounding this illness. The authors work focused on the crux of the pathophysiological conundrum: whether myocardial hypoperfusion is the cause, or a consequence of TTS. They referred to the literature about the conflicting reports showing myocardial hypoperfusion (often associated with attenuated metabolic rate), in clinical studies carried out several days after the admission of patients with TTS. The authors employed myocardial contrast echocardiography to evaluate regional myocardial perfusion in a rat model with TTS, mediated by infusion of isoproterenol (instead of epinephrine, as previously done) and documented the emergence of typical myocardial contraction abnormalities of TTS at a mean of 43 min later, and stable ratios of myocardial apical/basal perfusion close to 1.00 at all time-points, starting at baseline and ending at 90 min. The authors did not detect structural damage of myocardial vessels (i.e. intact microcirculation) in biopsies from the basal and apical myocardial regions by light and electron microscopy. Consequently, the authors concluded that there is no apical myocardial hypoperfusion in the early phase of TTS in their model, and thus regional hypoperfusion and/or damaged microvasculature noted later in the clinical course of the human form of the disease, most probably constitutes an epiphenomenon of TTS, rather than its cause. This reader will appreciate the response of the authors to the following comments/questions: (i) It would have been of interest to have some information on the course of the electrocardiographic appearances in the rats, and whether ST-segment elevation is associated with apical dyskinesia, whether it is stable or replaced by T-wave inversions at 90 min, and in such a case whether apical akinesia replaces dyskinesia at that time. (ii) Do the authors plan to further study their model via of some surviving rats with TTS, to evaluate whether eventually (hours or days later) myocardial hypoperfusion, microcirculation derangement, myocardial oedema, and T-wave inversion with QTc prolongation, ensue?

References

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doi:10.1093/ehjci/jet174
Online publish-ahead-of-print 8 October 2013

Normal apical myocardial perfusion in the rat model with Takotsubo syndrome: is subsequent microvascular dysfunction and hypoperfusion an epiphenomenon? Reply

We greatly appreciate the comments offered by Dr Madias in response to our original article ‘Myocardial contrast imaging reveals apparently normal coronary perfusion in stress-induced (takotsubo) cardiomyopathy’. Dr Madias, in his letter, poses several important questions that would be worthwhile to address in our model. The first point raised is the presence of tissue oedema in affected myocardial segments in Takotsubo patients. The rat model is well suited to study the temporal changes in regional myocardial water content (i.e. oedema). We are currently investigating myocardial water content post-mortem in tissue samples harvested at different time-points after injection of isoproterenol. Our preliminary post-mortem data from tissue harvested 2 h after isoproterenol show no significant difference in myocardial water content in apical tissue compared with basal tissue (Figure 1, n = 5, P = 0.5). Although one probably should not be too quick to draw conclusions based on only a few data points, these results indicate that myocardial oedema does not precede development of left ventricular akinesia. However, the best method for the in vivo evaluation of dynamic changes in regional myocardial tissue water is magnetic resonance imaging and we are currently working with this methodology in the rat model. In addition to imaging of tissue oedema, MR techniques can be used to evaluate fluxes in myocardial energy metabolites and may provide important information about myocardial energy metabolism in Takotsubo.

The second point relates to electrocardiographic characteristics in this Takotsubo-like animal model. Using standardized limb lead ECG, we have detected apparent ST-T segment deviation, including ST-segment elevation, understanding the mechanisms that underlie these electrocardiographic appearances would be of particular interest. It remains to be established which part, if any, electrophysiological perturbations play in Takotsubo. In other words, whether action potential transmission and ion fluxes are impaired in dysfunctional regions or if loss of function can be explained entirely by alterations in the contractile apparatus (Figure 2). We will be able to come back with a more detailed description of these electrophysiological perturbations and their temporal pattern in the near future. We have previously shown that excess isoprenaline impairs electrophysiological function in isolated cells. At present, we are focusing...
our attention on ex vivo electrophysiological studies of tissue harvested from the rat model, with particular emphasis on depolarization/repolarization patterns and regional differences in action potential duration.

It is our intention to address the issues discussed above as well as to study myocardial perfusion and tissue histology, including morphology of the microvasculature, at several additional time points, including at the very least daily assessment until time of recovery of cardiac function.4

Lastly, we would like to clarify that although we did not observe any apical perfusion defect and no microvascular damage preceded development of cardiac dysfunction in our model, we do not believe that these findings necessarily imply that perfusion defects and/or microvascular dysfunction described in some patients are merely epiphenomena. Instead impaired perfusion in the subacute phase of the disease may instead stem from microvascular obstruction secondary to tissue swelling (i.e. oedema). Alternatively, the akinetic myocardium within the affected areas may be metabolically less active and autoregulatory factors may redistribute blood flow towards unaffected hypercontracting regions with a higher metabolic demand. The points proposed by Dr Madias and discussed above would help to address this issue.

Conflict of interest: none declared.

References

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