# On the role of Echocardiography and beta-receptors downregulation in multi-pattern takotsubo

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To the Editor:

We enjoyed reading the case, authored by Janus and Hoit, of a 67-year-old woman with a subarachnoid hemorrhage (SAH) who presented with three different variants of takotsubo (TT).[i] We congratulate the authors on their interesting contribution to the literature. We would like to share some comments and questions on the chronology and management of the events between the first two episodes, which occurred a few days apart.

Although fascinating, this is not the first case of TT with a rapidly evolving pattern. We previously described a case of mid-ventricular takotsubo which replaced apical ballooning in 6 hours.[ii] A recent meta-analysis showed that almost 80% of TT recurrences exhibit a ballooning pattern different from the first presentation.[iii] In this regard, regional cardiac sympathetic innervation remodeling or denervation could hypothetically justify why the same territory is usually spared from further relapses. Even though images were not provided, the authors stated that "echocardiographic wall motion abnormalities quickly resolved after each acute stressor". One could therefore argue that this was not a case of multiple TT variants during the same episode, as noted by Madias,[iii] but rather an example of early recurrences. Additionally, if cardiac innervation remodeling were responsible for the different locations of the ballooning, we believe that the change in pattern would have taken longer to manifest. This would not support the observation of two distinct ballooning patterns emerging within days, let alone hours.[i, ii] In this case, a short-term change from the mid-ventricular to apical pattern could be reasonably explained by different β adrenergic-receptor (β-AR) subtype downregulation. We know that norepinephrine can downregulate β1-AR after a few hours. Beta1-ARs are markedly lower on biopsied patients with acute TT compared to healthy controls,[iv] whilst in the same study β2-ARs expression—which is predominant in the apical and mid-ventricular segments and thought to be involved in typical takotsubo pathogenesis[v]—was equivalent to normal.

Thus, the sequence of events could be interpreted as a relative local β2 prevalence due to dynamic β1 downregulation (β1:β2 mismatch), following a base:mid-ventricle, and ultimately a mid-ventricle:apex progression. What do the authors think about this theory? Is it possible that multi-faceted presentations might simply be under-recognized? Should this be the case, how do they think we could better understand this phenomenon in a noninvasive fashion? Could dobutamine stress echocardiography have utility to identify areas of β-AR downregulation and sympathetic denervation?

It would also be interesting to know more about the patient's medical therapy. Did she receive nonselective β-blockers, such as labetalol or carvedilol, usually prescribed after SAH? If so, this might indicate that β-blockers do not prevent recurrences,[vi] but rather create a maladaptive imbalance in regional β1:β2

distribution favoring early relapse(s), as this case suggests.

## References


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