We thank Dr. Madias for his interesting comment on our paper entitled “Impact of malignancies in the early and late time course of takotsubo cardiomyopathy”. In our clinical experience, a history of cancer was evidenced in a very large proportion of takotsubo syndrome (TTS) patients, in line with the pioneering observation by Burgdorf and coworkers. Although multiple case reports have indicated TTS as a possible cause of reversible myocardial injury, troponin elevation and LVEF dysfunction during cancer therapy, recognition of TTS or catecholaminergic cardiomyopathy as an important clinical concern was totally lacking in the very recent guidelines of the European Society of Cardiology on cancer treatments and cardiovascular toxicity.

Although a description of the physiopathological mechanisms linking cancer and catecholaminergic cardiomyopathy is far beyond the initial scope of our paper, several hypotheses could be raised. In oncologic patients, both the physical stress of surgeries and procedures, and the emotional stress associated with the diagnosis of cancer may favor increased catecholaminergic release and myocardial stunning. In addition, cardiac nervous system damage as a possible consequence of radiotherapy or chemotherapy may lead to sympathovagal imbalance characterized by inappropriate sinus tachycardia, altered heart rate variability and decreased sensitivity. The specific role of inflammation as a cofactor of epinephrine-induced myocardial stunning deserves further investigation in the specific context of malignancy frequently associated with enhanced inflammatory status. Initially interpreted as a consequence of catecholamine release possibly contributing per se to myocardial damage, it cannot be excluded that inflammation represents an important cofactor involved in myocardial stunning. According to the paradigm elegantly depicted by Lyon and coworkers, abundant catecholamine release triggers a switch in the β2-adrenergic receptor (β2-AR) intracellular signaling from a Gs to Gi protein. Recent insights have underlined that activation of the sympathetic nervous system promotes cardiac inflammation by upregulating ICAM-1 and integrin expression via p53 signaling to exacerbate cardiac dysfunction. Moreover, inflammation may lead to activation of p38 mitogen activated protein kinase, a downstream effector of β2-AR, therefore contributing to myocardial stunning.

As noted by Dr. Madias, we fully recognize that the “fuzzy boundaries” between chemotherapy-induced cardiomyopathy and TTS deserves further investigation. A lot remains to be elucidated. From a pragmatic point of view, in patients under chemotherapy, we believe that myocardial dysfunction, troponin elevation, QT prolongation, and minimal ECG changes should be interpreted in the light of the high burden of TTS. In the context of active malignancy, ignoring TTS as a possible reversible cause of myocardial injury could lead to inappropriate interruption of a potentially lifesaving cancer treatment. Strategies for prevention and attenuation of myocardial stunning during cancer therapy should be evaluated in view of the noxious effect of excess catecholamine release. In that setting, β-blockers could be the drug of choice to hamper myocardial stunning associated with TTS.

References


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