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Does autonomic re-innervation cause Takotsubo syndrome in a transplanted heart?

Comment on:

"Takotsubo cardiomyopathy in a young adult with transplanted heart: what happened to denervation?" by Chinali *et al.*

With interest, we read the report by Chinali *et al*. about Takotsubo syndrome (TTS) in a 21-year-old woman 10 years after heart transplantation.[1] This case raises questions and concerns with respect to the pathophysiology of TTS.

The majority of individuals with TTS are post-menopausal women aged 65–70 years. In most case series from Western countries, individuals $<$ 50 years of age and men represent $<$12% of the patients, respectively.[2] Thus, it would be interesting to know age and sex of the heart donor and if a TTS was observed already in the donor. Successful heart transplantations have been reported from donors with TTS.[3]

There are a number of case studies on TTS occurring in the acute, subacute, or chronic phase after lung,[4] renal,[5,6] and liver transplantation.[7,8] Besides emotional and physical stress associated with transplantation and post-transplantation recovery, combined immunosuppressive therapy might have contributed to the development of TTS.[5] Therefore, it would be interesting to know which immunosuppressive regimen was applied and if there was a pre-medication with beta-blockers, ACE-inhibitors, or oral contraceptives.

To exclude acute cardiac rejection, myocardial biopsy had been performed in the patient presented. However, it is not reported if contraction-band necrosis was documented, compatible with a catecholamine-mediated cardiac injury.

The authors hypothesize that TTS was due to re-innervation, which may be observed in nearly 40% of the patients within 1 year after transplantation, but diagnostic tests of the cardiac autonomic nervous system like tilt tests, spectral analysis of 24 h electrocardiogram, or ^{123}I metaiodobenzylguanidine imaging were not presented. Lacking are also nerve conduction studies to see if there was sensory neuropathy.

Another explanation for TTS is sympathetic overstimulation via catecholamines in the bloodstream occurring as a result of emotional or physical stress. It has been shown that plasma concentrations of catecholamines in patients with TTS are several times higher than those of patients with Killip III myocardial infarction.[9] Thus, serum catecholamine levels during the acute phase of TTS should be presented. A transplanted, denervated heart with loss of inhibitory parasympathetic innervation may exhibit an exaggerated response to endogenous and exogenous catecholamines and, therefore, may be more susceptible to TTS. This has been suspected in a woman developing TTS during dobutamine stress echocardiography 1 year after heart transplantation.[10]

A more detailed analysis of the presented case as well as a review of all reported TTS cases after transplantation might disclose new insights in the still incompletely understood pathogenesis of TTS.

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References

1. Chinali M, Formigari R, Grutter G. Takotsubo cardiomyopathy in a young adult with transplanted heart: what happened to denervation? *ESC Heart Fail* 2018; **5**: 197–200.
2. Lyon AL, Bossone E, Schneider B, Sechtem U, Citro R, Underwood SR, Sheppard MN, Figtree GA, Parodi G, Akashi YJ, Ruschitzka F, Filippatos G, Mebazaa A, Omerovic E. Current state of knowledge on Takotsubo syndrome: a position statement from the task force on Takotsubo syndrome of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2016; **18**: 8–27.
3. Redfors B, Ramunddal T, Oras J, Karason K, Ricksten SE, Dellgren G, Omerovic E. Successful heart transplantation from a donor with Takotsubo syndrome. *Int J Cardiol* 2015; **195**: 82–84.
4. Ghadri JR, Bataisou RD, Diekmann J, Lüscher TF, Templin C. First case of atypical Takotsubo cardiomyopathy in a bilateral lung transplanted patient due to acute respiratory failure. *Eur Heart J Acute Cardiovasc Care* 2015; **4**: 482–485.
5. Vailas MG, Vernadakis S, Kakavia K, Paizis I, Bokos J, Boletis J, Zavos G. A heartbreaking renal transplantation: is norepinephrine the culprit to blame? *Transplant Proc* 2016; **48**: 3088–3091.
6. Elapavaluru S, Gologorsky A, Thai N, Uemura T, Khalil R, Mareddy C, Dishart M, Gologorsky E. Perioperative stress cardiomyopathy in simultaneous liver and kidney transplantation: a call for early consideration of mechanical circulatory support. *J Cardiothorac Vasc Anesth* 2017; **31**: 248–253.
7. Anders MM, Comignani PD, Couce R, Prini N, Zerega AR, Santopinto M, Devetach G, Quinonez EG, Goldaracena N, McCormack L, Mastai RC. Takotsubo cardiomyopathy: a cardiac syndrome mimicking acute myocardial infarction in a liver transplant recipient. *Cardiol Res* 2011; **2**: 82–85.
8. Vachiat A, McCutcheon K, Mahomed A, Schleicher G, Brand L, Botha J, Sussman M, Manga P. Takotsubo cardiomyopathy post liver transplantation. *Cardiovasc J Afr* 2016; **27**: e1-e3.
9. Wittstein IS, Thiemann DR, Lima JA, Baughman KL, Schulman SP, Gerstenblith G, Wu KC, Rade JJ, Bivalacqua TJ, Champion HC. Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med* 2005; **352**: 539–548.
10. Gastwirth VG, Yang HS, Steidley DE, Scott RL, Chandrasekaran K. Dobutamine stress-induced cardiomyopathy in an orthotopic heart transplant patient. *J Heart Lung Transplant* 2009; **28**: 968–970.

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