

Takotsubo syndrome and dialysis: an uncommon association?

Journal of International Medical Research

2018, Vol. 46(11) 4399–4406

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DOI: 10.1177/0300060518794249

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Abstract

This review was performed to investigate the association between treatment with dialysis and Takotsubo syndrome in patients with end-stage renal disease. We systematically explored the PubMed database using the search terms “Takotsubo cardiomyopathy” and/or “stress-induced cardiomyopathy” and/or “Takotsubo syndrome” in combination with “dialysis” and “uremia.” Of 3630 articles found, 8 articles reporting 10 cases were selected for analysis. Most patients were women, and their age ranged from 51 to 84 years. Diabetes mellitus and hypertension were diagnosed in 40% of patients, and glomerular disease was diagnosed in 30%. One only patient was treated with peritoneal dialysis; all others were treated with hemodialysis. The outcome was unfavorable in only one patient. An association between Takotsubo syndrome and dialysis is uncommon, but not negligible, and comorbidities play a major role in determining the clinical outcome.

Keywords

Takotsubo syndrome, dialysis, end-stage renal disease, outcome, sex, cardiomyopathy, review

Date received: 2 May 2018; accepted: 23 July 2018

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Introduction

Takotsubo syndrome (TS), also termed stress-induced cardiomyopathy, broken heart syndrome, and transient left apical ballooning syndrome, presents as transient left ventricular dysfunction, electrocardiographic changes that can mimic acute myocardial infarction, and minimal release of myocardial enzymes in the absence of obstructive coronary artery disease.¹ The name of this syndrome was derived in reference to the pot with a round bottom and narrow neck used for trapping octopuses in Japan.²

The precise pathophysiologic mechanisms of TS are incompletely understood, but considerable evidence indicates that sympathetic stimulation is central to its pathogenesis. Enhanced sympathetic stimulation is central to TS; however, the mechanism by which catecholamine excess precipitates myocardial stunning in the variety of regional ballooning patterns that characterize this syndrome is unknown. Several hypotheses have been proposed to identify mechanisms by which catecholamine excess precipitates myocardial stunning: plaque rupture, multi-vessel epicardial spasm, microcirculatory dysfunction, catecholamine toxicity in cardiomyocytes, and activation of myocardial survival pathways.³ Additionally, the most common temporal patterns of onset are characterized by peak occurrence during the morning hours, during summer months, and on Mondays.⁴⁻⁶ These aspects are similar to those of myocardial infarction (MI) but different from those of other cardiac conditions.⁷

Many medical diseases have been associated with TS, such as infectious diseases,⁸ respiratory diseases,⁹ endocrine disorders,¹⁰ allergic diseases,¹¹ sepsis,¹² and even suicidal behavior.¹³ We previously investigated the association between chronic kidney disease and cardiovascular diseases including MI,¹⁴ pulmonary embolism,¹⁵ and stroke.¹⁶ In the present study, we evaluated the association

between treatment with dialysis and TS in patients with end-stage renal disease.

Methods and Results

Search method

Research of TS has dramatically increased in recent years. In the PubMed database alone, we identified 3630 documents containing the term “Takotsubo”, with our search including all articles published from the inception of the database to 31 December 2017. We systematically explored the PubMed database using the search terms “Takotsubo cardiomyopathy” and/or “stress-induced cardiomyopathy” and/or “Takotsubo syndrome” in combination with “dialysis” and “uremia.” A further search of Google Scholar was performed. For each case, we collected data regarding sex, age, renal diagnosis, type and duration of dialysis, possible triggers, outcome, author, journal, and year of publication. The end date of the electronic search was 31 December 2017. Of 3630 articles found, we selected 8 articles reporting 10 cases. The search strategy is illustrated in Figure 1.

Findings

The details of the 10 patients are shown in Table 1. Most patients were women (80%), and their age ranged from 51 to 84 years. Diabetes mellitus and hypertension were diagnosed in four patients each, and glomerular disease was diagnosed in three patients. Only one patient was treated with peritoneal dialysis; all others were treated with hemodialysis. An infectious trigger was recognized in five patients, while a psychological trigger was reported in only one. The outcome was unfavorable in only one patient (meningitis).

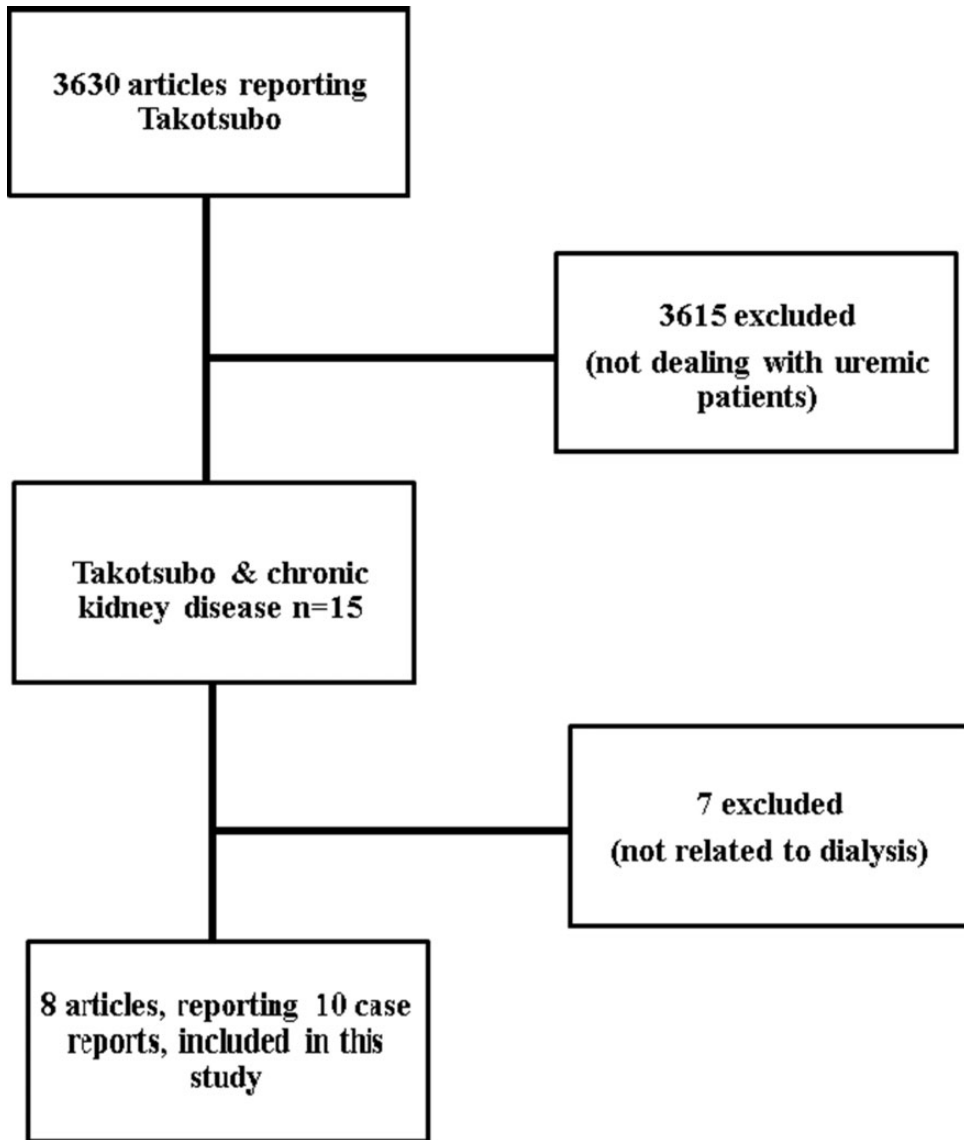


Figure 1. Search strategy.

Ethics

Approval by an ethics committee was not required for this study because it was a retrospective case review of the literature available in the PubMed database.

Discussion

Development of TS is commonly triggered by emotional or physical stress. The latter favors catecholamine excess, which is potentially harmful to the heart,¹ and

Table 1. Systematic review of case reports of patients treated with dialysis complicated by onset of Takotsubo syndrome.

Sex/age (years)	Underlying causes	Dialysis: type and duration	Trigger	Outcome	Authors/year
M/65	Diabetic nephropathy	Hemodialysis, 9 years	Meningitis	Tetraplegia, respiratory suppression	Kusaba et al., 2004 ³³
F/55	Unknown	Hemodialysis, unknown	Epilepsy	Favorable	Garea Garcia-Malvar et al., 2014 ³⁴
F/84	Nephritic syndrome	Hemodialysis, 2 years	Sustained chest discomfort	Favorable	Fukui et al., 2006 ³⁵
F/51	Membranous nephropathy	Hemodialysis, 1979–81 Renal transplant, 1981–2 Hemodialysis, 1982–95 Renal transplant, 1995–2009 Peritoneal dialysis, 2009–present	Stressful life event	Favorable	Musone et al., 2012 ³⁶
F/69	Hypertension	Hemodialysis, unknown	Unknown	Favorable	Mutler et al., 2013 ³⁷
F/61	Glomerulonephritis	Hemodialysis, 20 years	Chest pain and dyspnea during dialysis	Favorable	Takemoto et al., 2009 ³⁸
F/57	Unknown	Peritoneal dialysis, 3 years	Abdominal pain due to peritonitis	Favorable	Hassan et al., 2011 ³⁹
F/*	Diabetes mellitus, hypertension	Hemodialysis, unknown	Pneumonia	Favorable	Shin et al., 2013 ⁴⁰
F/*	Diabetes mellitus, hypertension	Hemodialysis, unknown	Infectious colitis	Favorable	Shin et al., 2013 ⁴⁰
M/*	Diabetes mellitus, hypertension	Hemodialysis, unknown	Pneumonia	Favorable	Shin et al., 2013 ⁴⁰

M, male; F, female.

*Shin et al.⁴⁰ indicated only the age range for the three cases reported (54–68 years).

catecholamine hypersecretion and actions on β -adrenoceptors could be the cause of cardiac damage in patients with TS.¹⁷ Catecholamine hyperactivity is also the cause of the typical regional negative inotropism of different segments of the heart, characterized by different densities of β_1 and β_2 adrenoceptors.¹⁷ Myocardial contraction is stimulated by activation of the sympathetic nervous system during stressful conditions, and the effect of catecholamines on the myocardium depends upon the distribution of sympathetic nerves in this tissue. The local concentration of catecholamines reportedly varies in different myocardial regions due to heterogeneities in sympathetic nerve innervation and local intramyocardial stores.¹⁸ However, Vink and Blankestijn¹⁹ reported that sympathetic activation is most likely to represent an early event in the pathophysiology of chronic kidney failure. Masue et al.²⁰ compared the hormonal mechanisms of blood pressure (BP) reduction during hemodialysis between patients with normotension and hypertensive uremia and found that hemodialytic BP reduction may be associated with abnormal sympathetic nerve responsiveness. BP may be highly variable during hemodialysis, whereas it appears to remain stable during peritoneal dialysis procedures, suggesting more variable catecholamine plasma levels during hemodialysis than during peritoneal dialysis. These concepts could explain, at least in part, the higher prevalence of TS in patients undergoing hemodialysis than peritoneal dialysis. However, we must take into consideration that the prevalence of patients undergoing hemodialysis treatment is much higher than the prevalence of uremic patients undergoing peritoneal dialysis treatment, and these data could bias our hypothesis.

The age and sex distribution of TS is not different between the general population and patients undergoing dialysis, and TS affects women after their fifth decade of

life.²¹ In one study, 826 patients with TS in the GEIST Registry were evaluated, and all-cause mortality was compared between patients with and without diabetes mellitus.²² The authors found that the prevalence of diabetes was higher than 20%, and diabetic patients with TS were more likely to be older and male and have a higher prevalence of hypertension and physical triggers. Moreover, the multivariate regression analysis identified diabetes as an independent predictor of adverse outcomes.²² In another study, patients with TS showed a prevalence of dyslipidemia comparable with that of patients with MI, indicating that dyslipidemia in these patients may represent unrelated issues.²³

Our data suggest that in patients undergoing dialysis, physical triggers could be more important than psychological triggers, and diabetes mellitus is not an uncommon finding in uremic patients with TS. However, such a comorbidity does not appear to be related to increased short-term negative outcomes. In fact, diabetes-induced endothelial dysfunction in various vascular beds contributes to a wide range of complications and plays a negative role in microcirculatory regulation.²⁴

Infection was also found to be associated with TS in patients undergoing dialysis. This finding is not surprising because patients with diabetes and chronic kidney disease are more prone to complications, including acute cardiovascular disease and infections.²⁵ The reported risk factors for sepsis-induced myocardial dysfunction are a younger age, history of diabetes mellitus, history of heart failure, elevated brain natriuretic peptide level, and positive blood culture result.²⁶ In a recent analysis of the limited available evidence on this topic (13 cases), women were more prevalent than men, the mean age was 57 years, and bacterial infections were more frequent. The clinical outcome is favorable in most cases of TS and was likewise favorable in

the cases of the present review.¹² However, two case series of in-hospital mortality of patients with TS showed that men with sepsis exhibited significantly higher in-hospital mortality.^{27,28} Infection results in sympathetic nervous system overstimulation and increases catecholamine plasma levels, which exert direct toxic effects on the heart that are dependent upon inflammation, oxidative stress, and abnormal calcium handling. These changes result in myocardial stunning, apoptosis, and necrosis.²⁹

In general, however, clinical outcomes have been shown to be sex-related. A systematic review showed that the in-hospital mortality rate was 4.5%, with even higher rates among male patients (odds ratio, 2.6).³⁰ A Japanese series showed a significant difference between in-hospital and out-hospital patients with TS. The former group, characterized by a higher proportion of male patients, showed a higher incidence of chronic comorbidities and acute medical illnesses and a higher mortality rate (17.9% vs. 5.4%).²⁸

Conclusion

TS does not appear to be a frequent finding in patients undergoing dialysis, or it does not appear to be frequently reported. We suspect that there are more confounding factors associated with TC in patients undergoing dialysis. In any case, uncommon does not mean negligible, and the association between TS and dialysis requires investigation of further comorbidities. Based on this very limited evidence, it seems that although patients undergoing dialysis represent patients with highly complicated conditions, TS does not seem to negatively influence their clinical outcomes, at least in the short term. However, its management requires appropriate clinical skills because the prognosis could also depend on comorbidities. In contrast to previously common opinions, the mortality rates among patients with TS are not

significantly different from those among patients with MI,³¹ and TS should no longer be simply considered a benign disease. In fact, although the prognosis of TS is generally thought to be favorable with complete recovery of left ventricular function, the prognosis depends on many factors, including comorbidities, clinical presentation, sex, and in-hospital or out-hospital setting.³² A high level of caution and correct management of all aspects of TS, especially in patients with complicated conditions, is necessary to obtain a favorable outcome.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Acknowledgements

The authors thank Dr. Claudia Righini and Dr. Donato Bragatto, from the Biblioteca Interaziendale di Scienze della Salute, Azienda Ospedaliera-Universitaria 'S. Anna', Ferrara, for providing valuable assistance.

Funding

This study was supported by an institutional research grant (Fondo Ateneo Ricerca –FAR–) to Prof. Fabio Fabbian from the University of Ferrara.

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References

1. Bossone E, Savarese G, Ferrara F, et al. Takotsubo cardiomyopathy: overview. *Heart Fail Clin* 2013; 9: 249–266.
2. Dote K, Sato H, Tateishi H, et al. Myocardial stunning due to simultaneous

- multivessel coronary spasms: a review of 5 cases. *J Cardiol* 1991; 21: 203–214.
3. Ghadri JR, Wittstein IS, Prasad A, et al. International expert consensus document on takotsubo syndrome (Part I): clinical characteristics, diagnostic criteria, and pathophysiology. *Eur Heart J* 2018; 39: 2032–2046.
 4. Citro R, Previtali M, Bovelli D, et al. Chronobiological patterns of onset of Tako-Tsubo cardiomyopathy: a multicenter Italian study. *J Am Coll Cardiol* 2009; 54: 180–181.
 5. Manfredini R, Citro R, Previtali M, et al. Summer preference in the occurrence of takotsubo cardiomyopathy is independent of age. *J Am Geriatr Soc* 2009; 57: 1509–1511.
 6. Manfredini R, Citro R, Previtali M, et al. Monday preference in onset of takotsubo cardiomyopathy. *Am J Emerg Med* 2010; 28: 715–719.
 7. Manfredini R, Manfredini F, Fabbian F, et al. Chronobiology of Takotsubo syndrome and myocardial infarction: analogies and differences. *Heart Fail Clin* 2016; 12: 531–542.
 8. De Giorgi A, Fabbian F, Pala M, et al. Takotsubo cardiomyopathy and acute infectious diseases: a mini-review of case reports. *Angiology* 2015; 66: 257–261.
 9. Manfredini R, Fabbian F, Giorgi AD, et al. Heart and lung, a dangerous liaison-Takotsubo cardiomyopathy and respiratory diseases: A systematic review. *World J Cardiol* 2014; 6: 338–344.
 10. De Giorgi A, Fabbian F, Tiseo R, et al. Takotsubo cardiomyopathy and endocrine disorders: a mini-review of case reports. *Am J Emerg Med* 2014; 32: 1413–1417.
 11. Boccafogli A, De Giorgi A, Parisi C, et al. May allergic syndrome represent valid trigger for Tako-tsubo cardiomyopathy? A systematic review of reported cases. *Exp Clin Cardiol* 2014; 20: 5074–5087.
 12. Fabbian F, De Giorgi A, Tiseo R, et al. Takotsubo cardiomyopathy, sepsis and clinical outcome: does gender matter? *Am J Emerg Med* 2015; 33: 1525–1527.
 13. Manfredini R, Fabbian F, Cappadona R, et al. Attempted suicide as a trigger of Takotsubo syndrome: a minireview of available case reports. *Intern Emerg Med* 2018; 13: 629–631.
 14. Fabbian F, Pala M, De Giorgi A, et al. In-hospital mortality in patients with renal dysfunction admitted for myocardial infarction: the Emilia-Romagna region of Italy database of hospital admissions. *Int Urol Nephrol* 2013; 45: 769–775.
 15. Fabbian F, Gallerani M, Pala M, et al. In-hospital mortality for pulmonary embolism: relationship with chronic kidney disease and end-stage renal disease. The hospital admission and discharge database of the Emilia Romagna region of Italy. *Intern Emerg Med* 2013; 8: 735–740.
 16. Fabbian F, Gallerani M, Pala M, et al. Association between in-hospital mortality and renal dysfunction in 186,219 patients hospitalized for acute stroke in the Emilia-Romagna region of Italy. *Angiology* 2014; 65: 906–910.
 17. Lyon AR, Rees PS, Prasad S, et al. Stress (Takotsubo) cardiomyopathy—a novel pathophysiological hypothesis to explain catecholamine-induced acute myocardial stunning. *Nat Clin Pract Cardiovasc Med* 2008; 5: 22–29.
 18. Williams R, Arri S, and Prasad A. Current concepts in the pathogenesis of Takotsubo syndrome. *Heart Fail Clin* 2016; 12: 473–484.
 19. Vink EE and Blankestijn PJ. Evidence and consequences of the central role of the kidneys in the pathophysiology of sympathetic hyperactivity. *Front Physiol* 2012; 3: 29.
 20. Masuo K, Mikami H, Ogihara T, et al. Hormonal mechanisms in blood pressure reduction during hemodialysis in patients with chronic renal failure. *Hypertens Res* 1995; 18(Suppl 1): S201–S203.
 21. Schneider B and Sechtem U. Influence of age and gender in Takotsubo syndrome. *Heart Fail Clin* 2016; 12: 521–530.
 22. Stiermaier T, Santoro F, El-Battrawy I, et al. Prevalence and prognostic impact of diabetes in Takotsubo syndrome: insights from the international, multicenter GEIST registry. *Diabetes Care* 2018; 41: 1084–1088.
 23. De Giorgi A, Guarino M, Boari B, et al. Takotsubo cardiomyopathy, acute myocardial

- infarction and dyslipidaemia: a comparison of studies. *Clin Lipidol* 2016; 1: 33–38.
24. Kibel A, Selthofer-Relatic K, Drenjancevic I, et al. Coronary microvascular dysfunction in diabetes mellitus. *J Int Med Res* 2017; 45: 1901–1929.
 25. Winocour PH. Diabetes and chronic kidney disease: an increasingly common multi-morbid disease in need of a paradigm shift in care. *Diabet Med* 2018; 35: 300–305.
 26. Jeong HS, Lee TH, Bang CH, et al. Risk factors and outcomes of sepsis-induced myocardial dysfunction and stress-induced cardiomyopathy in sepsis or septic shock: A comparative retrospective study. *Medicine (Baltimore)* 2018; 97: e0263.
 27. Brinjikji W, El-Sayed AM, and Salka S. In-hospital mortality among patients with takotsubo cardiomyopathy: a study of the National Inpatient Sample 2008 to 2009. *Am Heart J* 2012; 164: 215–221.
 28. Isogai T, Yasunaga H, Matsui H, et al. Out-of-hospital versus in-hospital Takotsubo cardiomyopathy: analysis of 3719 patients in the Diagnosis Procedure Combination database in Japan. *Int J Cardiol* 2014; 176: 413–417.
 29. Schmittinger CA, Wurzinger B, Deutinger M, et al. How to protect the heart in septic shock: a hypothesis on the pathophysiology and treatment of septic heart failure. *Med Hypotheses* 2010; 74: 460–465.
 30. Singh K, Carson K, Shah R, et al. Meta-analysis of clinical correlates of acute mortality in Takotsubo cardiomyopathy. *Am J Cardiol* 2014; 113: 1420–1428.
 31. Redfors B, Vedad R, Angeras O, et al. Mortality in takotsubo syndrome is similar to mortality in myocardial infarction – A report from the SWEDEHEART registry. *Int J Cardiol* 2015; 185: 282–289.
 32. Templin C, Ghadri JR, Diekmann J, et al. Clinical features and outcomes of Takotsubo (stress) cardiomyopathy. *N Engl J Med* 2015; 373: 929–938.
 33. Kusaba T, Sasaki H, Sakurada T, et al. Takotsubo cardiomyopathy thought to be induced by MRSA meningitis and cervical epidural abscess in a maintenance-hemodialysis patient: case report. *Nihon Jinzo Gakkai Shi* 2004; 46: 371–376.
 34. Garea Garcia-Malvar MJ, Gonzalez-Silva Y and Epureanu-Epureanu V. Epileptic seizures complicated by Takotsubo syndrome. *Rev Neurol* 2014; 59: 407–410.
 35. Fukui M, Mori Y, Tsujimoto S, et al. ‘Takotsubo’ cardiomyopathy in a maintenance hemodialysis patient. *Ther Apher Dial* 2006; 10: 94–100.
 36. Musone D, Nicosia V, D’Alessandro R, et al. Acute heart failure secondary to takotsubo cardiomyopathy in a patient on peritoneal dialysis with residual renal function loss. *G Ital Nefrol* 2012; 29: 467–472.
 37. Mutluer FO, Madonna R, Cevik C, et al. Biventricular Takotsubo syndrome in a patient with coronary abnormality and end-stage renal disease. *Cor et Vasa* 2013; 55: E277–E280.
 38. Takemoto F, Chihara N, Sawa N, et al. Takotsubo cardiomyopathy in a patient undergoing hemodialysis. *Kidney Int* 2009; 76: 467.
 39. Hassan S, Hassan F, Hassan D, et al. Takotsubo cardiomyopathy associated with peritonitis in peritoneal dialysis patient. *Ren Fail* 2011; 33: 904–907.
 40. Shin MJ, Rhee H, Kim IY, et al. Clinical features of patients with stress-induced cardiomyopathy associated with renal dysfunction: 7 case series in single center. *BMC Nephrol* 2013; 14: 213.