Clinical features of patients with stress-induced cardiomyopathy associated with renal dysfunction: 7 case series in single center

Running title: Stress-induced cardiomyopathy associated with renal dysfunction

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Abstract

Background: Stress-induced cardiomyopathy (sCMP) is characterized by transient wall-motion abnormalities involving the left ventricular apex and mid-ventricle that are precipitated by emotional or physical stress. As the heart and kidney influence each other’s function through bidirectional pathways, sCMP can induce renal dysfunction or be induced by renal dysfunction. This study reviewed the clinical characteristics and outcomes of patients with confirmed sCMP associated with renal dysfunction.

Methods: We conducted a retrospective analysis of the medical records of all patients from our institution who were diagnosed with sCMP from March 2010 to April 2012. Each patient's demographic characteristics, presenting symptoms, triggering events, electrocardiographic characteristics, laboratory data, echocardiographic study findings, cardiac catheterization data, and outcomes were reviewed.

Results: Among 30 patients who were diagnosed with sCMP, 7 patients had associated renal dysfunction. Three patients were on maintenance hemodialysis (HD) and 4 patients had acute kidney injury (AKI). Their mean ejection fraction was 35.2% at initial echocardiography, and 57.2% at follow-up echocardiography. Pericardial effusion was detected in all HD patients initially; these patients were treated with intensive HD for suspected under-dialysis status. In patients with AKI, the mean peak serum creatinine was 4.17 mg/dL. Two patients were treated with continuous renal replacement therapy. One patient required maintenance HD, and 1 patient died. Two patients had full renal recovery to their baseline renal function at 7 and 14 days.

Conclusions: Patients with renal dysfunction including those with AKI and those undergoing HD can develop sCMP, renal function must be closely monitored in patients with sCMP. Additionally, it should be considered that patients on HD who develop sCMP may be under-
dialyzed.

**Keywords:** Stress Cardiomyopathy, Acute kidney injury, Hemodialysis
Background

Stress-induced cardiomyopathy (sCMP)—also known as takotsubo cardiomyopathy, broken heart syndrome, or transient left apical ballooning syndrome—usually presents as transient left ventricular dysfunction. It is common in middle-aged women following intense periods of emotional or physical stress. Recently, reverse or inverted takotsubo cardiomyopathy has also been identified [1,2]. Cardiorenal syndrome (CRS) is a disorder of the heart and kidney, whereby acute or long-term dysfunction in one of these organs may induce acute or long-term dysfunction of the other. Changes in the renin-angiotensin-aldosterone system, the sympathetic nervous system, an imbalance between nitric oxide and reactive oxygen species, and inflammation are the cardiorenal connectors in the development of CRS [3]. Similar to that observed in CRS, sCMP can induce renal dysfunction or be induced by renal dysfunction. However, there has been only 1 case report of sCMP with acute kidney injury (AKI) [4]. In this report, we reviewed a case series of 7 patients with confirmed sCMP associated with renal dysfunction including prevalent hemodialysis (HD) or acute kidney injury.
Methods

We conducted a retrospective analysis of the medical records of all patients from our institution who were diagnosed with sCMP from March 2010 to April 2012. Patients who met the following criteria of sCMP were included: (1) development of typical takotsubo or inverted takotsubo on echocardiography after emotional or physical stress; (2) no evidence of obstructive epicardial coronary artery disease on coronary angiography (CAG); for those patients who could not undergo CAG, follow-up echocardiography showing improvement of left ventricular function was used to demonstrate the absence of coronary artery obstruction; (3) new electrocardiographic (ECG) abnormalities, including ST-segment elevation, T-wave inversion, or arrhythmia and elevation in troponin I. We identified 30 patients with sCMP. Of these, 7 patients had associated renal dysfunction. Three patients were on maintenance HD with anuric state and 4 patients had AKI. AKI was diagnosed according to the RIFLE criteria, which can be used to classify patients with renal dysfunction according to the degree of impairment into “Risk,” “Injury,” “Failure,” “Sustained loss,” and “End-stage renal disease” categories [5]. Each patient's demographic characteristics, presenting symptoms, triggering events, ECG characteristics, laboratory data, echocardiographic study findings, cardiac catheterization data, and outcomes were reviewed. Three patients (42.8%) were women and the mean age was 65 years (range, 53 to 77 years). The protocol was approved by the institutional review board of Pusan National University Hospital (E-2012059). Informed consent was exempted by the board because of the retrospective nature of the study.
Results

Clinical characteristics and laboratory findings of the 4 patients with AKI and sCMP are listed in Table 1 and 2. Two patients had diabetes mellitus and atrial fibrillation, and 1 patient had anti-neutrophil cytoplasmic autoantibody (ANCA)-associated rapidly progressive glomerulonephritis (RPGN). The fourth was a patient with pyriform sinus cancer who underwent adjuvant chemotherapy. On admission, only 1 patient presented with chest pain; the remaining 3 patients presented with dyspnea. The triggering event in all 4 patients was physical stress, which consisted of pneumonia and hypoxemia in 2 patients, infectious colitis in 1 patient, and RPGN in 1 patient. The ECG findings on admission were diffuse T-wave inversion in leads V1 to V6 in 2 patients and ST-segment elevation in the precordial leads in 1 patient. The second patient had only QTc prolongation (QTc = 501 ms). All patients indicated a small increase in cardiac enzyme levels. On Echocardiography at presentation, 3 patients showed the typical takotsubo pattern with left ventricular dysfunction and the other patient had an inverted takotsubo pattern with left ventricular dysfunction. The mean ejection fraction (EF) was 36.2% (range, 30-48%). Three patients were evaluated with follow-up echocardiography and showed improvement of left ventricular function within a few weeks (range, 2-4 weeks). On follow-up echocardiography of 3 patients, the mean EF was 59.0% (range, 52-68%), and no regional wall motion abnormalities were noted. The second patient underwent CAG and indicated no evidence of obstructive epicardial coronary artery disease.

In all 4 patients, the mean baseline serum creatinine was 1.02 mg/dL and the mean serum creatinine at the time of initial echocardiography was 3.0 mg/dL. The first patient’s peak serum creatinine level was 3.76 mg/dL. As this patient had unstable blood pressure with inotropic agent use and decreased urine volume (<400 mL/day), continuous renal replacement therapy (CRRT) was initiated, using the mode of continuous venovenous
hemodiafiltration. She was treated with CRRT for 96 hours. After the CRRT was discontinued, she entered the polyuric stage and her renal function returned to baseline within approximately 7 days after diagnosed AKI. She exhibited normal renal function and no recurrence of sCMP at the last examination performed in the nephrology department. Therefore, the degree of renal impairment was “Failure,” according to the RIFLE criteria. The second patient had a maximum creatinine level of 3.45 mg/dL with decreased urine volume (urine volume <300 mL/day) and unstable blood pressure with inotropic agent use; therefore, CRRT was initiated. However, he died during the hospital period. His death was attributed to recurrent ventricular tachycardia. The third patient had biopsy-proven ANCA-associated RPGN and received steroid pulse therapy and cyclophosphamide therapy along with conventional hemodialysis. Despite the immunosuppressive regimen, his renal function did not improve, and therefore, maintenance hemodialysis was initiated. He did not exhibit any recurrence of sCMP at his last follow-up examination. The degree of renal impairment was “End-stage renal disease” according to the RIFLE criteria. In the fourth patient, the serum creatinine level reached to 2.19 mg/dL and then decreased to baseline levels after 14 days, with no recurrence of sCMP. The degree of renal impairment according to the RIFLE criteria was “Injury.”

Clinical characteristics and laboratory findings of the 3 patients under prevalent hemodialysis who developed sCMP are listed in Table 3 and 4. All 3 patients had diabetes mellitus and hypertension, and 1 patient had atrial fibrillation and bronchial asthma. All 3 patients were under prevalent hemodialysis with anuric state; their weekly Kt/V values were 3.0, 2.58, and 3.52, respectively. At admission, these 3 patients presented with dyspnea. The triggering event for each of these patients was physical stress, which included pneumonia and hypoxemia in 2 patients and infectious colitis in 1 patient. The ECG findings at admission
were diffuse T-wave inversion in leads V1 to V6 in 1 patient, ST-segment elevation in the precordial leads in 1 patient, and QTc prolongation (QTc = 504 ms) in 1 patient. Two patients indicated a small increase in cardiac enzyme levels. On echocardiography at presentation, all patients indicated a typical takotsubo pattern with pericardial effusion, and the mean EF was 34.0% (range, 30-37%). Two patients were evaluated with follow-up echocardiography and showed improvement of left ventricular function with a mean EF of 55% within a few weeks (range, 1-2 weeks). The other patient underwent CAG and had no evidence of obstructive epicardial coronary artery disease. Because pericardial effusion was detected in all patients and 2 of them had uremic encephalopathy, these 3 patients were treated with intensive hemodialysis for suspected under-dialysis status. All the patients were treated with conventional hemodialysis and did not exhibit any complications or recurrence of sCMP during the last examination performed in the nephrology department.
Discussion and conclusions

The cases described in this study illustrate that sCMP can occur in patients with renal dysfunction, including end-stage renal disease (ESRD) or AKI. Although sCMP was initially described in Japanese patients, there have been several cases reported in other parts of the world. It is characterized by transient hypokinesia of the apical portion of the left ventricle with compensatory hyperkinesia of the basal walls, resulting in apical ballooning that gives the heart the appearance of a Japanese octopus trap or “takotsubo.” This syndrome is triggered by severe physical or emotional stress and mimics an acute coronary syndrome. ECG often reveals ST-segment elevations or T-wave inversions in the precordial leads. The levels of cardiac enzymes are elevated, but angiography shows normal coronary arteries or only minor disease inconsistent with the ECG changes. Interestingly, the stressor in all of our patients was physical in nature. In previous studies, 30-40% of patients with sCMP have been reported to have experienced emotional stress [6] and >50% of patients have been reported to have experienced a preceding emotional or physical condition that was perceived as a stressor [7]. Cathecholamines are known to be closely associated with the initiation of sCMP [8]. Plasma catecholamine concentrations at the time of onset were increased in patients with sCMP when compared to patients with myocardial infarction [9]. During stressful conditions, the sympathetic nervous system is activated, and this may influence myocardial contraction. In addition, a different distribution of sympathetic nerves in the myocardium may also be associated with the peculiar wall-motion abnormality. It has been known that sympathetic nervous system hyperactivity is observed in patients with ESRD. Activation of the sympathetic nervous system, assessed using plasma norepinephrine levels, is observed in patients with ESRD treated with HD and in those with early ESRD without HD treatment; the plasma norepinephrine levels in these patients is significantly higher than those in blood
pressure-matched and body mass index-matched hypertensive patients or healthy normotensive subjects [10]. Additionally, it has been demonstrated that vitamin E levels are lower in dialysis patients, both before and after treatment, compared to controls, indicating that there is a significant level of oxidative stress in chronic renal patients [11]. Thus, it can be presumed that, given the condition of sympathetic nervous hyperactivity in ESRD patients, triggering of stress might induce sCMP more frequently in these patients than in healthy subjects. Further, all 3 of our patients under maintenance hemodialysis were suspected to have an under-dialysis status because of pericardial effusion and uremic encephalopathy. Therefore, we can presumed that the under-dialysis status itself may be a triggering factor for sCMP as a stressor, although further studies are needed to confirm these associations.

Various patterns of sCMP have been recently recognized. In the inverted takotusbo pattern, which is a variant of sCMP, the left ventricular wall exhibits akinesia of the base and hyperdynamic apex [12,13]. This pattern has been known to present at an earlier age compared with other types of sCMP and has been triggered by emotional or physical stress in all patients [13]. This difference in presentation has been attributed to differences in the sympathetic innervations of the heart with the abundance of adrenoreceptors at the apex compared with the base. One of our patients had an inverted takotusbo pattern in initial echocardiography. The ECG showed the QTc prolongation, and he died because of recurrent ventricular tachycardia. Sufficient data are not available on the incidence of arrhythmias according to the various patterns of sCMP. Recently, as the clinical spectrum of sCMP became broader and the disease entity was better understood, it was suggested that it is impractical to routinely perform invasive coronary angiography for definitive diagnosis of sCMP. In fact, current criteria for confirming sCMP include invasive coronary angiography, to exclude the possibility of obstructive coronary artery disease or acute plaque rupture. A
recent study demonstrated that a combination of typical LV morphologic change of sCMP and noninvasive demonstration of the absence of significant plaque rupture can be possible alternative diagnostic criteria [14]. However, these modified criteria require further evaluation. As mentioned earlier, 1 of the patients in the present study died during hospitalization; the death was attributed to recurrent ventricular tachycardia. The in-hospital mortality due to sCMP ranges from 0 to 8%. In view of the associated mortality, the overall outcome is better than that of patients with myocardial infarction. Recurrence of this syndrome is rare and infrequent. In the largest series so far, which consisted of 88 patients, a recurrence rate of 2.7% was reported [15]. In our patients, there has been no recurrence after a mean duration of 11 months.

Cardiac diseases are independently associated with deterioration in kidney function and progression of existing kidney diseases [16]. Conversely, both decrease in glomerular filtration rate and proteinuria are independent risk factors for the development of cardiovascular disease [17]. CRS is a disorder of the heart and kidney, whereby acute or long-term dysfunction in 1 of these organs may induce acute or long-term dysfunction of the other. The 2 organs are connected to regulate blood pressure, vascular tone, diuresis, natriuresis, peripheral tissue perfusion and oxygenation. Changes in renin-angiotensin-aldosterone system, an imbalance between the levels of nitric oxide and reactive oxygen species, the sympathetic nervous system, and inflammation are known as cardiorenal connectors in the development of CRS [3]. Recently, a new classification of CRS has been developed to reflect the likely primary and secondary pathology and time-frame [18]. Type 1 CRS consists of an abrupt worsening of cardiac function leading to AKI. Type 2 CRS comprises chronic abnormalities in cardiac function causing progressive chronic kidney disease. Type 3 CRS reflects an abrupt worsening of renal function causing acute cardiac dysfunction. Type 4 CRS
comprises a state of chronic kidney disease that contributes to a decline in cardiac function. Type 5 CRS reflects a systemic condition such as sepsis causing both cardiac and renal dysfunction. The use of this classification can help physicians characterize groups of patients and provides the rationale for specific management strategies. In our patients, 4 had AKI (injury, failure, and ESRD in 1 each) associated with sCMP. Because the serum creatinine level was already increased at the time that sCMP was diagnosed, we could not appropriately classify the patients according to the CRS classification; instead, we divided them into acute CRS (type 1 or type 3) depending on the clinical course.

Two (50%) of the patients with AKI were treated with CRRT to manage the congestive symptoms and correct the abnormalities in electrolyte levels and acid-base status, accompanying hemodynamic instability. In fact, it has been known that the coexistence of heart and kidney failure in the same subject is associated with an extremely bad prognosis [19]. In patients with acute heart failure, an acute increase in serum creatinine level of >0.3 mg/dL is associated with longer hospitalization time, increased mortality, and more frequent re-admissions [20]. Although diuretics have been the mainstay of treatment, they are often unsuccessful in reversing the vicious cycle of volume overload, worsening cardiac function, and azotemia. Renal replacement therapy (RRT) in the form of isolated or continuous ultrafiltration, with or without a component of solute clearance (hemofiltration or hemodialysis), has been increasingly utilized as a therapeutic tool in this setting. A previous study examined the isolated ultrafiltration strategy in 100 patients with hypervolemic congestive heart failure compared with the intravenous diuretics strategy adopted in 100 patients. It demonstrated greater weight loss, decreased need for vasoactive drugs, and fewer rehospitalizations and emergency department visit in the ultrafiltration group, but no difference in mortality [21]. Although the clinical necessity of RRT in cases of life-
threatening hyperkalemia or acidemia with AKI is clear, the adjunctive role of RRT (hemofiltration or hemodialysis) in the treatment of acute decompensated heart failure is not obvious. A previous study suggested that because severe hypocalcemia is a potential cause of reversible heart failure and acute or acute on chronic renal dysfunction is often hypocalcemic, correction of hypocalcaemia via continuous venovenous hemofiltration might improve cardiac function in acute decompensated heart failure [22]. However, further research examining the use of RRT in CRS is necessary.

In conclusion, these cases showed that concomitant sCMP can occur in patients with renal dysfunction including ESRD or AKI, especially associated with CRS. Therefore, the renal function of any patient with sCMP should be closely monitored to facilitate the early diagnosis of AKI. ESRD patient who develops sCMP could be considered to be under-dialyzed, but further studies are needed to confirm this.

**Competing interests:** The authors have declared no conflict of interest.

**Authors’ contributions:** EYS contributed substantially to the design and conception of the manuscript. MJS collected the clinical data, analyzed data, and wrote the manuscript. HR, IYK, and BYY was involved in the interpretation of the data. SHS, DWL, and SBL contributed substantially to the writing of the manuscript. ISK revised the manuscript. JHC collected the echocardiographic data. All authors read and approved the final manuscript.

**Acknowledgements:** This study was supported by biomedical institute of Pusan National University Hospital.
References


13. Ramaraj R, Movahed MR: **Reverse or inverted takotsubo cardiomyopathy (reverse left ventricular apical ballooning syndrome) presents at a younger age compared with the mid or apical variant and is always associated with triggering stress.** Congest Heart Fail 2010, 16:284-6.


Table 1. Clinical characteristics of patients with acute kidney injury and stress-induced cardiomyopathy

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age (year)</th>
<th>Underlying disease</th>
<th>Presenting symptom</th>
<th>Triggering event</th>
<th>RIFE classification</th>
<th>Renal replacement therapy</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>72</td>
<td>DM, HT, AF</td>
<td>Chest pain</td>
<td>Infectious colitis</td>
<td>Failure</td>
<td>CRRT</td>
<td>Recovery to baseline renal function and no recur of sCMP</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>77</td>
<td>DM, AF</td>
<td>Dyspnea</td>
<td>Pneumonia</td>
<td>—</td>
<td>CRRT</td>
<td>In-hospital death from recurrent VT</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>53</td>
<td>ANCA-RPGN</td>
<td>Dyspnea</td>
<td>ANCA-RPGN</td>
<td>ESRD</td>
<td>Conventional HD</td>
<td>Maintenance HD and no recur of sCMP</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>70</td>
<td>Pyriform sinus cancer</td>
<td>Dyspnea</td>
<td>Pneumonia</td>
<td>Injury</td>
<td>No</td>
<td>Recovery to baseline renal function and no recur of sCMP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>ECG abnormality</th>
<th>Echocardiographic Abnormality at presentation</th>
<th>Peak troponin I (ng/mL)</th>
<th>Coronary angiography</th>
<th>EF at follow-up</th>
<th>Baseline SCr (mg/dL)</th>
<th>Peak SCr (mg/dL)</th>
<th>Follow-up SCr (mg/dL)</th>
<th>Time to recovery of SCr (day)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>T-wave inversion</td>
<td>Typical takotsubo, EF=33%</td>
<td>0.15</td>
<td>NA</td>
<td>57%</td>
<td>1.0</td>
<td>3.76</td>
<td>1.03</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>QTc prolongation</td>
<td>Inverted takotsubo, EF=30%</td>
<td>0.38</td>
<td>Normal</td>
<td>NA</td>
<td>0.73</td>
<td>3.45</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>T-wave inversion</td>
<td>Typical takotsubo, EF=34%</td>
<td>3.74</td>
<td>NA</td>
<td>52%</td>
<td>1.44</td>
<td>7.29</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>ST-segment elevation</td>
<td>Typical takotsubo, EF=48%</td>
<td>3.56</td>
<td>NA</td>
<td>68%</td>
<td>0.9</td>
<td>2.19</td>
<td>1.02</td>
<td>14</td>
</tr>
</tbody>
</table>

ECG: electrocardiography, EF: ejection fraction, NA: not available, SCr: serum creatinine
Table 3. Clinical characteristics of patients under prevalent hemodialysis with stress-induced cardiomyopathy

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age (year)</th>
<th>Underlying disease</th>
<th>Weekly Kt/V</th>
<th>Presenting symptom</th>
<th>Triggering event</th>
<th>Renal replacement therapy</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>M</td>
<td>68</td>
<td>ESRD, DM, HT</td>
<td>3.0</td>
<td>Dyspnea</td>
<td>Pneumonia</td>
<td>Intensive HD</td>
<td>No recur of sCMP</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>54</td>
<td>ESRD, DM, HT</td>
<td>2.58</td>
<td>Dyspnea</td>
<td>Infectious colitis</td>
<td>Intensive HD</td>
<td>No recur of sCMP</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>65</td>
<td>ESRD, DM, HT, AF, Asthma</td>
<td>3.52</td>
<td>Dyspnea</td>
<td>Pneumonia</td>
<td>Intensive HD</td>
<td>No recur of sCMP</td>
</tr>
</tbody>
</table>

Table 4. ECG characteristics, laboratory data, echocardiographic studies, cardiac catheterization data of patients under prevalent hemodialysis with stress-induced cardiomyopathy

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>ECG abnormality</th>
<th>Echocardiographic abnormality at presentation</th>
<th>Peak troponin I (ng/mL)</th>
<th>Coronary angiography</th>
<th>EF at follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>ST-segment elevation</td>
<td>Typical takotsubo, Pericardial effusion, EF=35%</td>
<td>11.61</td>
<td>NA</td>
<td>51%</td>
</tr>
<tr>
<td>6</td>
<td>T-wave inversion</td>
<td>Typical takotsubo, Pericardial effusion, EF=37%</td>
<td>4.73</td>
<td>Normal</td>
<td>NA</td>
</tr>
<tr>
<td>7</td>
<td>QTc prolongation</td>
<td>Typical takotsubo, Pericardial effusion, EF=30%</td>
<td>0.28</td>
<td>NA</td>
<td>58%</td>
</tr>
</tbody>
</table>

ECG: electrocardiography, EF: ejection fraction, NA: not available