Characterising the Clinical Spectrum, Diagnosis and Outcomes in Secondary Stress Cardiomyopathy

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Introduction: Available literature on takotsubo cardiomyopathy excludes critically ill patients due to challenges in angiographic confirmation. Secondary stress cardiomyopathy (sSC) occurs in patients already hospitalised for other critical illnesses. Diagnosis of sSC is challenging, while clinical presentation and outcomes are significantly different from primary stress cardiomyopathy. Our aim was to better characterise the clinical picture of sSC. Methods: The diagnosis of sSC was confirmed based on characteristic clinical and morphological features, applying our diagnostic algorithm suited for critically ill patients. We were able to characterise these sSC patients and differentiate their presentation from takotsubo registry population. Data on selected patients was extracted manually on Microsoft Excel worksheets with relevant patient demographics, presenting features and outcomes. Results: We developed a profile of sSC based on 18 consecutive confirmed cases diagnosed at our university hospital between April 2016 and September 2018. sSC differed from takotsubo cardiomyopathy in several key clinical aspects – younger people may develop sSC (range 21–86 years) and men were more frequently affected in comparison to takotsubo cardiomyopathy (29%). Dyspnoea was noted in 22% of our patients and angina was rare. Apical ballooning occurred in only 33% of the patients, while mid (39%) and basal left ventricular (11%) variants accounted for half of the patients. Mortality was much higher (28%) due to underlying medical comorbidities. Conclusions: Our series illustrates significant clinical and morphologic differences in the presentation of sSC. Shifting the emphasis to serial echocardiography would reduce the need for invasive catheterisation and downstream comorbidity in critical care settings.
Due to these challenges in the available studies, systematic serial data defining the characteristics of patients with sSC and their prognosis, are largely lacking. This case series was our attempt to define the clinical and morphologic characteristics of patients with sSC.

Our group has been interested in the non-invasive diagnosis of SC for over a decade. Our echocardiography-based algorithm to diagnose sSC without requiring invasive catheterisation has been published elsewhere. In our 2017 review, we defined sSC as acute cardiac dysfunction developing during the course of hospitalisation for critical medical, surgical or neurological illness. The present single-centre experience of consecutive sSC cases was collected to gain a better understanding of its true clinical spectrum in a university hospital setting.

Materials and methods

For the purpose of this study, 26 consecutive patients with characteristic echocardiographic patterns of regional wall motion abnormalities noted by a single cardiologist, were included. The five patterns of echocardiographic patterns of regional wall motion abnormalities considered were: apical ballooning/hypokinesis associated with basal hyperkinesis, isolated mid-ventricular hypokinesis, isolated basal hypokinesis, focal hypokinesis, and biventricular dysfunction/global hypokinesia. Patients with wall motion abnormalities thought to represent a single epicardial coronary distribution were excluded. Since a significant proportion of these patients could not be taken to cardiac catheterisation due to underlying comorbidities, angiographic exclusion of CAD was not required to diagnose sSC. If a repeat echocardiogram obtained up to a few months later showed recovery of these wall motion abnormalities, then the diagnosis of sSC was made non-invasively. If a follow-up echocardiogram was not available, due to mortality within 30 days of hospitalisation, those patients were still included in the study.

A detailed algorithm representing the study design is presented in Figure 1. Data were collected retrospectively from the hospital’s electronic medical record system on the identified patients. We specifically collected demographic information, specifics of presentation, electrocardiograms, possible triggers, echocardiographic patterns of wall motion abnormalities and outcome data which primarily included in-hospital cardiac symptoms were not the primary reason for seeking medical care; catheterisation due to underlying comorbidities, angiographic exclusion of CAD was not required to diagnose sSC. If a repeat echocardiogram obtained up to a few months later showed recovery of these wall motion abnormalities, then the diagnosis of sSC was made non-invasively. If a follow-up echocardiogram was not available, due to mortality within 30 days of hospitalisation, those patients were still included in the study.

ESC = European Society of Cardiology; LV = left ventricular; pSC = primary stress cardiomyopathy; sSC = secondary stress cardiomyopathy.

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A total of 26 consecutive patients were initially included in this study; results this algorithm, all 18 patients with sSC were included in the study. One patient underwent catheterisation excluding CAD. With the application of the algorithm, all 18 patients with sSC were included in the study. Data are presented as n (%).

**Results**

A total of 26 consecutive patients were initially included in this study: 18 patients were diagnosed with sSC and 8 with pSC. All patients had critical illness on presentation to the hospital. The baseline characteristics are presented in Table 1. The average age of patients in our series was 61 years, ranging from 21 to 86 years. This sSC group had a significantly higher proportion of younger patients compared to pSC in the INTERTAK registry. Women were affected more frequently than men as traditionally quoted for patients with SC, although the proportion of men was higher. Key triggers for sSC in our group were cardiac arrest, ventricular tachycardia, ventricular fibrillation, pulseless electrical activity, respiratory failure, attempted suicide by hanging, intracranial haemorrhage, stroke, sepsis, surgery and motor vehicle accident. None of the patients in our series had previously documented left ventricular (LV) dysfunction.

In contrast to patients with pSC, the majority of patients in our series did not seek medical attention due to angina (Table 2). Dyspnoea was noted in some patients (22%) on presentation. Other patients presented with neurological, psychiatric, or non-specific symptoms. Electrocardiograms (ECGs) demonstrated a variety of changes including ST segment elevation (not meeting criteria for ST segment elevation myocardial infarction) or depression, QRS prolongation, atrial or ventricular tachy-arrhythmias. We also collected serial troponin T levels obtained during hospitalisation for all patients in the series (Table 3). In general, serum troponin level elevations were modest (<1 ng/mL) in most patients, without any significant upward or downward trend, in contrast to the classical peaking noted in acute coronary syndromes. This troponin trend further supported the absence of a plaque rupture event that may have initiated the decrease in LV function or wall motion abnormalities noted on echocardiograms.

The most common echocardiographic wall motion abnormalities noted were isolated mid ventricular hypokinesis and apical ballooning, occurring in 39% and 33% of the patients, respectively (Table 4). Other echocardiographic patterns were not as frequent. Only limited follow-up data was available in four patients because of in-hospital mortality. In two of these patients, follow-up echocardiograms showed normalisation of LV function with no residual wall motion abnormalities and cardiac catheterisation showed normal coronaries in one patient. One patient had a follow-up echocardiogram within 2 days of the first study which did not show improvement in cardiac function yet. Echocardiographic follow-up data in all other patients showed resolution of wall motion abnormalities, confirming the diagnosis of sSC as per our criteria. Not surprisingly, cardiac catheterisation data was only available in 28% (n=5) patients, and showed non-obstructive CAD or normal coronaries.

The average follow-up duration in our patient series was 7 months. Six (33%) patients died over the course of follow-up. Out of these patients, five (28%) died within 30 days and four (22%) died during hospitalisation. This underscores the significantly high mortality burden faced by these patients, likely due to underlying critical illnesses.

**Discussion**

A significant proportion of critically ill patients develop ECG, troponin, or echocardiographic abnormalities suggestive of SC during the course of their hospitalisation. Many of these patients meet the current definition of...
Table 4: The key clinical, morphological, imaging and outcome differences between primary and secondary stress cardiomyopathy

|                                      | Primary stress cardiomyopathy (data from the InterTAK Registry) (n=1,750) | Secondary stress cardiomyopathy (n=18) |
|--------------------------------------|--------------------------------------------------------------------------|----------------------------------------|
| Age range, years                     | 60–75                                                                    | 21–86 (average 61)                     |
| Male, n (%)                          | 179 (10)                                                                 | 5 (28)                                 |
| Female, n (%)                        | 1,571 (90)                                                               | 13 (72)                                |
| Angina, n (%)                        | 1,229 (76)*                                                             | 0 (0)                                  |
| Clinical picture                     | Acute angina, dyspnoea, ischaemic ECG changes – similar to acute coronary syndrome | Non-cardiac critical illness, neuro-psychiatric symptoms, non-specific symptoms |
| Echocardiographic regional wall motion abnormality patterns, n (%) | Apical ballooning 1,430 (82)                                          | Apical ballooning 6 (33)               |
|                                      | Mid ventricular 255 (13)                                                | Mid ventricular 7 (39)                 |
|                                      | Basal variant 39 (2)                                                    | Basal variant 2 (11)                   |
|                                      | Focal variant 26 (2)                                                   | Focal variant 1 (6)                    |
|                                      | Global hypokinesia 0 (0)                                               | Bi-ventricular/global 2 (11)           |
| Cardiac catheterisation, n (%)       | 1,750 (100)                                                             | 5 (28)                                 |
| Shock, n (%)                         | 170 (10)                                                                | 8 (44)                                 |
| Hospital mortality, n (%)            | 72 (4)                                                                  | 4 (22)                                 |

Data from InterTAK registry is used for primary stress cardiomyopathy. All percentages given have been rounded to whole numbers.

Figure 2: Morphologic variants in secondary stress cardiomyopathy in our series

Morphologic variants are expressed in percentages (%). n=18.

sSC, since they present to the medical setting without any major cardiac symptoms and develop abnormalities suggestive of SC during the course of illness. Given the presence of concomitant comorbidities and other acute medical issues that take precedence, many of these patients are not ideal candidates for cardiac catheterisation to exclude obstructive CAD or plaque rupture. Elevations in serum troponin in these patients may be related to a variety of causes like sepsis, shock, hypoxia, respiratory failure, intracranial haemorrhage, stroke and inotrope use, and appear to be an independent predictor of poor prognosis in these patients with sepsis. Even when such patients are diagnosed with SC based on current Mayo criteria, clinical course and outcomes should not be presumed to be similar to those predicted by currently available data. The characterisation of the clinical presentation and outcomes of sSC are therefore very relevant to clinicians taking care of these critically ill patients.

Our study highlights several features of sSC which appear to be different from the widely recognised takotsubo or pSC. It affects a higher proportion of younger patients and males. These patients commonly present without angina. Atypical patterns of wall motion abnormalities on echocardiography, especially the mid-ventricular variant, appear more common in sSC. Other forms, including basal hypokinesia and biventricular/global hypokinesis, also seem to be more common in sSC, whereas apical ballooning accounts for over 80% of pSC cases. It is also important to note that patients with sSC have a poor outcome with a 30-day mortality rate of 28% in our series. pSC could be complicated by hypotension, cardiogenic shock, dynamic outflow obstruction, malignant arrhythmias, or cardiopulmonary arrest with a 30-day mortality of 4%. The much higher mortality in sSC is likely due to underlying critical illness.

Overlap of several clinical features makes the differentiation of pSC and sSC difficult in some situations. As noted in our series, while some patients might have had a significant mental stress leading up to attempting suicide or from motor vehicle accident, by the time echocardiographic wall motion abnormalities were noted, these patients were already in the intensive care unit. Often, it is challenging to identify the primary problem. Some patients with cardiopulmonary arrest feature in this series because cardiac dysfunction was noticed in the intensive care unit post-resuscitation. However, there is no way to completely exclude the possibility of SC being the primary issue, leading to heart failure or arrhythmia that degenerates into cardiopulmonary arrest. History of angina just prior to the arrest, absence of underlying cardiac comorbidities or other significant metabolic derangements may suggest pSC in some of these instances.

While apical ballooning with anterior and apical wall motion abnormality may be challenging to differentiate from left anterior descending artery disease and acute coronary syndrome, the basal, mid-ventricular and bi-ventricular variants do not conform to a single coronary territory. This might play a crucial role in the early recognition of SC noninvasively, especially in those who do not present to medical attention for acute cardiac problems. For patients who have prolonged hospitalisation, follow-up echocardiograms showing resolution of regional wall motion abnormalities may be a reliable indicator of sSC. As noted in this small series, coronary angiograms in such patients typically showed absence of obstructive CAD or plaque rupture.
Although this study suggests several important differences in the presentation of sSC and pSC, large scale data are needed to confirm these findings and further characterise the entity of sSC. There is some room for bias since this is a single-centre experience with patients chosen by a single physician, although we have been publishing diagnostic methods on sSC over the last decade.\cite{sato1990,lyon2016} Given the complicated comorbidities typically associated with critically ill patients, coronary angiography should be considered as an additional diagnostic tool in a selected group of patients in whom the benefits of angiography outweigh the risks. It is also important to look at the trend of serum troponins during the course of illness, which may identify patients with type I myocardial infarction. This may avoid misclassification of patients who have resolution of wall motion abnormalities following revascularisation, or in the setting of myocardial stunning. Myocarditis should be considered in the differential in the appropriate clinical scenario and magnetic resonance imaging can be considered for additional non-invasive evaluation in this setting.

**Conclusion**

Our consecutive sSC patient series illustrates the significant differences in clinical presentation, morphological variants, age distribution and clinical outcomes in these patients. It also highlights the importance of serial echocardiography for diagnosis and management, since invasive catherisation is neither safe nor feasible for many such patients. sSC carries much a higher mortality risk. High clinical suspicion and non-invasive diagnosis may help optimise outcomes in these challenging patients. Serial data on larger patient populations with sSC are needed to definitively establish the clinical characteristics of this entity.

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