Seasonal variation in Takotsubo syndrome compared with myocardial infarction: ANZACS-QI 16

Jen-Li Looi, Mildred Lee, MSc, Corina Grey, Mark Webster, Andrew To, Andrew J Kerr

ABSTRACT

BACKGROUND: The incidence of myocardial infarction (MI) is characterised by seasonal variation, with a winter peak and summer trough. Takotsubo syndrome (TS) mimics MI, but is thought to have a distinct aetiology and may exhibit a reversed pattern of seasonal variation. This study investigated the seasonal variation in the incidence of TS in comparison to MI.

METHODS: Two hundred and sixty consecutive patients with TS (95% women, median age 66 years) admitted between March 2004 and December 2016 in the Auckland region of New Zealand were identified. The study population was grouped into three-month intervals (seasons) according to the date of admission to analyse for potential seasonal variations in the incidence. The TS cohort was compared with 36,376 patients who presented with acute MI in the Auckland region (40% women, median age 71 years) between March 2004 and December 2016.

RESULTS: The onset of TS differed as a function of season (p=0.02), with the events most frequent in summer (n=77, 30%) and least so in winter (n=46, 18%). In contrast, incidence of MI also varied by season (p=0.0003), with highest events in winter and lowest in summer.

CONCLUSION: The pattern of seasonal variation in TS is reversed compared with MI, with peaks during summer.

Several cardiovascular events, including acute myocardial infarction (MI), show well-defined temporal patterns in their occurrence throughout the year, which is characterised by a peak in winter and a trough in summer. Takotsubo syndrome (TS) is known as apical ballooning syndrome or stress-induced transient left ventricular dysfunction. TS closely mimics the presentation of MI. It is characterised by acute but rapidly reversible left ventricular (LV) dysfunction in the absence of obstructive coronary disease. TS was named on the basis of similarities between the appearance of the LV in systole and the round-bottomed narrow-necked Japanese fishing pot used for trapping octopuses. The condition tends to occur in postmenopausal women after a stressful event. The prevalence of TS is reported to be 1% to 2.5% in patients presenting with acute coronary syndrome (ACS) and 12% in women presenting with anterior ST-elevation myocardial infarction (STEMI). Thus, coronary angiography is necessary for definitive differentiation between TS and ACS. Despite its favourable long-term prognosis and low in-hospital mortality (1–3%), TS is not considered a benign condition because of the occurrence of life-threatening complications during the acute phase, related to haemodynamic instability (eg, acute heart failure and cardiogenic shock) in a substantial proportion of patients. Templin et al recently reported almost 22% of TS patients had serious in-hospital complications with rates equal...
to or higher than those of patients with ACS. They found that in-hospital death occurred more frequently among men than among women. Furthermore, TS patients also had severe complications, including ventricular tachycardia, ventricular thrombus and ventricular rupture.

The aetiology of TS is currently poorly understood but appears to be distinct from myocardial infarction. One line of evidence suggesting a distinct aetiology for TS is a possible reversed pattern of seasonal variation in presentation. Citro R et al recently reported a chronobiological pattern of onset of TS, with most events occurring during the morning hours and summer. Other studies subsequently reported a circadian (morning) and a seasonal (summer) higher frequency of TS. Two studies had previously demonstrated a different circadian pattern between TS and ST-segment elevation MI, suggesting that the two conditions do not share a common pathophysiology. There is no study to date comparing the chronobiological variations in the occurrence of TS and MI in the Southern Hemisphere, and there is little data on the seasonal variation in the occurrence of MI between men and women. Therefore, we aimed to investigate whether there is any difference between the seasonal variation of TS in comparison to patients who presented with MI.

Method
The TS study population was prospectively identified from three coronary care units in the public hospitals in the Auckland region (Middlemore Hospital, Auckland City Hospital and North Shore Hospital) between March 2004 and December 2016, and comprised 260 consecutive patients who fulfilled the diagnostic criteria of TS proposed by the Mayo Clinic group: transient hypokinesis, akinesis, or dyskinesis in the left ventricular mid segments with or without apical involvement; regional wall motion abnormalities that extend beyond a single epicardial vascular distribution; and frequently, but not always associated with a stressful trigger; the absence of obstructive coronary disease or angiographic evidence of acute plaque rupture; new ECG abnormalities (ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin; and (4) the absence of phaeochromocytoma and myocarditis clinical (age, gender, presentation, coronary risk factors), laboratory, electrocardiographic (ECG), echocardiographic and angiographic data of the study population were obtained at the time of the index admission. After TS diagnosis was made, clinical staff involved in the care of the patients (ie, nurses and doctors) made specific enquiry regarding possible stressors.

The MI comparison cohort comprised of all patients who presented to the three major public hospitals in the Auckland region with acute MI between March 2004 and December 2016. A total of 36,376 of patients (21,790 men and 14,586 women) with acute MI as the primary discharge diagnosis were identified (International Classification of Disease 10 (ICD10) code consistent with MI (I21x, I22x). Transfers (intra- and inter-hospital) were accounted for in each patient by bundling together all episodes of care that occurred within 24 hours of each other. The data was extracted for the All New Zealand Acute Coronary Syndrome Quality Improvement (ANZACS-QI) programme from the National Health Board (Ministry of Health) from the National Minimum Dataset, a national collection of public hospital discharge information collected by the Ministry of Health, New Zealand.

Chi-square goodness of fit test was performed to analyse for potential seasonal variations in the incidence of TS. To analyse the potential seasonal variations in the incidence of TS and MI, the study population was grouped into three-month intervals (seasons) according to the date of admission. Seasons were classified as December through February (summer), March through May (autumn), June through August (winter) and September through November (spring). The mean, minimum and maximum atmospheric temperatures (°C) were obtained from the Meteorological Service of New Zealand for the day each TS patient was admitted. TS patients were then grouped according to month of presentation and the monthly mean data calculated. The role of gender in the seasonal variations in the incidence of MI was also analysed.
Statistical analysis

Categorical data were summarised in terms of frequency and percentage. Continuous data were presented in terms of mean ± standard deviation, and median (inter-quartile range). For continuous variables, comparisons between groups were performed by the non-parametric Mann-Whitney U test as the data were not normally distributed. For categorical variables, Pearson’s chi-squared test was used. All P-values reported were two tailed and a p-value <0.05 was considered significant. Data were analysed using SAS statistical package, version 9.4 (SAS Institute, Cary, NC).

Access to the ANZACS-QI national ACS cohort is as part of the Vascular Informatics using Epidemiology & the Web (VIEW) research programme was approved by the Northern Region Ethics committee Y in 2003 (AKY/03/12/314) and by the national Multi-Region Ethics Committee in 2007 (MEC/01/19/EXP). The data for the TS cohort is obtained from the clinical audit investigating clinical features, prognostic predictors and outcomes of TS to assess the recurrence rates of TS, and was approved by the Health and Disability Ethics Committees (NTX/11/EXP/288).

Results

Clinical characteristics

The clinical characteristics of the TS and MI populations are summarised in Table 1. The median age of the TS population was 66 years (IQR 56–72 years). The majority of patients were women (n=247, 95%) and the majority of both cohorts were European. A stressful trigger (defined as an unusual emotional or physical stress occurring before symptom onset) was identified in 200 (77%); 118 patients had an emotional stressor and 82 patients reported a physical stressor (defined as medical conditions that trigger TS). Sixty TS patients had no identifiable stressor.

There were more men in the MI population (n=21,790, 60%, p<0.0001) in comparison to the TS population (Table 1) and the MI population was older than the TS population (median age 71 years, IQR 59–82 years, p<0.0001).

Seasonal variation in TS presentation

The onset of TS differed as a function of season (p=0.02, Figure 1), with the peak in summer (n=77, 30%) and the nadir in winter (n=46, 18%). In contrast, there was

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>TS (n=260)</th>
<th>MI (n=36,376)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13 (5.0)</td>
<td>21,790 (59.9)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Female</td>
<td>247 (95.0)</td>
<td>14,586 (40.1)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>63.9±11.9</td>
<td>70.0±14.7</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>66 (56–72)</td>
<td>71 (59–82)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Māori</td>
<td>41 (15.8)</td>
<td>2,795 (7.7)</td>
<td></td>
</tr>
<tr>
<td>Pacific</td>
<td>13 (5.0)</td>
<td>4,376 (12.0)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>15 (5.8)</td>
<td>3,429 (9.4)</td>
<td></td>
</tr>
<tr>
<td>European</td>
<td>191 (73.5)</td>
<td>25,776 (70.9)</td>
<td></td>
</tr>
<tr>
<td>Stressor on admission, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional</td>
<td>118 (45.4)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Physical</td>
<td>82 (31.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No stressor</td>
<td>60 (23.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TS, Takotsubo syndrome; MI, myocardial infarction; N/A, not applicable.
significant seasonal variation in the occurrence of MI compared to TS (p=0.0003, Figure 1) with more MI cases occurring in the winter quarter (28%) than the other seasons and least in the summer quarter (21%). Figure 2 demonstrates the average monthly temperature in Auckland region and the monthly incidence of TS during the study period. The temperature was lowest during June through August (winter) and was highest during December through March (summer and early fall).

Because TS occurs predominantly in women, we investigated the seasonal variation in MI in men and women separately. The seasonal variation was very similar for both sexes. (p=0.48, Figure 3).

To analyse for potential variation in the incidence of TS according to stressor types (physical stressor, emotional stressor and no stressor), the TS patients were grouped into three subgroups. The seasonal variation in TS incidence was similar for each stressor subgroup (p=0.7, Figure 4).

Figure 1: Seasonal variation in the occurrence of Takotsubo syndrome (TS) and myocardial infarction (MI).

Figure 2: The average monthly temperature (left y-axis, diamonds) in the Auckland region and the monthly incidence of Takotsubo syndrome (right y-axis, crosses).
Discussion

To our knowledge, this is the first study to date investigating the seasonal patterns of presentation of TS and MI in the Southern Hemisphere. The annual variation in TS with the highest incidence in summer is in contrast to the seasonal variation in MI incidence where winter was characterised by the highest frequency of cases in our cohort and is consistent with TS and MI being distinct pathophysiological entities. Overall, the clinical features of TS in our population were similar to the published studies in other areas of the world.18–21

Figure 3: Gender and seasonal variation in the occurrence of myocardial infarction (MI) compared with Takotsubo syndrome.

Figure 4: Seasonal variations in the incidence of Takotsubo syndrome according to type of stressor.
Prior reports from the Northern Hemisphere regarding seasonal variation in TS incidence are conflicting. While one previous Italian study (n=90) reported a summer preference for TS onset,\textsuperscript{12} other studies from the US (n=186), France (n=51), Italy (n=116) and Japan (n=107) did not confirm a consistent seasonal pattern.\textsuperscript{13,14,22,23} The major limitation of epidemiological studies on TS derives from the limited size of the populations. In our cohort, we are confident the diagnostic criteria for TS were consistently applied. An alternative case finding approach is to use large administrative datasets where there may be less diagnostic precision. It is, however, reassuring that our finding is similar to Aryal MR et al,\textsuperscript{24} who used an administrative dataset to identify 10,989 patients with TS in North America and reported that the peak of TS seems to be during Northern Hemisphere late summer months and early fall.

The reasons underlying this seasonal variation observed in TS are unclear. Various stressors in summer have been evoked.\textsuperscript{25} Although little is known regarding the seasonal variation in catecholamines, which are thought to be important in the aetiology of TS, several studies have reported a summer peak for norepinephrine and epinephrine excretion.\textsuperscript{26,27} Concentrations of urinary catecholamines have been shown to be higher even in healthy women during summer than in the other months, with a high within- and between-subject variation, not explained by menstrual cycle or behavioural, emotional or cognitive stress reactions.\textsuperscript{27} Chen et al previously described a case of heatstroke complicated by TS.\textsuperscript{28} Prolonged exposure to high ambient temperature resulting in an excessive high core temperature >40.5°C is a detrimental physical stress. An observational post-mortem study of fatal heatstroke revealed elevated levels of plasma catecholamines\textsuperscript{29} suggests that heatstroke and TS may share the same pathophysiology.

Presentation was preceded by a physical or emotional stressor in three quarters of our TS patients, but in the remaining quarter there was no identifiable pre-event stressor despite specific enquiry after the diagnosis was made. Our study found that the temporal variation in TS was similar regardless of the type of precipitating stress. This is consistent with one prior study.\textsuperscript{30}

A considerable amount of evidence shows that cardiovascular diseases such as acute myocardial infarction, acute aortic dissection and cerebrovascular accidents do not randomly occur along time, but seem to exhibit specific temporal patterns in their onset, according to time of day, month or season, and day of week, independent of gender.\textsuperscript{31–34} Data from the US Second National Registry of Myocardial Infarction reported 53% more cases of MI in the winter than in the summer, and winter was characterised by the highest frequency of fatal cases.\textsuperscript{35} Manfredini et al\textsuperscript{3,12} also confirmed this temporal pattern where the lowest frequency of MI onset was in the summer and the highest frequency during winter. Our study confirmed this temporal pattern in 34,483 cases of acute MI hospitalised between January 2005 and December 2013, demonstrating the highest frequency of MI cases during winter. Multiple factors might play a role in this seasonal variation in MI. The seasonal change in ambient temperature, with consequences on coagulation, blood pressure and endothelial function has been described as potential factors for the winter peak of MI.\textsuperscript{36} In addition, our study demonstrated that gender does not influence the variation in the incidence of MI, which is consistent with previous studies.\textsuperscript{31,32}

**Study limitations**

This was a retrospective study using a prospective analysis, and the results are limited by the relatively small number of TS patients, as we only included patients admitted to the major public hospitals in the Auckland region. However, this is the largest study in Australasia and one of the largest internationally to investigate the seasonal variation in TS onset. We are also the first study to date investigating the seasonal patterns of TS in the Southern Hemisphere demonstrating a reversed pattern in the incidence of TS in comparison to the Northern Hemisphere. We did not record the time of symptom onset in our database and so could not report on diurnal variation in onset. We were unable to assess the association between the onset of this syndrome and climate (i.e., temperature, atmospheric pressure and humidity) due to the relatively small number of TS patients. Analyses of meteorological or environmental phenomena potentially associated with TS...
such as temperature at the time of onset of TS, however, are difficult to perform, as the exact time of onset of the TS is often difficult to ascertain clinically. We have not assessed the variation in presentation according to the day of the week or by major recurring annual events such as public holidays. We also did not compare the role of gender in the temporal patterns of TS occurrence as there were only 13 men in the TS population.

Conclusion

There is seasonal variation in the incidence of TS with a peak in summer in comparison to the well-known winter peak of acute MI. Stressor patterns do not influence these temporal patterns of occurrence of TS. Further studies are needed to investigate the potential link between seasonal variation in TS onset and its underlying pathophysiologic mechanisms.

Competing interests:
Nil.

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