Chronobiology of Acute Aortic Syndromes

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KEYWORDS

• Chronobiology • Acute aortic syndrome • Aortic dissection • Aortic disease

KEY POINTS

- Acute aortic syndromes have a high morbidity and mortality, with the need for quick recognition and treatment.
- The chronobiology of acute aortic syndromes seems to mirror that of several other cardiovascular conditions, with a peak in the winter months and in the morning hours of the day.
- There are several proposed mechanisms for the pathobiology behind the unique chronobiology of acute aortic dissection, with differential circadian and seasonal effects playing a role in the vascular and endothelial milieu leading to the cascade that ultimately results in the acute aortic syndrome.

INTRODUCTION

Acute aortic syndromes, and particularly acute aortic dissection (AAD), are highly morbid conditions that require prompt diagnosis and management. Dissection of the thoracic aorta, especially the ascending portion, has an extremely high mortality, with a death rate of 1% to 2% per hour for the first 24 hours in patients who do not receive treatment.[1] In recent years, for those patients who survive to reach a hospital, the mean hospital mortality for AAD is still about 25%.[2]

Chronobiology is a field of medicine and biology that studies the presence of rhythms and their effects on physiology. Many cardiovascular conditions show rhythmic patterns, with notable peaks at certain points in the 24-hour day as well as weekly and seasonal variations. Previous studies have described these cycles in myocardial infarction,[3] stroke,[4] pulmonary embolism,[5] ventricular arrhythmias[6] and, more recently, takotsubo cardiomyopathy.[7] This issue outlines expert reviews on many of these conditions. Although several studies examined the chronobiology of AAD in the general population, further investigations are needed to discover its pathophysiology and how the risk for dissection in the population can be minimized.[8]

REVIEW OF THE LITERATURE

Several studies have examined AAD in relation to circadian and seasonal variation. The seminal article on this topic was from the International Registry for Acute Aortic Dissection (IRAD) consortium in 2002.[9] IRAD is the world's largest registry of AADs, and encompasses more than 45 international sites. In their 2002 article on the chronobiology of AADs, the IRAD group analyzed data from 689 patients for circadian rhythms and 932 patients for seasonal analysis. There was a higher frequency of AAD in the morning (6:00 AM to 12:00

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PM) as well as during the winter months (December 21 to March 20) in the general population, as seen in **Figs. 1** and **2**, respectively.[9] Moreover, data from the IRAD Registry also showed the lack of significantly different rates of clinical outcomes (including mortality) during the 24-hour and seasonal periods.[9]

In a separate analysis of the IRAD database, the presence of a winter peak in AAD occurred in both cold and warm climate settings, giving credence to the hypothesis that there was a specific seasonal influence on the incidence of AAD.[10] DeAnda and colleagues[11] analyzed data from hospitals in the Unites States and United Kingdom, compared with those in Argentina, Australia, and New Zealand, and found a winter peak of AAD in both the northern and southern hemispheres, further strengthening the hypothesis that there is a seasonal effect on incidence of AAD.

A recent meta-analysis found 42 studies and a total of more than 80,000 patients that reported on the chronobiology of AAD.[8] Ten studies including 58,954 patients were used in the analysis of seasonal distribution, 14 studies with 46,231 patients were used in the analysis of monthly distribution, 5 studies including 22,731 patients were used in the day-of-week analysis, and 7 studies with 1,695 patients were used for hourly distribution analysis.[8] Similar to the findings in most individual studies, the meta-analysis showed an increased incidence of AAD in winter, with a relative risk of 1.17 compared with all other seasons, and 1.33 compared with summer. Monthly meta-analysis showed that December had a peak in AAD, with a relative risk of 1.14 compared with other months. Weekly analysis of AAD showed an increased incidence on Mondays compared with all other days of the week, with a relative risk of 1.21. Circadian analysis of hourly variation in AAD, grouped by 6-hour intervals, showed a peak from 6 AM to noon, with a relative risk of 1.58 compared with the remaining intervals of the day.[8] **Fig. 3** shows a summary of these data from the meta-analysis.

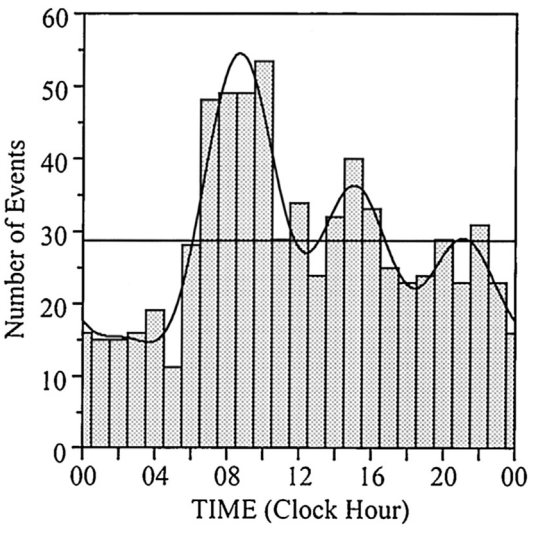

Fig. 1. IRAD data for circadian variation in onset of AAD. Histograms represent number of total events occurring in each hour of the day. Superimposed is overall best-fitting curve calculated by rhythm analysis, resulting from 4 significant harmonics with 24-hour, 12-hour, 8-hour, and 6-hour periods. (*From* Mehta RH, Manfredini R, Hassan F, et al, International Registry of Acute Aortic Dissection (IRAD) Investigators. Chronobiological patterns of acute aortic dissection. Circulation 2002;106(9):1112; with permission.)

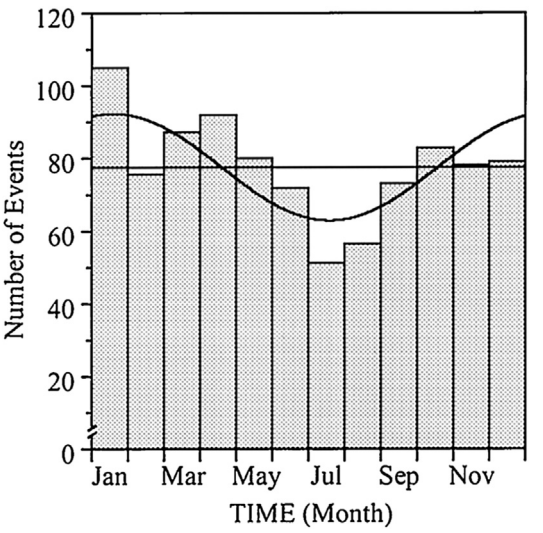

Fig. 2. IRAD data for seasonal variation in onset of AAD. Histograms represent number of total events occurring in each month of the year. Superimposed is overall best-fitting curve calculated by rhythm analysis resulting from single component with period of 8766 hours. (*From* Mehta RH, Manfredini R, Hassan F, et al, International Registry of Acute Aortic Dissection (IRAD) Investigators. Chronobiological patterns of acute aortic dissection. Circulation 2002;106(9):1113; with permission.)

A study combining patients with Marfan syndrome (MFS) from IRAD and the National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC) examined the chronobiology of AAD in patients with genetic conditions.[12] The aim of this study was to evaluate whether AAD in this higher risk population followed the chronobiological patterns seen in the general population, as described earlier. The results of this study included 257 unique subjects with MFS, and replicated findings similar to that of the general population. Specifically, this study