Chronobiology of Acute Aortic Syndromes

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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. In recent years, for those patients who survive to reach a hospital, the mean hospital mortality for AAD is still about 25%.

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, stroke, pulmonary embolism, ventricular arrhythmias and, more recently, takotsubo cardiomyopathy. 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.

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. 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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as well as during the winter months (December 21 to March 20) in the general population, as seen in Figs. 1 and 2, respectively. 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.

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. DeAnda and colleagues analyzed data from hospitals in the United 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. 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. 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.

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. 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

**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.)

**Fig. 3.** Shows a summary of these data from the meta-analysis.
showed that AAD was more likely in the winter/spring season (November–April) than in the other half of the year (57% vs 43%; \( P < 0.05 \)), and during the daytime hours, with 65% of dissections occurring from 6 AM to 6 PM (\( P < 0.001 \)). Therefore, despite having a genetic predisposition to aortic aneurysms and dissection, the MFS population reflects a chronobiology of AAD that is similar to that of the general population.\(^{12} \)

**PROPOSED PATHOPHYSIOLOGY**

The cardiovascular system shows multiple levels of chronobiologic variation, including arterial blood pressure, heart rate, vascular tone, coagulation, and fibrinolysis.\(^{13} \) **Fig. 4** shows the various possible modulators of this chronobiological pattern.\(^{14} \) Chronobiological patterns in other diseases and organ systems may shed light on how daily and seasonal variations alter disorders and physiology. The most frequently studied and understood chronobiological rhythm is the circadian rhythm, a 24-hour cycle that is regulated by multiple internal and external cues (zeitgebers).\(^{15} \) Light is the most significant zeitgeber, and regulates various physiologic effects through its action on the suprachiasmatic nucleus of the hypothalamus. Important in this system are various neurohormonal regulators of the cardiovascular system, including melatonin,\(^{16} \) aldosterone, glucocorticoids,\(^{17} \) catecholamines,\(^{18} \) and growth hormone.\(^{19} \) Through these mediators and others, the activity of multiple genes throughout the body and cardiovascular system is regulated.\(^{20} \)

The genes implicated in this regulatory mechanism include clock, casein kinase 1ε (\( CK1 \varepsilon \)), period (\( per1, per2 \)), arntl (\( bmal1 \)), rev/erb-a, and cryptochromes.\(^{21} \) None are known to interact specifically with fibrillin-1 or the transforming growth factor beta signaling pathway, which are particularly involved in the pathophysiology of MFS.

**Fig. 3.** Meta-analysis of available studies regarding AAD showing relative frequency of AAD with average variation (99% CI) by (A) season, (B) month, (C) day of week, (D) hour. (From Vitale J, Manfredini R, Gallerani M, et al. Chronobiology of acute aortic rupture or dissection: a systematic review and a meta-analysis of the literature. Chronobiol Int 2015;32(3):385–94; with permission.)

**Fig. 4.** Concurrent pathophysiologic mechanisms underlying circadian variation of aortic rupture or dissection. BP, blood pressure; coag, coagulation; HR, heart rate; PAI-1, plasminogen activator inhibitor-1; tPA, tissue plasminogen activator. (From Manfredini R, Boari B, Gallerani M, et al. Chronobiology of rupture and dissection of aortic aneurysms. J Vasc Surg 2004;40:385; with permission.)
Important mediators of these circadian effects on the cardiovascular system include the activity of multiple enzymes, like the matrix metalloproteinases (MMPs) and tissue inhibitors of matrix metalloproteinases (TIMPs). These enzymes are thought to play a role in the changes seen in the aortic wall during the development of aneurysms and before dissection.22 Various members of the MMP and TIMP families, as well as genes regulating collagen, have recently been identified as being controlled by circadian clock genes.23 No data are available regarding a possible temporal variation of MMP and TIMP, with the exception of patients with ocular diseases, such as corneal erosions and ulceration.24 Concentrations of MMP-9 in the tears are negligible during the day and completely inhibited by TIMP-1 but, on awakening, MMP-9 shows a 200-fold increase, so it cannot be completely inhibited by TIMP-1.24 In addition, studies have shown associations between variation and increases in blood pressure, heart rate, vascular tone, platelet aggregability, and hematocrit, leading to altered plasma viscosity and the incidence of cardiovascular events.3,13 Fig. 4 shows some proposed mechanisms that could be involved in this circadian pattern of AAD.

Seasonal rhythms are also important in the incidence of various physiologic and pathophysiologic conditions. In the cardiovascular system, multiple studies have established that there is a clear seasonal pattern to the incidence of coronary events25 and acute myocardial infarction.26 Similarly, recent work has described seasonal changes in protein expression patterns associated with the immune system.27 Although the pathophysiology of the increase in cardiac disorders in the winter months is not clear, there are several plausible hypotheses. Hematological changes in platelet and blood viscosity have been thought to be possibly associated with the weather, which in turn could affect the forces acting on a vulnerable aorta that could lead to an AAD.28

SUMMARY

Retrospective and registry-based studies have shed some light on the chronobiology of AAD. Individual studies, like the original IRAD study, along with a large meta-analysis of all available studies have shown that AAD seems to share a similar chronobiology to many other cardiovascular maladies. Specifically, there is an increased incidence of reported AAD during the morning hours (6 AM–12 PM), as well as in the winter months. Although the pathobiology behind these chronobiological patterns is not well elucidated, the interaction of various internal cues and clocks along with changes in seasonal and circadian environments seem to lead to a predilection for AAD. These insights are important clinically because they may help inform therapeutic decisions about medication dosing and timing, as well as shedding light on possible targets of intervention to prevent this catastrophic event.

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