Aortic Aneurysm Disease – Make Room for Chronobiology

Running Head: Aortic aneurysm chronobiology

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ABSTRACT

Background

Aortic Aneurysm (AA) is a common atherosclerotic condition, accounting for nearly 6,000 deaths in England and up to 175,000 deaths globally each year. The pathological outward bulging of the aorta typically results from atherosclerosis or hereditary connective tissue disorders. AAs are usually asymptomatic until spontaneous rupture or detected on incidental screening. 8 in 10 patients do not survive the rupture and die either before reaching hospital or from complications following surgery. Similar to other cardiovascular pathologies (CVPs), AA is thought to be subject to chronobiological patterns of varying incidence.

Methods

We performed a literature review of the current literature to evaluate the association between circadian rhythms, seasonal variations, and genetic factors and the pathogenesis of AA, reviewing the impact of chronobiology.

Results

The incidence of AA is found to peak in the early morning (6 AM – 11 AM) and colder months, and conversely troughs towards the evening and warmer months, exhibiting a similar pattern of chronobiological rhythm as other CVPs such as myocardial infarcts, or cerebrovascular strokes.

Conclusion

Literature suggests there exists a clear relationship between chronobiology and the incidence and pathogenesis of ruptured AA; incidence increases in the morning (6am - 11am), and during colder months (December – January). This is more pronounced in patients with Marfan Syndrome, or vitamin D deficiency. The underlying pathophysiology and implications this has for chronotherapeutics, are also discussed. Our review shows a clear need for further research into the chronotherapeutic approach to preventing ruptured AA in the journey towards precision medicine.

INTRODUCTION

Aortic Aneurysm (AA) is one of the most common atherosclerotic conditions affecting patients worldwide. It accounts for approximately 6,000 yearly deaths in England, with 4% of men aged 65 to 74 suffering from AA.[1] It causes up to 175 000 deaths globally per year, accounting for 1% of deaths in male patients over 65 years of age.[2] Approximately 8 in 10 patients do not survive the attack of rupture of AA and die either before reaching the hospital or they do not survive the surgery and complications.[3] The aetiology of disease involves blood vessel dilation, including swelling of the aorta. The aneurysms differ in sizes and growth rate, but the large ones are usually bigger than 5.5cm and grow around 2mm per year.[4]

In this paper we will review the current literature available around the topic of periodicity and recurring changes affecting the AA and we will investigate different methods of reducing the risk of developing AA and reducing the risk of its rupture. We will specifcially focus on the developing area of sciences and medicine, the chronobiology, that studies the influence of time and seasonal changes on the various processes in biology.

AORTIC ANEURYSMS

There are a few classification systems for AA, the first one simply stating which part of the aorta is affected (abdominal, thoracic). The other one is the Stanford classification which discerns type A and type B aneurysms. Type A affects the ascending aorta and accounts for over 60% of cases.[5] It may often result in incompetence of the aorta, cardiac tamponade, or occlusion of coronary arteries, with surgical management then being usually required. Type B AA involves distant

parts of aorta including the descending aorta, and its prevalence reaches around 40% across all AA cases – this usually managed non-surgically and requires tight blood pressure control. The other division is the DeBakey's classification into three types. Type I affects both ascending and descending aorta, type II involves ascending aorta only, and type III involves the descending aorta only.[6] These classifications are useful for categorizing the localization and origin of aneurysms. On the contrary to aortic dissections, when around 40% of patients die immediately with the hourly mortality rate of 1-2% if ascending aorta is involved,[7] the aneurysm itself does not pose a major threat to life if it is well-controlled and detected early; its rupture would typically present acutely.[8] The symptoms are often non-specific but involve sudden onset of sharp and severe pain in the abdominal area, feeling clammy and sweaty with the pain, and feeling breathless or losing consciousness.[4] These are usually a result of severe blood loss and need to be managed immediately by the surgical team.

Some factors increase patients' prevalence of AA and most of them, apart from the genetic background and family history, can be managed on a daily basis. These risk factors include smoking, high cholesterol, and history of hypertension.[3] One of the genetic conditions predisposing for AA is Marfan Syndrome, a condition affecting elastin fibers and fibrillin, influencing the composition of connective tissue.[9] This, in turn, directly influences the elasticity of the blood vessels and their compliance. In such cases, there is an increased risk of aortic bulging or enlargement, hence increased risk of aneurysm's burst.

CHRONOBIOLOGY

Chronobiology is the study of biological rhythms and periodic changes in living organisms. There are various levels of expertise on types of chronobiology in medicine, but all of them are particularly concerned with circadian changes. The 3 sectors of medical chronobiology are: occurrence and severity of symptoms, affected by 24-hour periods; diagnostic procedures and tests influenced by episodic changes; and effects of specific medical treatments.[10] The field of chronobiology allows for pattern recognition in clinical practice. There are various suggestions and proposals going forward about how the statistical analysis of circadian changes could affect the laboratory work and results interpretation, but also how chronotherapeutics might influence the outcomes of pharmacotherapy in patients with long term conditions.[11]

This specific branch of chronobiology discovers the timely variation and manifestation of diseases and the individual differences in treatment effectiveness when it comes to drug treatment. Chronobiology is divided into even more areas of expertise, including chronopathology, the studies of disruption of timely biological processes and its influence on the patient's condition, as well as the chronophysiology of systems, such as the circadian and seasonal changes in the cardiovascular system, affecting AA rupture.

Various researchers have looked into the incidence of AA and its relation to the time of the day. The study of 91 consecutive inpatients with spontaneous rupture, by Manfredini et al. has concluded that there were 2 daily peaks of abdominal AA, at 8AM and 8PM, p= <0.001.[12] The single-center study by Gallerani et al, assessing 67

cases, used analysis of variance to show a significant pattern ($p<0.001$), showing an increase in cases of thoracic AA twice a day, at 10AM and 8PM.[13] A multi-centre analysis by the International Registry of Acute Aortic Dissections, investigating 547 patients, has published data proving the hourly peak between 8AM and 9AM in cases of thoracic AA, including various subgroups examined, such as male and female patients, type A or B dissections, and across various age groups.[14] In addition, the study by Sumiyoshi et al. analysed data from 312 cases (214 males) from three institutions, comparing younger (≤60 years) and older (≥61 years) subjects. The results showed the significant difference from an even distribution ($p=0.042$), with occurrence of two peaks during the course of a day – primary in the morning between 8AM and 11AM, and secondary in the evening between 5PM and 7PM.[15]

Some studies have shown that the burst of AA is influenced by the circadian rhythm of the body as well as some other seasonal changes. As most of the aneurysms are reported to burst in the morning, it is a proof of association with circadian rhythm and chronobiology. These two concepts state the correlation between specific biological processes affected by rhythmicity over a period of time, with circadian rhythm influencing the wake and sleep cycle. The pattern of increased frequency of AA, ischaemic and haemorrhagic strokes, pulmonary embolism, or acute myocardial infarction cases in the morning hours, may suggest a common origin of the factors triggering the incidents. Some of the pathophysiological events of early morning are an increase in blood pressure, heart rate, sympathetic vascular activity, and vasoconstrictive hormones. These in turn, can affect the prothrombotic tendency, viscosity of plasma, and haematocrit, which might be negatively affecting the

underlying cardiovascular pathologies.[16] The previously mentioned factors, such as increased sympathetic activity and increased shear forces, hypercoagulability, and hypofibrinolysis, lead to weakening of the aortic wall. In addition, with underlying artheroscleroses, or genetic conditions, this may increase the risk of AA rupture.

EFFECT OF CIRCADIAN RHYTHMS ON THE PATHOGENESIS OF AORTIC ANEURYSM

Circadian rhythm provides an internal body system of sleep and wake cycle, and control of homeostatic physiology. This pattern is primarily affected by the external light changes, radiation, or temperature, and aims to adapt to the surrounding conditions. The central nervous system functions as the control of the circadian rhythm, and its pacemaker is the suprachiasmatic nucleus in the hypothalamus.[17]

The control works via release of molecules that work via positive and negative feedback loops to influence the cellular function. 'Clock genes' such as *BMAL1, BMAL2*, *CLOCK*, *CRY1*/*CRY2,* are able to regulate the transcription and translation to allow for identification of time and adjustment of activities and functions in the organism. The study of Floras has uncovered a pattern of the blood pressure increase before awakening in young people, and increase with first physical activities in the morning in the elderly[18] with some studies emphasising the heart rate increase on awakening.[19] Another interesting point is the morning increase of blood noradrenaline and renin levels, both of which can induce coronary vasoconstriction,[20] alongside the alpha-sympathetic vasoconstriction activity increase in the morning[21] and its relation to alpha-sympathetic vasoconstrictor activity. On the other hand, the plasma cortisol secretion variations, dependent on circadian rhythm, provide the

highest levels of the hormones on awakening and make the arterial vessels more prone to alpha-sympathetic vasoconstrictor activity.[22] Another theory for the peak of AA ruptures in the morning hours, is the morning imbalance between the coagulation and fibrinolytic properties of blood. As previously mentioned, there are increased levels of fibrinogen, increased plasma viscosity and haematocrit, and platelet aggregability, that lower the fibrinolytic activity. The increased viscosity of the blood increases the sheer forces on the aortic wall which, with the additional strain of underlying genetic conditions or atherosclerosis, may be under too much pressure and begin to rupture, causing acute AA.[23]

The above evidence may suggest that the homeostatic systems are not capable of protecting the organism in the same competent way for the whole day, and that there might be specific, more vulnerable periods of the day or even the year. This concept might be supported further by the theory of chronorisk, the distribution of risk of an event occurrence within different periods of the day, month, or year. Hence, the underlying conditions' treatment could be further supported by chronotherapeutic approach, when patient's medicine regimen is tailored to the most susceptible periods of the day. For example, hypertensive patients may experience wide fluctuations of blood pressure levels throughout the day, which has been proved by a number of 24-hour blood pressure monitoring systems.[23] Hence, some of the short-acting hypertensive agents are not recommended, and a long-acting treatment would be more suitable. For some medicines, such as long-acting calcium antagonists, the morning administration may not control the late night to early morning blood pressure variations. According to chronotherapeutics, the lower doses of drugs should be administered at the times of the day when the risk of developing symptoms or

relapses of long-term conditions, is the lowest. It is important to bear in mind when prescribing certain medications, that the increase in frequency may also cause pathological hypotension in the elderly, and this should be avoided. There are many variations to be considered when prescribing antihypertensive medications, but hypertension is only one of the conditions that affect the AA. The tailoring of medicines specific to patient's condition and long-term disorder may further be developed and supported by the field of personalized medicine.

EFFECT OF SEASONAL VARIATIONS ON THE PATHOGENESIS OF AORTIC ANEURYSM

Variations in the patterns of AA disease occur not only with circadian rhythms, but also according to the time of year in regions with distinct seasons (summer/winter). Contemporary studies argue that the complex interplay between environmental provocations (ambient climate, temperature, sunlight exposure, and atmospheric pressure), and the behavioural and physiological responses thereto, lead to distinct seasonal patterns in de novo and secondary cardiovascular events, including AA rupture.[12]

Various contemporary studies have documented increased incidence of AA rupture during winter seasons compared to a lower incidence thereof in warmer, summer months. These are summarised in Table 1. Ballaro et al. evaluated 19,599 deaths from ruptured abdominal (rAAA) in England and Wales between January 1991 and December 1995.[24] Cosinor analysis showed that across all age groups and sexes, there was a markedly greater incidence of fatal rAAA in October, December, and January, than in June and July ($p = 0.003$ across all deaths). Incidence was found to

be highest in December (n > 18,000), and lowest in June (n < 14,000). This large nationwide study is reliable and indeed benefits from a large sample size and statistically significant outcome.[24] A single-centre study by McCarthy et al. found that, between January 1991 and December 2000, admissions (on average) for rAAA at the Leicester Royal Infirmary (UK) peaked in December and troughed in August. Of 223 confirmed cases of rAAA, 14% (n=35) of patients were admitted in December, whereas 5% (n=11) were admitted in August. Notably, admissions for rAAA in October, November, and January were also found to exceed that of June, July, and August.[25] A similar single-centre study by Manfredini et al. evaluated 85 cases of thoracic AA referred to St Anna Hospital, Ferrera, Italy, between January 1985 and December 1996.[26] Cosinor analysis demonstrated a peak in referrals in January (n=15), and a trough in July (n=0). Despite the relatively small sample size, across both sexes and all age groups, the observed seasonal trend was found to be statistically significant (p =0.032).[26] Furthermore, a meta-analysis by Wu et al. that included 24 studies examining the seasonal variations of rAAA incidence, and 38,506 cases in total, demonstrated that pooled rAAA incidence in the winter exceeded that of summer (p=0.04). 26% of cases occurred in winter, compared to 23% in summer. A further 25% occurred in spring, and 26% in autumn.[27] Similar trends have also been observed in incidence of acute aortic dissection (AAD), a known clinical consequence of AA. Kumar et al. used a nationwide inpatient database to evaluate hospital admissions for AAD between 2004 and 2011 in the US. It was found that out of a total 89,365 admissions for AAD, 26.5% occurred in the winter, 26.4% in autumn, 24.6% in spring, and 22.4% in summer (p < 0.0001). Mean admissions peaked in January and troughed in July, and mean winter admissions exceeded that of summer across age, gender, and hypertension status.[28]

It is useful to consider statistics surrounding AAD in conjunction with rAAA as the pathogeneses of both conditions are similar, hence are possibly affected by chronobiological influences in a similar way.[29]

The seasonal variations in onset of acute AA rupture and dissection are therefore clear, and there has been much speculation on what factors drive the seasonality of ruptured AA. Of key interest are the effects of ambient temperature and climate, atmospheric pressure, and vitamin D. Colder ambient temperature is known to elicit peripheral vasoconstriction and shivering as primary thermoregulatory responses. Peripheral vasoconstriction serves to minimise dermal heat loss while shivering increases endogenous thermogenesis.[30] Because both responses are mediated by increased sympathetic tone, there is an established association between colder ambient temperature and increased heart rate and blood pressure. In addition, acute exposure to low temperatures is known to cause increased platelet activation and haematocrit, as well as decreased relative nitric oxide bioavailability.[31] A study by Radke et al. investigated seasonal haemodynamic changes and reported that plasma aldosterone, noradrenaline, adrenaline, and renin increased by 59%, 19%, 2% and 17% respectively from summer to winter.[32] Further experimental data has shown that acute exposure to 10ºC air for 120 minutes in healthy male volunteers can cause an increase in serum noradrenaline from 4.5 to 6.4 nmol/L.[33] It is therefore reasonable to suggest that the physiological responses to colder ambient temperatures may well predispose patients with a weakened aortic wall (due to pre-existing genetic and acquired disorders) to aneurysm rupture or dissection. Elevated blood pressure, heart rate, vasoconstrictive mediators, and haematocrit possibly augment sheer forces exerted on the aortic intima, thereby precipitating aneurysm

rupture or dissection.[28] Additionally, Manfredini et al. argue that seasonality in aortic dissections is enhanced by the protective effect of warmer ambient temperature on the aortic intima - patients are noted to have significantly lower blood pressure values in the summer than winter (regardless of antihypertensive medications); a similar view could be taken for AA.[12]

Conversely, there is data to suggest that individuals acclimatised to colder ambient temperatures are less susceptible to cardiovascular seasonality. Indigenous peoples with traditional ways of living have been demonstrated a greater ability to withstand colder temperatures. Cold acclimatisation due to physiological habituation, higher basal metabolic rate, and more rapid localised vasoconstriction is associated with decreased rates of harmful consequences due to cold weather.[34] Therefore acclimatisation potentially negates an extensive physiological response to cold ambient temperature. This is supported by data from a study into thyroid physiology, which found that exposure to moderate cold (4ºC) for 1 hour elicits increased blood pressure, aldosterone, cortisol, and noradrenaline only when subjects wore summer clothing, but not when subjects were insulated with winter clothing.[35]

In addition to changes in ambient temperature, seasonal change in atmospheric pressure has also been proposed as a contributing factor towards the seasonality of AA rupture.[25] However, studies suggest there exists no statistically significant relationship between atmospheric pressure and risk of AA rupture. McCarthy et al. noted that although the monthly admission rate between January 1991 and December 2000 seemed to be inversely associated with the monthly mean atmospheric pressure, this relationship was not statistically significant ($p=0.069$, $r^2 =$

0.37).[25] Similarly, Kurtoglu et al. noted that the association between rAAA admissions and mean atmospheric pressure between January 1995 and May 2003 in Istanbul, Turkey was not statistically significant. Although admissions for rAAA peaked in December, when mean atmospheric pressure was notably higher than that of May, the monthly distribution of rAAA admissions was not statistically significant ($p > 0.05$).[36] It is worth noting, however, that both McCarthy et al. and Kurtoglu et al. were both single-centre studies that used a relatively small sample size (223 and 24 cases of rAAA, respectively). Additionally, both Sterpetti et al. and Upshur et al. reported no evidence of rAAA seasonality being driven by atmospheric pressure.[37, 38] Perhaps larger-scale studies may help elucidate further any relationship between atmospheric pressure and AA rupture.

Yearly changes in vitamin D levels have also been explored as a factor in rAAA seasonality. Vitamin D deficiencies are a well-established consequence of decreased exposure to UV light in high-latitude countries, especially during winter months. Notably, vitamin D deficiency (<10 ng/mL) has a prevalence of approximately 80% in Mongolia during the winter, compared to only around 4% during summer months.[31] Indeed, there exists an established link between vitamin D deficiency and the risk of developing cardiovascular diseases. Vitamin D is thought to be cardioprotective by down-regulating pro-inflammatory mediators (e.g. TNF-a, IL-6, CRP, and COX-2), decreasing RAAS activity, and improving glucose sensitivity. Additionally, vitamin D deficiency seems to up-regulate aortic sclerostin (a clinical marker of vascular disease).[39] Vitamin D deficiency may therefore heighten ongoing deleterious processes occurring within the aortic wall in individuals at risk of AA: an in vivo study has demonstrated that vitamin D deficiency in mice promotes the

development of rupture-prone, large AA, which appeared to chiefly be mediated by up-regulation of sclerostin. Interestingly, the same study noted that administration of cholecalciferol in vitamin D-deficient mice seemed to limit the growth and rupture of established AA.[40]

GENETICS AND CHRONOBIOLOGICAL VARIATIONS IN AORTIC ANEURYSM

Having explored the mechanisms and implications of chronobiological rhythms on the pathogenesis of AAA, it is worth evaluating whether there exists a link between genetic aetiologies of AA and chronorisk. Genetic mutations affecting proteins of the aortic medial extracellular matrix (ECM) have been shown to be strongly associated with familial trends in AA. For example, Brownstein et al. highlight that mutations in *FBN1, TGFBR1, TGFBR2,* and *SMAD3* account for up to 14% of cases of familial thoracic AA, and Keramati et al. note that over 20% of thoracic AA cases are the direct result of inherited monogenic disorders.[41,42] Of particular interest is the role of *FBN1* in AA pathogenesis. Mutated *FBN1* leads to expression of dysfunctional fibirilin-1, resulting in autosomal dominant connective tissue disorder Marfan Syndrome (MFS).[41] Up to 75% of MFS cases are thought to be inherited, and the majority of MFS patients exhibit a dilated aortic root with medial degeneration and elastic fibre fragmentation.[43] Further, Keramati et al. noted that 12 relatives of their index patient were found to have non-syndromic thoracic AA, with *FBN1* strongly suggested to be the causative gene.[42] Hence, considering AAD has long since been recognised as the leading cause of death in MFS, it would be appropriate to determine whether there exists an association between *FBN1* mutations and circadian/seasonal rhythms. Siddiqi et al. used data from IRAD and the Genetically Triggered Thoracic AA and Cardiovascular Conditions (GenTAC) register to examine

circadian and seasonal trends in AAD incidence in MFS patients. Across 257 patients with MFS that suffered AAD between 1980 and 2012, it was found that AAD incidence was significantly higher during the colder seasons (57%) than the warmer seasons (43%) (p=0.05), and that the majority (65%) of dissections occurred between 6AM and 6PM (p=0.001).[43] Indeed these findings are broadly in line with those discussed previously, where MFS has not been a factor taken into consideration, and indeed the study benefits from being multi-centre, database-wide and from having a relatively large sample size. Siddiqi et al. also note that there seems to be no direct interaction between genes involved in regulating the circadian rhythm and the expression of fibrillin-1 (or indeed TGF-β and SMAD2 pathways, which also play a role in the pathogenesis of AA and dissection).[43] Therefore, it is reasonable to hypothesise that MFS patients reflect the same chronobiological patterns in aortic dissection and aneurysm as the general population because expression of fibrillin-1 is not itself modulated by circadian or seasonal factors. Rather, it seems that the same circadian and seasonal factors that increase risk of AA in the general population simply further increases the risk of genetically triggered AA. Data from both Siddiqi et al. and Keramati et al. underscores the importance of AA screening and cardioprotective therapy to both identify non-syndromic AA and improve clinical outcomes.[42,43]

FUTURE MANAGEMENT STRATEGIES

Circadian and seasonal rhythms play a clear role in triggering the rupture of AA. Since chronobiological factors seem to have no effect on the prognosis of ruptured AA, chronotherapeutics should focus on prevention, rather than post-event treatment.[44] Research into the therapeutics of cardiovascular circadian rhythms

suggests that targeting the implicated circadian mechanisms to reduce the risk of cardiovascular events during vulnerable periods is a promising approach.[45] Attenuating surges in blood pressure, heart rate, and coagulability may indeed mitigate the risk of triggering aneurysmal rupture in the morning. Studies have revealed that the time of administration of beta-blockers, ACE-inhibitors, calcium channel blockers, and aspirin may enhance or mitigate their effect in regulating the aforementioned triggers.[45] These are outlined in Table 2.Therefore, it seems the risk of morning AA rupture can be reduced by adjusting dosing times for patients already prescribed the above therapies; pharmacological prevention would be rendered when the patient is at greater risk of rupture.[45] This, along with preventing vitamin D deficiency, could also reduce the risk of AA rupture in the winter: the long-term benefits of a chronotherapeutic approach would be felt throughout the year, and would also protect against the aforementioned harmful effects of the physiological responses to cold weather.

CONCLUSION

The findings of our investigation into the chronobiological influences on ruptured AA has revealed several key points, outline in Table 3. Multiple studies have shown that there exist statistically significant circadian and seasonal variations in the incidence of ruptured AA – incidence is notably higher in the morning (6AM – 11AM), and during colder months (Dec-Jan).[12] The suggested pathophysiological basis for the circadian and seasonal variations in rAAA incidence implicates mainly increased blood pressure, heart rate, haematocrit, and coagulability, which augment sheer forces exerted on the typically already weakened aortic intima.[22, 23, 28] These factors are particularly pronounced in the morning due to physiological surges in

sympathetic activity and catecholamine release.[22, 23] The physiological response to colder climate leads to similar effects, and are often coupled with vitamin D deficiencies.[31] Following our analysis of the chronobiology of AA rupture, it is clear that a chronotherapeutic approach may well benefit affected patients. This could involve adjusting dosing times of medications such as beta blockers, calcium channel blockers, ACE-inhibitors, and aspirin, such that their effect is strongest when the patient is most vulnerable.[42] As a result, this paper recommends further research into the chronotherapeutic approach to managing ruptured AA.

HUMAN STUDIES

No ethical approval required as no patient identifiable information involved.

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