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Chronobiology in Aortic Diseases – "Is This Really a Random Phenomenon?"

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ABSTRACT

Although acute aortic rupture or dissection is relatively uncommon, it ranks in third position among necropsy-confirmed causes of out-of-hospital sudden death in the general population. Similar to other acute cardiovascular events (e.g., acute myocardial infarction, sudden death, stroke, and pulmonary embolism) there is a growing body of evidence regarding temporal patterns in onset, characterized by circadian, seasonal and weekly variations for aortic aneurysms. On one hand, it is possible that these cardiovascular diseases share common underlying pathophysiologic mechanisms, e.g., increase in blood pressure, heart rate, sympathetic activity, basal vascular tone, vasoconstrictive hormones, and prothrombotic tendency.

On the other hand, the possibility exists that the connecting link is an internal disruption (dyssynchrony) of some molecular mechanisms intrinsic to the peripheral biological clock (that of cardiomyocyte is the most widely investigated). Such disruption may contribute to cardiovascular disease and biological rhythms – an intriguing hypothesis for future research.

Why speculate about timing and aortic aneurysms?

The answer to this simple and essential question may be found in the following paragraph originally reported by Leonard in the British Medical Journal,[1] and a couple of decades later cited also by Hagan et al.[2] in the presentation of the International Registry of Acute Aortic Dissection (IRAD):

> On 25 October 1760 George II, then 76, rose at his normal hour of 6 AM, called as usual for his chocolate, and repaired to the closet-stool. The German valet de chambre heard a noise, memorably described as 'louder than the royal wind", and then a groan; he ran in and found the King lying on the floor, having cut his face in falling. Mr. Andrews, surgeon of the household, was called and bled his Majesty but in vain, as no sign of life was observed from the time of his fall. At necropsy the next day Dr. Nicholls, physician to his late Majesty, found the pericardium distended with a pint of coagulated blood, probably from an orifice in the right ventricle, and a transverse fissure on the inner side of the ascending aorta 3.75 cm long, through

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Abbreviations and Acronyms

BP = Blood pressure

IRAD = International Registry of Aortic Dissection

MI = Myocardial infarction

MMPP = Matrix metalloproteinase

PE = Pulmonary embolism

SCD = Sudden cardiac death

SCN = suprachiasmatic nucleus

TIA = Transient ischemic attack

TIMP = Tissue inhibitors of matrix metalloproteinase

which blood had recently passed in its external coat to form a raised ecchymosis, this appearance being interpreted as an incipient aneurysm of the aorta.

Beyond King George's anedoctal report: Early morning and abrupt onset of aortic diseases: is it only a coincidence?

The cardiovascular system is organized according to a specific temporal order that is oscillatory in nature, and most normal cardiovascular functions exhibit circadian changes. Such predictable-in-time differences in the physiological status of the cardiovascular system give rise to rhythmic variations in the *susceptibility* of human beings to morbid events. On the other hand, the pathological mechanisms of cardiovascular disease themselves exhibit temporal changes in both their manifestation and severity, leading to predictable-in-time differences in their *ability* to precipitate the overt expression of disease.[3] Acute aortic dissection is uncommon, but complications develop rapidly and the outcome is often fatal.[2] Although its incidence has been estimated at from 5 to 30 per 1 million people per year,[2] rupture of aortic aneurysm ranks in third position, after coronary heart disease and pulmonary embolism (3.8% of cases), among necropsy-confirmed causes of out-of-hospital sudden death in the general population.[4] Even if the typical presentation is characterized by acute onset of severe pain, clinical manifestations are diverse, and classic symptoms and signs are often absent.[2] Despite significant advances in diagnostic and therapeutic techniques, morbidity and mortality rates remain high. Thus, rhythmicity and predictability of an acute life-threatening event might be important.

Circadian rhythm and cardiovascular diseases

Chronobiology is a branch of biomedical sciences aimed at the study of biological rhythms. Biological rhythms exist at many levels in living organisms and, according to their cycle length, may be divided into: a) circadian (period of ~24 hours), b) ultradian (period <24 hours), c) infradian (period >24 hours). Circadian rhythms are the widely studied, and are driven by circadian clocks. Circadian clocks can be defined as a transcriptionally based molecular mechanism, based on both positive and negative feedback loops, with a free-running period of approximately 24 hours.[5] The principal circadian clock or *master clock*, located in the suprachiasmatic nucleus (SCN), is entrained by light and is supposed to entrain peripheral clocks via neurohumoral modulation.[5] However, circadian clocks have been identified within almost all mammalian cell types, including cardiomyocytes,[6] vascular smooth muscle cells and endothelial cells.[7] The onset of various pathological events, such as myocardial infarction (MI), stroke, arrhythmias, pulmonary embolism, and sudden cardiac death (SCD) have all been shown to be time-of-day–dependent in humans, peaking near the sleep-to-wake transition (ie, early morning).[8]

Circadian clocks and their role in cardiovascular diseases

The principal role of cellular biological clocks is driving circadian rhythms to adapt the organism to further needs in an anticipatory manner, thus providing selective advantage.[9] However, it has been recently shown that external or internal disruption (*dyssinchrony*) of circadian control may result in overt diseases. For example, mice exposed to a 20-hour instead of 24-hour circadian rhythm show a complete disruption of sleep/wake behavior and a marked progression of myocyte hypertrophy and fibrosis.[10] Again, for example *bmal1* knockout mice or *clock* mutant mice exhibit impairment of normal protective endothelial responses to vascular injury with pathological remodelling and predisposition to vascular thrombosis,[11] and mice with mutation in the Per2 gene show endothelial dysfunction characterized by decreased production of nitric oxide (NO) and vasodilatory prostaglandins, and increased release of cyclooxygenase-1-derived vasoconstrictor substances.[12]

The cardiomyocyte circadian clock may play a role in the modulation of fibrosis. The early stage of fibrosis development involves degradation of the existing extracellular matrix by extracellular matrix metalloproteinases (MMPs). MMPs play a key role in cardiovascular disease, in particular aneurysm formation and plaque rupture. In particular, matrix metalloproteinase-9 (MMP-9) is the predominant enzyme targeting elastin and collagen present in the walls of the abdominal aorta, and a significant association was found between MMP-9 genotype and abdominal aortic aneurysm..[13] Many pathological conditions associated with fibrosis, such as heart failure, myocardial infarction, and hypertension, have also been reported to be associated with increased levels and activities of MMPs.[13–15] The activity of MMPs is normally counterbalanced by the presence of tissue inhibitors of matrix metalloproteinases (TIMPs). During times of extracellular matrix breakdown MMP levels have been shown to be elevated and TIMP levels repressed. This is followed by a decrease in MMP activity (by TIMP inhibition) and collagen deposition.[16] Two MMPs (*mmp14* and *mmp24*) and 2 TIMPs (*timp1* and *timp3*), as well as a large number of collagen genes were identified as clock regulated (*col3a1, col4a1, col4a2, col5a1,* and *col6a3*) were identified as being circadian clock regulated.[17] It is extremely interesting that, at least in the tears, MMPs exhibit a diurnal variation as well. Concentrations of MMP-9 are negligible during the day and completely inhibited by TIMP-1. On awakening, MMP-9 increases 200-fold, an increase that is not completely inhibited by TIMP-1.[18]

The master clock, located in the SCN, is entrained by light. Alterations in light/dark cycle conditions can have profound effects on both central and peripheral clocks. The rate of resynchronization of cellular clocks following a shift in the