Editorial Comment

Chronobiology and Stroke

GEORGE S. STERGIOU

3rd Dept. of Internal Medicine, University of Athens, Sotiria Hospital, Athens, Greece

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Address:
George S. Stergiou

3rd University Dept. of Medicine,
Sotiria Hospital,
Athens, Greece
e-mail:
gstergi@med.uoa.gr

In this issue of the Hellenic Journal of Cardiology, Spengos et al[1] provide new information about the daily and seasonal variations in the incidence of cardiovascular events. This study focuses on cerebrovascular events and in particular on embolic stroke in patients with atrial fibrillation.

Although cerebrovascular and coronary events are considered to have the same pathogenetic mechanism, via the atheromatic process as a consequence of long term exposure to risk factors, they are known to differ in regard to their natural history and their association with the risk factors (e.g. coronary events occur at a younger age than strokes and are more closely related with hypercholesterolaemia and smoking than with hypertension). However, observation studies have shown an impressive similarity between the various cardiovascular events with regard to their diurnal variation, with a significant increase in the incidence of events during the morning hours after awakening and the lowest incidence during nocturnal sleep.[2] This typical diurnal variation has been found to hold for a number of cardiovascular events, including myocardial infarction, stroke (thrombotic or intracerebral or subarachnoid haemorrhage), angina (stable, unstable, or silent) and sudden death.[2] The similarity in the daily distribution of the onset of these different events suggests that they are likely to share a common triggering mechanism.

In contrast to the extensive literature supporting the morning increase in the incidence of cardiovascular events, little attention has been given to a second peak in event incidence that some studies have reported later in the day.[3-9] A second peak has been observed between 6 and 7 p.m. in the incidence of sudden cardiac death,[4] and of myocardial infarction, verified by measurements of creatine phosphokinase.[3,6] Similar observations have been made in studies of stroke. A secondary peak in the late afternoon was found in all types of stroke in a British study,[5] in ischaemic stroke in the USA,[7] and in fatal stroke in Japan.[8] Subarachnoid haemorrhage was also found to show an afternoon peak during its diurnal variation.[9] A study of ischaemic stroke in Greece did not show any statistically significant afternoon peak: it did, however, show a progressive decrease in the incidence of events after 10 a.m., with the lowest incidence between 2-4 p.m. (not exceeding that of nocturnal sleep) followed by a small increase.[10] A more recent Greek study showed a clear increase in the incidence of stroke during the late afternoon hours.[11]

Interestingly, a similar diurnal variation pattern, with a large morning increase and a drop during the night, has been observed for various phenomena that are related with haemodynamics and thrombogenesis, such as systolic and diastolic blood pressure,[12,13] heart rate,[13] plasma catecholamines,[14] platelet aggregability,[15] and fibrinolytic activity.[16] These changes have been related with the diurnal variation in onset of cardiovascular events.[16] The diur-

nal variation in these parameters does not seem to be determined by an endogenous circadian rhythm, but rather through changes in physical activity over the 24-hour period.[13,17]

A recent Greek study carried out a combined analysis of data from stroke patients from the same centre where the paper by Spengos et al[1] originates, with data for blood pressure, heart rate and physical activity from a second research centre.[13] The study included data from 1063 individuals and compared the diurnal variation in the onset of stroke with the 24-hour variation in blood pressure, heart rate and physical activity (continuous recording using wrist Actigraph devices[18]). The study showed significant morning and evening surges in stroke onset as well as in systolic and diastolic pressure, heart rate and physical exercise. The 24-hour curves for stroke onset, pressure, heart rate and physical activity were strictly parallel, suggesting a clear relationship between them.[13] The evening increase in physical activity was obviously due to awakening from siesta, given that 75% of the patients included in the study reported that they had taken an afternoon nap during the 24-hour monitoring.[13] These data support the view that changes in physical activity during the 24-hour period result in changes in neurohormonal, haemodynamic and thromboregulatory phenomena that are related with the triggering of cardiovascular events.

Stroke onset has also been recognised to have a seasonal variation, with the highest incidence during the winter months.[19-21] A seasonal variation has also been found in various phenomena that are causally related with stroke, such as blood pressure,[22] fibrinogen,[23] antiphospholipid antibodies,[24] endothelin,[25] and nitric oxide.[25]

Muller[2,26] set out a unified hypothesis for the mechanism of triggering cardiovascular events that provides an explanation of the diurnal variation in their occurrence (Figure 1). According to the Muller hypothesis, morning awakening is accompanied by an abrupt increase in sympathetic nervous system activity (as central mechanism) that results in an increase in blood pressure and heart rate, as well as platelet aggregability, and a reduction in fibrinolytic activity. These simultaneous changes create conditions of vasoconstriction, an increase in wall stress and thrombogenesis. In pre-existing unstable atheromatous plaques these conditions create a predisposition for thrombus rupture, namely for the triggering of a cardiovascular

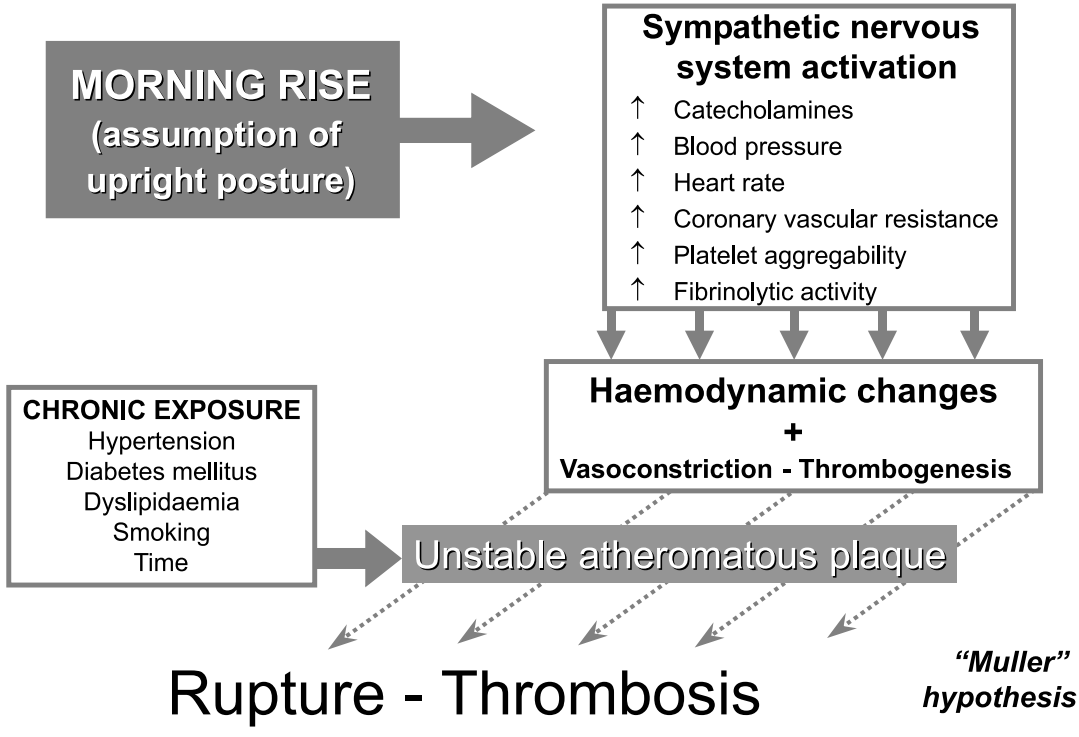

Figure 1. The Muller hypothesis.

event (Figure 1).[2,26] The seasonal variation in episodes with the highest incidence in the winter months might also be explained by the Muller hypothesis, given that during the winter months there is an increase in the levels of various haemodynamic and thrombogenic factors that are implicated in the pathogenetic mechanism through which the events are triggered.[22-25]

The study by Spengos et al[1] is of special interest, mainly because it concentrates on embolic cerebrovascular stroke in patients with atrial fibrillation. The paper's interest lies in the facts that embolic stroke, firstly, differs pathogenetically from classical atherothrombotic events (myocardial infarction and atherothrombotic stroke) and, secondly, seems to be on the increase in recent years.[27,28]

The appearance of arrhythmias such as atrial fibrillation[29] and supraventricular[30] and ventricular[31] tachycardias also shows a typical diurnal variation with an increase in the morning hours. The referenced studies showed a second small surge in arrhythmia appearance in the late afternoon.[29-31] In accordance with these data, as well as with a previous publication from the same research group in Athens[11] that showed a morning and an evening peak in stroke incidence, Spengos et al[1] now show that the double-peaking diurnal variation in stroke incidence is also seen in patients with atrial fibrillation.

The Muller hypothesis[2,26] may be used to interpret the findings of this study (Figure 1). Arrhythmogenic action due to sympathetic nervous system activation during morning and evening awakening is accompanied by haemodynamic changes via an increase in blood pressure and heart rate and by parallel phenomena related with thrombogenesis and fibrinolysis. These phenomena can explain the instigation of atrial fibrillation during awakening (via sympathetic activation), the creation of thrombi (thrombogenic mechanisms), as well as their transportation from the heart to the brain (haemodynamic changes) (Figure 1).

A further important issue discussed in the Spengos paper[1] is the implementation in clinical practice of guidelines for the administration of anticoagulant medication to patients with atrial fibrillation. It is well-known that there is prejudice about administering anticoagulants in the elderly and that the anticoagulant regimen supplied is often unsuccessful.[32] The authors provide indirect evidence showing an increasing use of anticoagulant therapy during the last decade in patients admitted to the hospital with atrial fibrillation and stroke.[1] However, even in the 2002 data, 80% of those patients were not taking anticoagulants and of those who were, 85% had not reached the recommended INR level. Given the increasing incidence of embolic stroke, encouraging physicians to widen the use of prompt and effective anticoagulation would definitely contribute significantly to the primary prevention of severe complications in the cerebral circulation. Studies like that of Spengos et al[1] can help the move in that direction.

Stroke is the second or third cause of death in industrialised countries.[33] In Greece the incidence of stroke in men is equal to that of coronary events, while in women it is double.[34] Recent studies of survival in hypertensive patients have shown that during the last decade the incidence of stroke has exceeded that of coronary events.[35] The serious consequences of stroke include not only death, but also permanent neurological damage, complications (mainly infections), long term hospitalisation, depression, loss of production and cost.[33] Unfortunately, many crucial questions remain unanswered with regard to both our understanding of the pathogenetic mechanisms and the indicated therapeutic intervention. The development of stroke units, like the one in "Alexandra" hospital, is essential, both for systematic research and the new scientific information they provide, and for the most effective patient management.[36]

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