Circadian Variation in Cardiovascular Events

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Serious adverse cardiovascular events, including myocardial infarction, sudden cardiac death, and stroke, frequently result from thrombotic processes and rupture of atherosclerotic plaques. These events exhibit a pronounced circadian rhythmicity, with a marked peak in the morning hours when the patient assumes an upright posture and begins daily activities. However, it is not known if plaques rupture more frequently in the morning. This review will examine the epidemiologic evidence documenting this circadian phenomenon, consider its physiologic underpinnings, and discuss the implications of this pattern for rational pharmaceutical development. Finally, some practical implications regarding potential triggers of cardiovascular events will be discussed. Am J Hypertens 1999;12:35S–42S © 1999 American Journal of Hypertension, Ltd.

KEY WORDS: **Diurnal variation, sudden cardiac death, myocardial infarction, stroke, cardiovascular triggers.**

In recent years, evidence has mounted supporting the clinical significance of diurnal patterns that affect the onset of a spectrum of myocardial events.[1–6] These include sudden coronary death (SCD), ischemia, myocardial infarction (MI), unstable angina and non–Q-wave MI, and ischemic stroke. Data imply that a diurnal variation in certain functional changes, such as increased platelet activation, rise in arterial blood pressure, and increases in catecholamine and cortisol levels, may combine with the morning initiation of activities of daily living to trigger these cardiovascular events.

Skeptics of the circadian argument for cardiovascular disease raise the objection that the classification of morning events might be artifactual or biased. In particular, unwitnessed events, such as SCD occurring during sleep, might be falsely attributed to the morning hour when the deceased patient is discovered. In addition, the patient might sleep through the onset of a heart attack, wake up at 8 AM, and report pain.

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EPIDEMIOLOGIC AND CLINICAL EVIDENCE FOR DIURNAL VARIATION IN CARDIOVASCULAR EVENTS

In the following studies, such objections were addressed when investigators attributed unwitnessed events to the interval between midnight and 6 AM. In addition, creatine kinase (CK) curves, which produce a relatively objective determination of the time of a MI, also confirmed a morning peak. Holter monitoring of ischemic phenomena is continuous and further corroborates the morning peak, thus leaving little doubt as to the adequacy of surveillance.

Sudden Cardiac Death (SCD) *Framingham Heart Study* In the Framingham Heart Study,[1] the time of day of SCD was analyzed among 5209 people in the original cohort over a follow-up interval of 38 years. Definite sudden death was defined as death of an apparently healthy person soon after onset of symptoms. In addition, if the cause of death was not attributable to some potentially lethal disease other than coronary heart disease, it was considered sudden death and was attributed to coronary heart disease.

The Framingham investigation also discriminated between actual circadian variation in primary SCD and the diurnal rhythmicity of underlying MI, which

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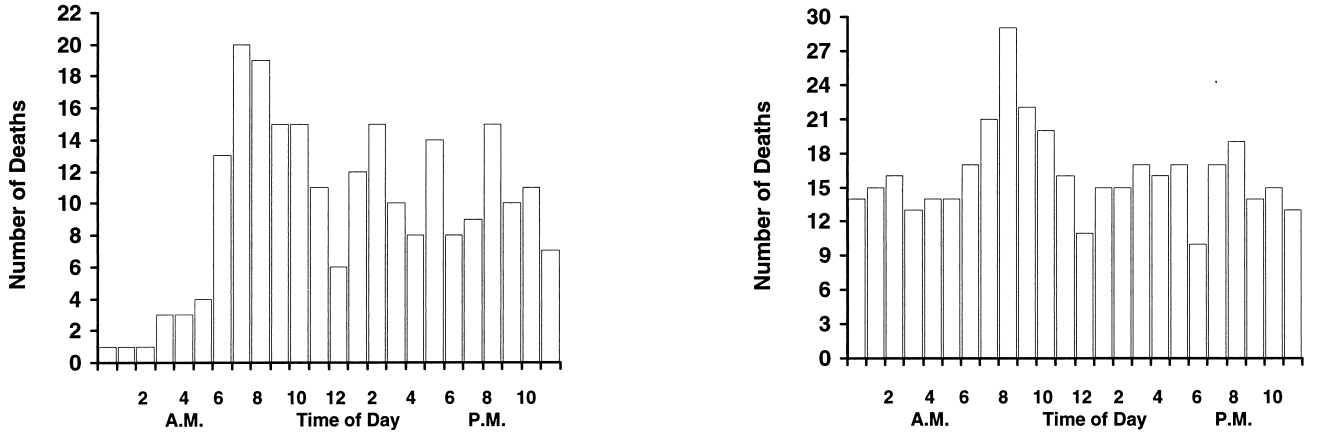

FIGURE 1. Left: *Time of day of definite SCD (n = 264). The decrease in incidence from 9 AM to 1 PM, compared with the morning peak, occurs during an interval in which observation is likely to be constant.* **Right:** *Time of day of definite or possible SCD (n = 429). The hourly risk of SCD is approximately 70% higher from 7 to 9 AM than the mean risk during the remaining 22 h of the day. Adapted with permission from Excerpta Medica Inc. from Willich et al: Circadian variation in the incidence of SCD in the Framingham Heart Study Population. Am J Cardiol 1987;60:801–806.*[1]

may cause secondary SCD. To do so, two assumptions were made: first, that MI occurs in about one-third of all cases of SCD; and, second, that a morning MI is not more likely to have a fatal outcome than is MI at other intervals. To determine the true distribution of primary sudden cardiac fatalities, the hourly number of secondary SCD was subtracted from the hourly number of all definite or possible SCD. A 33% sequential rise in the assumed proportion of secondary SCD was used to establish the highest proportion that could have been due to MI and still result in a substantial circadian variation in primary SCD.

The results of this analysis compellingly supported a morning peak. There was a pronounced circadian variation in the occurrence of definite or possible SCD (n = 429; $P < .01$), with a peak incidence between 7 and 9 AM, a decreased frequency from 9 AM to 1 PM, and a low frequency during the night. The risk of SCD was 70% or more during the peak interval than was the mean risk during the remaining 22 h of the day. In another look at the data, significantly more SCD ensued between 6 AM and noon than during other quarters of the day ($P < .01$) (Figure 1).

Massachusetts Survey To establish whether SCD manifests a circadian rhythm similar to that of nonfatal MI, Our group[2] assessed the time of death as recorded on death certificates from the Massachusetts Department of Public Health among 2203 individuals who died out of hospital in Massachusetts during 1983.

Sudden death was defined as death from cardiac disease occurring within 1 h of symptom onset. Because the normal rhythmicity of deaths can be disrupted among hospital inpatients, SCD were further classified as those occurring out of hospital (encompassing death on arrival at the hospital). The Ninth Revision of the International Classification of Disease (ICD-9) was used to categorize deaths resulting from circulatory diseases, including ischemic heart disease (eg, MI, chronic ischemic heart disease) and cardiac dysrhythmias.

These data also revealed a prominent circadian variation in SCD, with a low incidence during the nighttime hours and a peak between 7 and 11 AM. The increased incidence in the morning is consistent with assumptions that SCD is a sequel of ischemia or a primary arrhythmic event. A statistically significant circadian rhythm was reported with a primary peak from 10 to 11 AM ($P < .01$) and a secondary peak was noted between 5 and 6 PM. SCD occurred during sleep in only 85 of the 689 (12.3%) sleeping patients examined; this incidence is significantly less than the 29% that would be anticipated if the time of occurrence were evenly distributed throughout 24 h ($P < .001$), assuming a 7-h sleep interval (Figure 2) . Interestingly, among in-hospital deaths, for which circadian influences may be attenuated, the frequency of SCD was approximately evenly distributed throughout 24 h.

Myocardial Infarction Our group[3] studied the extensive database created from 1978 through 1983 for the Multicenter Investigation of Limitation of Infarct Size (MILIS) study to determine whether MI occurs with an even distribution throughout 24 h. The authors considered both onset of pain and elevations in serial determinations of CK MB-band (CK-MB) concentrations among 703 patients admitted with acute MI. The CK-MB–approximated onset of MI was assumed to have occurred 4 h before the initial elevation.

As with SCD, a statistically significant circadian

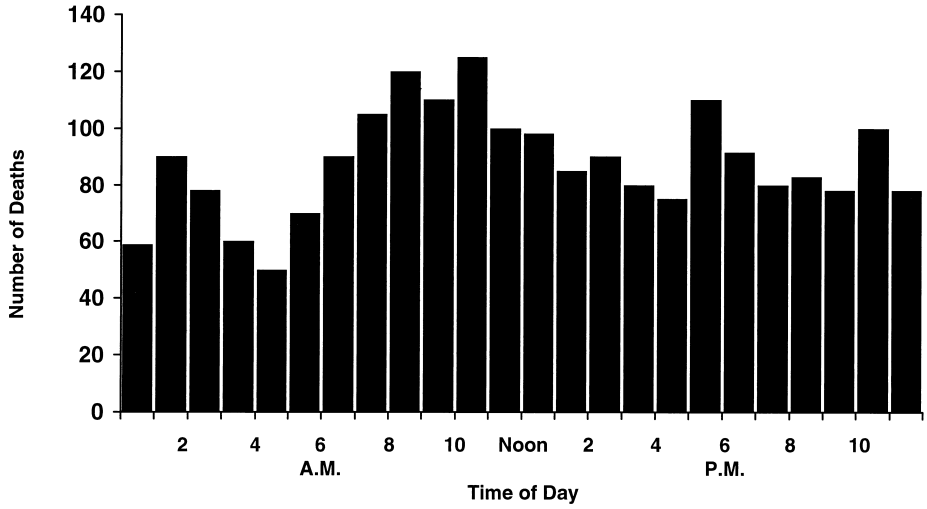

FIGURE 2. *Time of day of out-of-hospital SCD (≤1 h from onset of symptoms to death) for 2203 persons who died in Massachusetts during 1983. A statistically significant ($P < .001$) diurnal variation is evident, with a primary peak between 7 and 11 AM. Adapted with permission from Muller et al: Circadian variation in the frequency of SCD. Circulation 1987;75:131–138.*[2]

rhythm in incidence of MI onset was detected ($P < .01$), with peak occurrence between 6 AM and noon. CK-MB estimates of MI confirmed this pattern. Compared with the trough period (11 PM), CK-MB–established MI was three times more frequent at 9 AM (Figure 3).

Unstable Angina and Non–Q-Wave Acute MI Before the prospective analysis of the Thrombolysis in Myocardial Ischemia (TIMI) III Registry and the TIMI IIIB trial,[4] the role of circadian rhythmicity in the ischemic phenomenon of unstable angina and non–Q-wave MI was not clearly known. A study had reported no diurnal variation in the symptom onset of evolving non–Q-wave myocardial infarction.[5]

In the TIMI III trials, the investigators scrutinized times of onset of ischemic pain in 7731 patients, 3318 of whom were entered in the prospective TIMI III Registry study and 1473 of whom were enrolled in the TIMI IIIB trial. The former database was drawn from

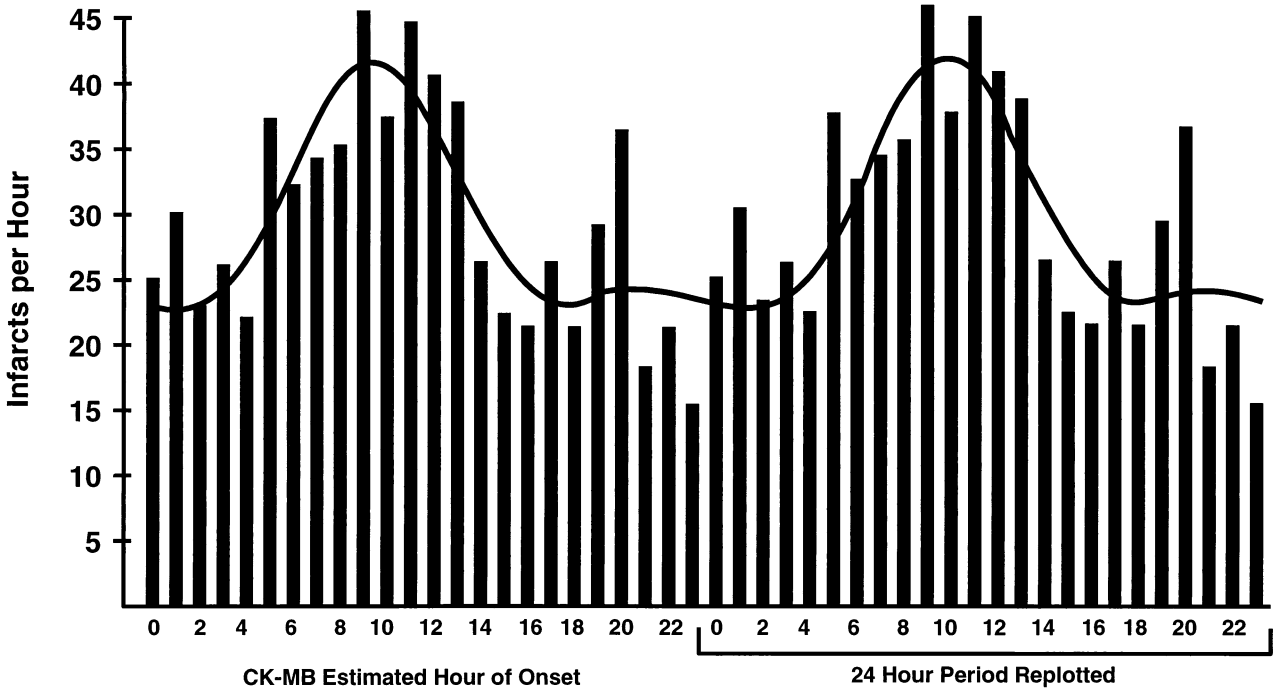

FIGURE 3. *The number of infarctions (in the MILIS database) beginning during each hour of the day is plotted at* **left**. *At* **right**, *the identical findings are plotted again to display the relationship between the end and beginning of the day. A two-harmonic–regression equation for the frequency of onset of MI has been fitted to the data (ie, curved line). A pronounced circadian variation is evident, with a primary peak frequency of MI at 9 AM and a secondary peak at 8 PM. Adapted with permission from Muller et al: Circadian variation in the frequency of onset of acute myocardial infarction. N Engl J Med 1985;313:1315–1322.*

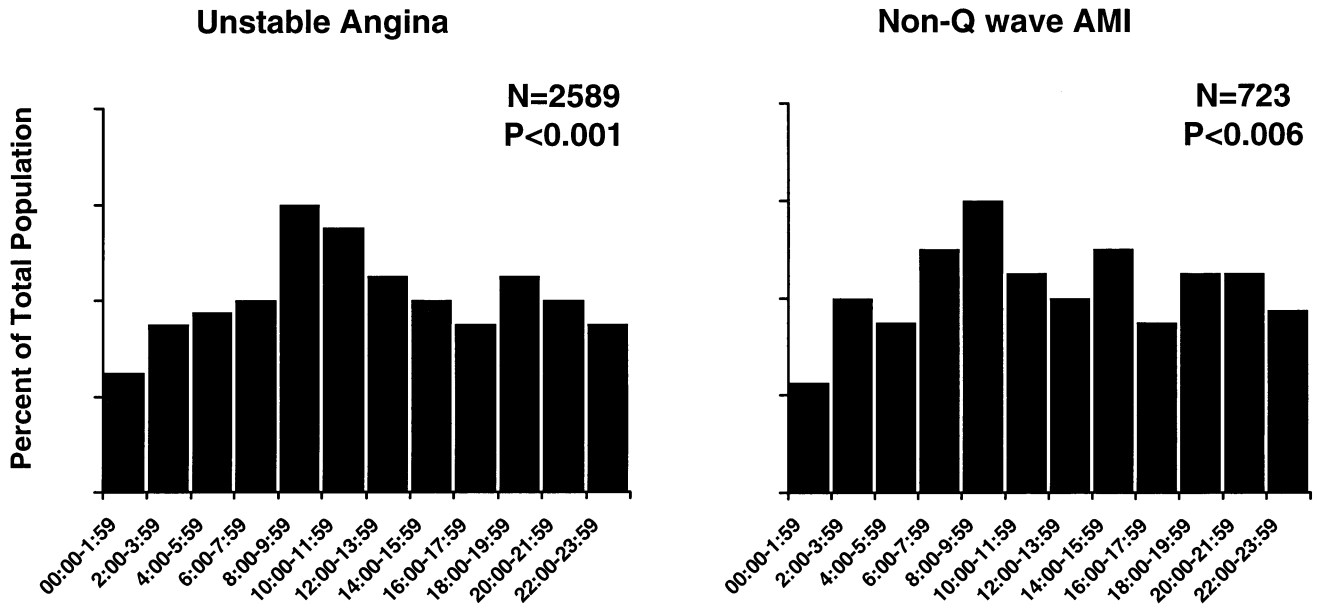

FIGURE 4. *Circadian variation in the onset of pain in patients with unstable angina and non–Q-wave AMI in the TIMI IIIB trial. Both unstable angina and non–Q-wave AMI peak in the interval from 6 AM to noon. Adapted with permission from Excerpta Medica Inc. from Cannon et al: Circadian variation in the onset of unstable angina and non–Q-wave acute myocardial infarction (The TIMI III Registry and TIMI III B). Am J Cardiol 1997;79:253–258.*[4]

patients at 18 clinical institutions (14 in the US and 4 in Canada) who were evaluated between October 1990 and April 1993. Inclusion criteria encompassed the presence of angina (believed to be ischemic) with a duration of at least 5 min and beginning within 96 h of hospital admission. A further requirement was that pain exhibit an unstable pattern (ie, rest pain, new onset, severe, or frequent angina, accelerating angina, or angina observed within 21 days of MI).

The TIMI IIIB database was derived from patients presenting with progressive or new pain thought to be ischemic in nature. Inclusion criteria were pain with a duration of at least 5 min but less than 6 h, with objective evidence of ischemic heart disease; either transient electrocardiographic findings of ischemia (ie, $<$ 30 min ST-segment elevation of $\geq$ 0.1 mV, ST-segment depression of $\geq$ 0.1 mV, T-wave inversion or pseudonormalization, or documented coronary artery disease [history of MI or a $\geq$ 70% stenosis]).

A substantial, statistically significant circadian rhythmicity in pain onset was recorded in the TIMI III Registry ($P < .001$), with a rise in incidence of pain recorded between 6 AM and noon. This morning peak was observed for both unstable angina and evolving non–Q-wave acute MI (AMI). These data were corroborated in the TIMI IIIB trial (Figure 4) and imply that a diurnal variation governs the onset of the vast majority of myocardial ischemic events.

The circadian variation in ischemic pain onset was observed uniformly in several subgroups analyzed: patients with or without prior MI, smokers or nonsmokers, diabetics or nondiabetics, and recipients or nonrecipients of medications (ie, aspirin, heparin, calcium-channel blockers, nitrates) within the previous week (TIMI III Registry); in the TIMI IIIB trial, analyzed subgroups included men or women, age greater than or less than 65 years, white or nonwhite, diabetic or nondiabetic, prior or no prior MI, and recipients or nonrecipients of specific medications.

Ischemic Stroke In a study coordinated largely by the National Institute of Neurological and Communicative Disorders and Stroke of the National Institutes of Health (NIH),[6] the time of ischemic cerebrovascular accident (CVA) was recorded for 1167 patients at four academic institutions; in 106 patients the time of stroke onset could not be determined.

More strokes occurred from 10 AM to noon in awake patients than in any other 2-h period (Figure 6). From 8 to 10 AM, manifestations of CVA were evident in 44% of patients; for 12% of these patients, it could not be established whether the stroke had occurred before awakening. Nevertheless, if only patients in whom stroke was known to occur after awakening are examined, the number of CVA occurring between 8 and 10 AM (124) significantly exceeds the value anticipated (62) if the time of onset were evenly distributed throughout 24 h ($P < .001$). Statistically significant 2-h frequency peaks occurred between 8 and 10 AM for the onset of ischemic strokes worsening in hospital (283) and CVA occurring among patients with prominent

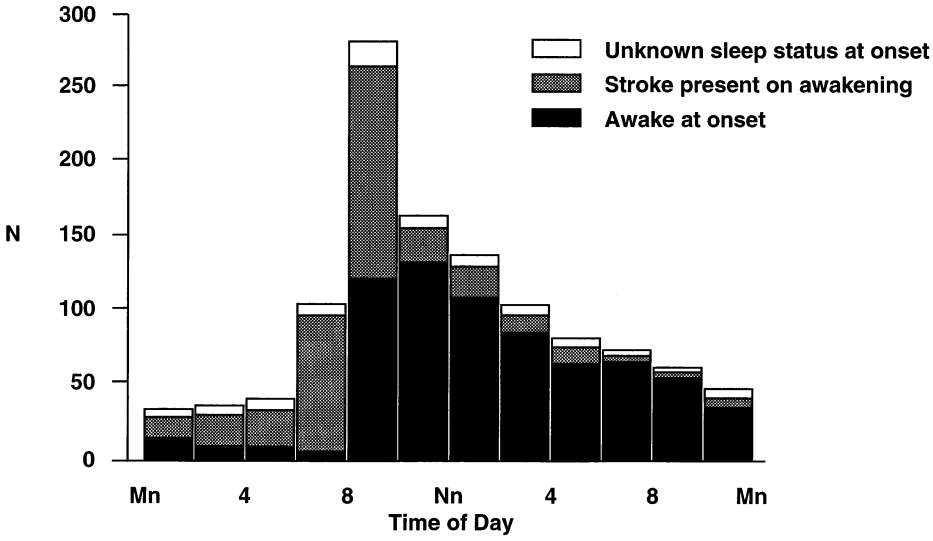

FIGURE 5. *Frequency, in 2-h intervals, of onset of ischemic stroke for 1167 patients. Mn, midnight; Nn, noon; N, number of patients. Filled areas = 744 patients with onset while awake; shaded areas = 331 patients with stroke symptoms present on awakening; open areas = 92 patients for whom time of stroke onset was unknown. Adapted with permission from Marler et al: Morning increase in onset of ischemic stroke. Stroke 1989;20:473–476.*[6]

signs or symptoms (171), such as severe headache, seizures, or emesis at onset ($P < .01$).

PHYSIOLOGIC REASONS FOR THE MORNING INCREASE IN CARDIOVASCULAR EVENTS: ACUTE RISK FACTORS

The key pathophysiologic process underlying SCD, MI, and stroke due to thrombosis is rupture of vulnerable atherosclerotic plaques.[7] Such disruption exposes intimal collagen and tissue factor, which in turn serve as foci for platelet aggregation and resultant thrombus formation. Vulnerable atherosclerotic plaque has a rich lipid core and thin fibrous cap; the strength of the cap is derived from collagen and elastin produced by smooth muscle cells. These proteins are degraded by proteases produced by macrophages, which develop into foam cells. This degradation of collagen and elastin in the fibrous cap may lead to plaque rupture. There is a possibility that matrix metalloprotease inhibitors could blunt the activity of these macrophage proteases, thereby stabilizing the plaque.

It appears that the increased morning onset of events is caused primarily by exogenous factors, such as assumption of upright posture and initiation of daily activities. The role of endogenous factors intrinsic to the morning hours is not well characterized.

Platelet aggregability, which can promote thrombosis, has a sharp peak in the morning among patients who assume an upright posture and engage in activities of daily living, as Tofler and colleagues reported.[8] When examining platelet activity in 3-h periods over an entire day in 15 healthy men, in vitro platelet aggregability was decidedly lower before patients arose (6 AM) than 60 min after arising (9 AM). This change in platelet responsiveness was expressed as the concentrations of two agonists, adenosine diphosphate (ADP) and epinephrine, necessary to produce biphasic platelet aggregation. These concentration levels declined (ie, aggregability increased) from 6 to 9 AM. ADP concentration declined from 4.7 ± 0.6 to 3.7 ± 0.6 μmol/L ($P < .01$) and epinephrine decreased from 3.7 ± 0.8 to 1.8 ± 0.5 μmol/L ($P < .01$).

This rise in platelet activity was decidedly exogenous, as it was due to assumption of upright posture and participation in daily activities. Conversely, among 10 subjects who remained supine and inactive, no morning rise in platelet aggregability was recorded.

Another potential trigger for plaque rupture and thrombosis is the morning rise in arterial blood pressure.[9] This increase is paralleled by elevations in catecholamines upon assuming an upright posture, as they tend to increase coronary vascular tone.[10] The resulting vasoconstriction could worsen flow reduction induced by a fixed stenosis. Catecholamines also exert positive inotropic and chronotropic effects on the heart.

Elevations in plasma cortisol levels are among the best-established endogenous morning changes, and these could enhance coronary-arterial sensitivity to the vasoconstrictor effects of catecholamines.[11] Finally, blood viscosity rises in the morning hours,[12] and tissue plasminogen activator (t-PA) shows an insufficient countervailing increase[13,14]; this imbalance might culminate in a relative attenuation of fibrinolysis that would thus promote a hypercoagulable state, increasing the risk that an otherwise innocuous mural thrombus overlying a minute plaque fissure could propagate and become occlusive.

Our group[7] has advanced a general theory explaining the manner in which exogenous daily activities can trigger coronary thrombosis (Figure 6). The first pathophysiologic step in the process is age- and diet-dependent evolution of vulnerable atherosclerotic plaques, which are especially prone to rupture. Dis-

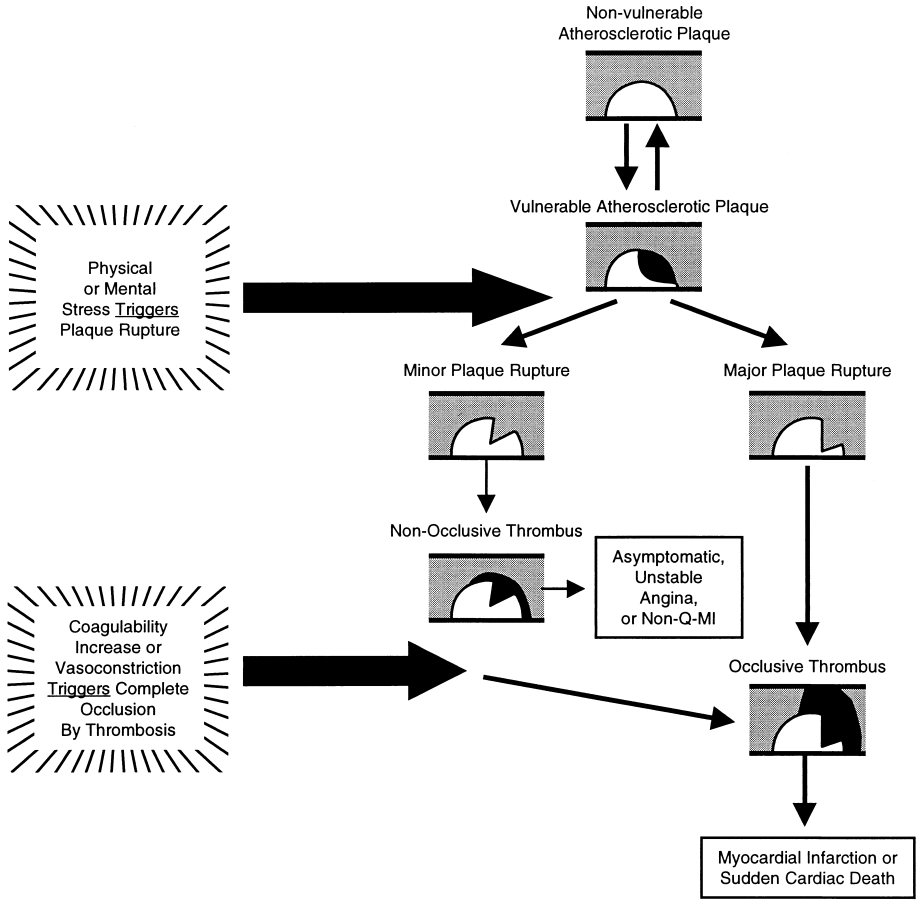

FIGURE 6. *Illustration of a hypothetical method by which daily activities may trigger coronary thrombosis. Three triggering mechanisms—(1) physical or mental stress producing hemodynamic changes leading to plaque rupture; (2) activities causing a coagulability increase; and (3) stimuli leading to vasoconstriction (smoking meets both criteria 2 and 3)—have been added to the well-known scheme depicting the role of coronary thrombosis in unstable angina, MI, and SCD. Adapted with permission from Muller et al: Circadian variation and triggers of onset of acute cardiovascular disease. Circulation 1989;79:733–743.*[7]

ease onset could occur when mental or physical stress caused mechanical forces (arterial pressure surge or vasoconstriction) to promote rupture of a vulnerable plaque. Alternatively, the plaque might have ruptured due to endogenous forces and the trigger may act by promoting hypercoagulability and vasoconstriction.

Degree of plaque vulnerability would by definition vary inversely with the intensity of the triggering stresses necessary to induce rupture. Furthermore, disease onset may often occur as the result of aggregate stressors, as in the case of a patient who undergoes physical exertion, possibly eliciting a minor plaque disruption, and then smokes, which elevates coronary arterial tone and promotes coagulability.

Plaque rupture varies in intensity from relatively minor to major, depending on the degree of exposure of intimal components that promote platelet aggregation. Minor rupture may elicit only an asymptomatic mural thrombus or result in unstable angina or non–Q-wave MI. However, a major rupture that causes an intense thrombogenic focus may culminate in MI or sudden death through induction of an occlusive coronary thrombus.

Uchida and coworkers conducted angioscopy in a cohort of patients with stable angina.[15] The Japanese investigators determined that glistening, yellow (lipid-laden) plaques result in ischemic complications in 68% of patients within 1 year, whereas white plaques exhibit a 1-year complication rate of only 3%. However, angioscopy requires coronary artery occlusion and the results are subjective. Our group is developing a near-infrared catheter that may be able to identify vulnerable plaques based on the reflected near-infrared signals.

PHARMACEUTICAL DEVELOPMENTS TO BLUNT THE MORNING SURGE IN CARDIOVASCULAR EVENTS IN HYPERTENSIVE PATIENTS

Given the morning rise in physiologic process that can lead to cardiovascular events, strategies to attenuate morning arterial blood pressure surges in hypertensive patients have been developed. The goal of such strategies is to blunt the circadian variation in SCD, MI, and ischemic stroke.

Controlled-onset extended-release (COER-24) verapamil (Covera, Searle, Skokie, IL) is one pharmaceutical agent specifically designed to blunt the morning peak in arterial pressure. Through a unique formulation, in which the outer coating of the tablet dissolves

gradually, this product delivers verapamil in alignment with the morning rise in MI and other adverse cardiovascular events. An ongoing trial, entitled Controlled Onset Verapamil Investigation of Cardiovascular Endpoints (CONVINCE), has been designed to test the hypothesis that this type of chronotherapy will have a beneficial effect on cardiovascular morbidity and mortality.[16] The results of this study are eagerly awaited.

IMPLICATIONS OF CARDIOVASCULAR TRIGGERS

The 1994 Los Angeles earthquake, which struck at approximately 4:30 AM, provided an opportunity to study the effects of synchronized stress on a population. A medical investigative team led by Dr. Robert Kloner demonstrated a pronounced rise in the incidence of cardiovascular death on the day of the quake, compensated for by a decrease during the 14 days afterwards.[17] The events were triggered principally by mental stress (chiefly fear) rather than physical stress (such as lifting heavy objects).

In the absence of an earthquake, cardiovascular triggers are spread throughout the day. In an NIH-supported study, 1712 post-MI patients were interviewed to identify possible precipitating factors. Many respondents reported that they had either just awakened, or experienced psychological stress, heavy physical exertion, or anger. A small number of patients had engaged in sexual activity.[18] The first prospective trigger examined was heavy exertion. In sweat-producing activities, such as singles tennis, there was a sixfold rise in risk of MI in the subsequent hours. Among people who exercised five times each week, the risk of MI after an activity such as singles tennis rose only twofold, whereas those who were habitually sedentary and then suddenly exerted themselves sustained a hundredfold increase in MI risk. This supports recommendations by clinicians, especially those treating hypertensive patients, in support of regular physical activity, even if moderate.

An important distinction must be made between absolute risk and the relative risks discussed earlier. For a healthy 50-year-old man who exercises regularly, the absolute risk of MI is only 1 chance/million/hour. Therefore, if a person who exercises regularly doubles this risk with singles tennis, the absolute risk is only 2/million/hour. For a post-MI patient who has been in a rehabilitation program, the absolute risk of MI is 10/million/hour. Although singles tennis doubles the risk, the absolute risk is still only 20/million/hour. Such statistics, when communicated to the patients in our care, should go a long way toward reassuring them of the safety of physical activity. There are some situations in which heavy exertion should be discouraged. A sedentary patient who is post-MI and wishes to participate in an activity such as an annual softball game can expect a 100-fold increase in MI risk, to 1000 chances/million or 1 chance in 1000. This risk approaches the level at which patients should be advised to avoid the activities.[19]

The likelihood that psychologic stress, a subjective phenomenon, may trigger a cardiovascular event is much more difficult to study; one person's stress is another's challenge, and studies are complicated by recall bias. Therefore, Mittleman and Maclure[20] used a possible trigger that is uniformly considered stressful, the death of a significant person (ie, first-degree relative, spouse, child). Such stress was associated with a 14-fold higher probability of MI on the first day after the death. The risk remained elevated for more than a week.

Anger may also trigger MI.[21] However, regular users of aspirin have lower relative risk of MI after anger, possibly because aspirin may reduce the chance of acute occlusive thrombus formation after an incidence of anger.[21] This effect of aspirin therapy is a good example of the severance of the link between a potential trigger and MI.

Sexual activity also doubles the risk of MI in the subsequent hour. However, as with other triggers, it is essential to consider the absolute rather than the relative risk. The baseline risk that a patient who has suffered an initial MI will experience a second MI in an hour is only 10 chances/million; doubling this to 20 chances/million is not a major increase in risk.[19] Such data should be used to reassure the post-MI patient, for whom fear of another MI can be a psychologic deterrent to resumption of sexual activity.

CONCLUSIONS

MI, SCD, ischemic stroke, unstable angina, and non–Q-wave AMI manifest a clear circadian variation, exhibiting a peak in the morning. This pattern results from processes that occur after assumption of upright posture and initiation of daily activities. Increased vascular tone, arterial pressure, and coagulability may all play a role. The morning rise in cortisol also increases arterial sensitivity to catecholamines. Chronotherapeutic regimens designed to block acute risk factors that increase in the morning might confer protection against adverse cardiovascular events.

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