Evidence obtained over the past decade indicates that myocardial infarction (MI) and sudden death are not random events but rather, in many cases, may be triggered by the daily activities of the subject. The importance of physical or mental stresses as triggers is suggested by the parallel morning increased onsets of MI, sudden cardiac death, and stroke.

Unstable angina and MI are usually precipitated by thrombus formation over a disrupted plaque that causes partial or complete obstruction of coronary artery blood flow. This process may be caused by physiologic factors that lead to rupture of a vulnerable plaque and subsequent thrombosis. β-Blockers and aspirin, which can diminish these physiologic processes, have been shown to blunt or abolish the morning peak of onset of acute MI.

It is hypothesized that occlusive coronary thrombosis occurs when an atherosclerotic plaque becomes vulnerable to rupture, and mental or physical stress causes the plaque to rupture. Increases in coagulability or vasoconstriction triggered by daily activities may also contribute to complete occlusion of the coronary artery lumen.

Recognition of the circadian variation of the onset of acute cardiovascular disease suggests the need for pharmacologic protection of patients during the vulnerable periods and provides clues to the mechanism of disease onset, the investigation of which may lead to improved methods of prevention. Am J Hypertens 1996;9:22S-28S

KEY WORDS: Circadian rhythm, plaque rupture, arterial thrombosis, triggers, acute cardiovascular disease, vulnerable plaque, acute myocardial infarction.

Recent studies have demonstrated that myocardial infarctions (MIs) are at least three times more likely to occur in the morning than in the late evening.1-4 This evidence suggests that the timing of MI occurrence is not a random event, but rather may be triggered or precipitated by the activities of the subject. Daily activities result in hemodynamic, vasoconstrictive, and prothrombotic forces, which are hypothesized to cause the disruption of a vulnerable atherosclerotic plaque and subsequent thrombosis, leading to MI.5 Insight into triggering mechanisms may provide a new approach to the prevention of MI through the consequent identification and treatment of plaques found to be prone to disruption.

Although triggering appears to be a novel concept, the original description of an MI by Obraztsov and Strazhesko in 1910 noted, “Direct events often precipitate the disease; the infarct began in one case on climbing a high staircase, in another during an unpleasant conversation, and in a third during emotional distress associated with a heated card game.”6

MORNING INCREASE OF MYOCARDIAL INFARCTION

During the 1930s, as a result of several retrospective studies, it was believed that MIs occurred irrespective of the physical activity being performed at the time.
of the event. However, two studies—the Multicenter Investigation of the Limitation of Infarct Size (MILIS) and the Intravenous Streptokinase in Acute Myocardial Infarction (ISAM)—conducted using modern epidemiologic approaches, demonstrated that MIS occur at least three times more frequently in the morning than in the late evening (Figure 1). Both studies determined the onset of MIS objectively through creatinine kinase measurement. Earlier studies that used pain as the marker of MI onset had reported the morning increases, but these results were not widely accepted because of the possibility of reporting biases. Goldberg and colleagues have further clarified this evidence by reporting an increased incidence of infarctions during the first 4 h after awakening and onset of activity.

Further insight into the mechanism of infarction has been gained through analysis of data obtained from the Thrombolysis in Myocardial Infarction Phase II study (TIMI II). In the overall study population, there was a higher frequency of an onset of infarction in the morning, with 34.4% of episodes occurring between 6 AM and noon. Certain subgroups had an even higher rate of morning infarction, including those who experienced no chest pain within the preceding 48 h, had not taken a β-blocker within the preceding 24 h, had no history of current cigarette smoking, and experienced onset of infarction on a weekday.

Sudden cardiac deaths and strokes have also been shown to occur with increased frequency in the morning. Transient myocardial ischemia studied using Holter monitoring has consistently shown a peak incidence between 6 AM and noon. Like the onset of MI, transient myocardial ischemia occurs more often in the hours after awakening and while initiating the day’s activities. This characterization of transient ischemia serves to reinforce the finding that nonfatal infarctions have an increased rate of onset in the morning.

ACTIVITIES THAT TRIGGER DISEASE ONSET

Data from the MILIS study revealed that 48.5% of patients reported a possible trigger of their infarction. The most commonly reported possible precipitating events included emotional upset (18.4%), moderate physical activity (14.1%), and heavy physical activity (8.7%). The TIMI II study revealed that the independent predictors of an infarction beginning during physical activity were male gender, no calcium antagonist or nitrate use during the prior 24 h, no history of hypertension, and being a nonsmoker.

The data discussed above involving possible triggering events are difficult to interpret in the absence of adequate control data. It is essential to estimate the expected level of activity in the hours before the infarction in order to assess the relative risk of infarction development following the occurrence of a suspected stressor. The usual exposure to a stressor must also be considered when comparing possible triggering elements among groups; for example, differences exist in the likelihood that patients with specific characteristics, such as older age, will perform certain activities.

Such limitations are being overcome in an ongoing study—the Determination of Onset of Myocardial Infarction Study (the Onset study)—that uses a novel method termed the case-crossover design. Patients are asked not only about their activity in the hour preceding their infarction, but about the usual frequency of exposure to the potential trigger. These data permit calculation of the relative risk of infarction following a trigger. Through use of this method, it has now been demonstrated that heavy physical exertion
(estimated to be > 6 metabolic equivalents of the task [METS]) produced a 5.9-fold relative risk of MI in the subsequent hour. The risk of MI during heavy exertion was significantly higher (107-fold) in those individuals who were sedentary than in those who exercised regularly (two-fold).17

AUTOPSY AND ANGIOGRAPHIC DATA

Most Q-wave Mls are the result of coronary artery thrombosis.17 In patients with unstable angina, coronary angiographic and angioscopic studies18,19 have demonstrated a high frequency of nonocclusive coronary thrombosis. Pathologic studies20 have shown the underlying cause of acute coronary syndromes to be thrombus formation over a disrupted plaque. This finding is supported by an angiographic study that demonstrated outpouching of contrast media, indicative of plaque rupture, in patients who had undergone successful thrombolysis.21 Angiographic evidence indicates that in a large percentage of patients surviving an MI, the degree of stenosis of the culprit atherosclerotic plaque is relatively mild, and an obstructive thrombus accounts for most of the obstruction to blood flow.

MORNING INCREASE OF PHYSIOLOGIC PROCESSES POSSIBLY CAUSING INFARCTION

The morning increase in Mls may be due to accentuation of physiologic processes during the hours after awakening. These physiologic factors may act on a vulnerable plaque to promote plaque rupture and thrombosis. The morning arterial pressure surges (Figure 2)22 may initiate plaque rupture, while an increase in coronary tone may reduce an already decreased coronary blood flow resulting from a fixed stenosis. Although serum cortisol levels fall during the morning period, they are increased above basal levels.23 The relative increase in serum cortisol levels could enhance the sensitivity of the coronary arteries to the vasoconstricting effects of catecholamines, which have a prominent surge after assumption of the upright posture.24 Increases in coronary tone and blood pressure in the morning hours may act together to promote plaque disruption and subsequent platelet deposition.

An increase in platelet aggregability,24,25 blood viscosity,26 and an insufficient rise in circulating tissue plasminogen activator (tPA) activity27 may act to cause a state of relative hypercoagulability in the morning. This heightened thrombotic state may act to increase the size of a thrombus once plaque fissuring occurs, and may convert a small, harmless, mural thrombus into a thrombus that can occlude the lumen of a coronary artery.

It is likely that the same physiologic processes that occur in the morning and predispose to circulatory events onset also occur at other times of the day. The peak morning incidence of cardiovascular events onset probably results from the synchronization of the population for morning triggers. Throughout the rest of the day, the exposure of the potential triggers is random and no other prominent peaks of an incidence are observed.

OTHER TRIGGERING CYCLES

There are cycles other than circadian cycles that can provide further insight into triggering. The relatively greater morning frequency of infarction during weekdays compared with weekends observed in the TIMI population may be due to a greater intensity of physical and mental activity during weekdays.4 Alternatively, on weekends, the population has a greater dispersion of wake times and consequent initiation of activities than during the week that may attenuate the morning peak by the decrease of synchronization of these wake times.

There are also annual cycles of ischemic heart disease, with winter yielding the peak of acute coronary events. While the peak of ischemic episodes in the northern hemisphere occurs in December, January, and February,25,29 the peak in the southern hemisphere occurs in June, July, and August, indicating that seasonal variation is the significant factor, not the time of the year.30,31 A portion of the peak of coronary events during the winter appear to be due to the cold temperature. It has been reported that in men older

![Figure 2](https://academic.oup.com/ajh/article-abstract/9/S1/229/129660)
than 65 years of age there was a 16% increase in the number of sudden coronary deaths with a 4.4°C decline in temperature, and a 25% increase with an 8.3°C decrease in temperature. Another factor that may contribute to the winter peak of coronary events is the association of cardiac deaths and snowfall. One group reported an 88% increase in the rate of sudden cardiac death with 10.2 cm of snowfall. This increase in sudden death persisted during the 3 days following the snowfall. The increased mortality rate may be due to the excessive exertion associated with shoveling snow or even walking in the snow. An additional effect of the winter months that may influence the rate of coronary events may be the seasonal increase in arterial pressure that occurs during the winter months, a factor whose effect may be similar to that of morning triggering of ischemic events.

Using the case-crossover study design method, the Onset study has evaluated other possible triggers of coronary events. The investigators have determined that physical or sexual activities, as well as the presence of anger, increase the relative risk that a coronary event will occur. While relative risks increase in the presence of these potential triggers, it is important to note that the increases in absolute risk are quite small because the baseline hourly risk is extremely low even in cardiac patients. For example, while heavy exertion increases relative risk over 100-fold in a sedentary individual, the absolute risk increases only a small amount, since the baseline risk of an event occurring in any given hour is in the range of one chance in a million.

EFFECTS OF PHARMACOLOGIC AGENTS ON TIMING AND TRIGGERS

The effect of medication on the temporal pattern of acute cardiovascular disease may provide further understanding of the triggering mechanisms and disease onset. The mechanism by which β-blocking agents exert their protective effect against MI and sudden death in patients with ischemic cardiac disease is not well understood. Both the MILIS and the TIMI studies have demonstrated a blunting of the morning peak of onset of acute MI in patients receiving β-adrenergic blocking agents. It has been hypothesized that β-blockers prevent MI by minimizing those increases in contractility and arterial pressure that would cause increased plaque stress and possibly lead to plaque disruption and thrombosis. β-Blocking agents have also been shown to attenuate the morning peak of silent ischemic episodes, which is likely a result of the ability of β-blockers to decrease myocardial oxygen demand.

Aspirin has also been shown to reduce the occurrence of MIs, a benefit that is presumed to be secondary to its antiplatelet action. In the Physician's Health Study, aspirin (325 mg every other day) reduced the overall (24-h cycle) incidence of MI by 44% compared to placebo. Of particular interest was a 59% reduction in risk of MI during the morning peak waking hours. Aspirin, by inhibiting platelet aggregation, may diminish the morning surge of platelet activity that appears to be an acute risk for disease onset.

THE THEORY OF TRIGGERING OF CORONARY THROMBOSIS

Davies and Thomas and others have advanced the hypothesis that the cause of acute coronary syndromes is the disruption of an atherosclerotic plaque and subsequent thrombus formation. The data on triggering have led to a proposed description of a mechanism of onset of coronary thrombosis. It is proposed that the first stage in the process is the development of a plaque that is vulnerable to rupture—the "vulnerable atherosclerotic plaque." The physical properties of a vulnerable plaque are not well understood. However, it has been hypothesized that a vulnerable plaque has a higher lipid and lower collagen content, is less stenotic, and has monocytes on its periphery. Such vulnerability is presumably a dynamic process, and is potentially reversible. A plaque may become nonvulnerable if there is a change in the plaque constituents, such as a decrease in lipid content.

If a vulnerable plaque is present, the onset of an acute coronary event may occur when a physical or mental stress triggers a hemodynamic change sufficient to cause plaque disruption (Figure 3). The plaque disruption itself may have no consequences, but if sufficient prothrombotic forces are present, thrombosis will occur. If the thrombus is small, it may result in an increase in the coronary stenosis, and possibly angina. If the thrombus is occlusive, it is likely to cause an acute MI and possibly lead to sudden death.

The onset of some infarctions may result from the simultaneous occurrence of several events, each of little consequence by itself. For example, the combination of physical exertion that produces a small plaque rupture, followed by cigarette smoking that may produce coronary artery vasoconstriction and a relative hypercoaguable state, may be sufficient to trigger disease onset.

SIGNIFICANCE OF TRIGGERS

The immediate value of the recognition of the morning peak of acute coronary syndromes and their possible triggers is the emphasis that can be placed on pharmacologic protection. Although it remains to be proved, it seems reasonable that longer-acting antiischemic agents might have an advantage over shorter-acting agents by their ability to reduce ischemia and the effects of the triggers occurring at the time of awakening. The effects of shorter-acting medi-
Triggering of Coronary Thrombosis

Nonvulnerable Atherosclerotic Plaque

Vulnerable Atherosclerotic Plaque

Physical or Mental Stress Triggers Plate Rupture

Minor Plaque Rupture

Major Plaque Rupture

Asymptomatic, Unstable Angina, or Non-Q MI

Occlusive Thrombus

Myocardial Infarction or Sudden Cardiac Death

Coagulability Increase or Vasoconstriction Triggers Complete Occlusion by Thrombus

Nonocclusive Thrombus

Vasoconstriction Triggers

Myocardial Infarction or Sudden Cardiac Death

Q=Q wave; MI=myocardial infarction.

FIGURE 3. A hypothetical presentation of the manner in which daily activities may trigger coronary thrombosis. Three triggering mechanisms—physical or mental stress producing hemodynamic changes leading to plaque rupture, a coagulability increase, and vasoconstriction—have been added to the well-known scheme depicting the role of coronary thrombosis in unstable angina, myocardial infarction, and sudden cardiac death. Reproduced with permission from Muller et al.5

The lack of significance of triggering information currently available as grounds for advising against individual activities, as well as its relatively limited value in patient management, should not obscure the enormous importance of this field of research for the prevention of cardiovascular disease. When triggering is assessed not in healthy individuals, but in those who have had an infarction—a view from the opposite end of the telescope—the value of this field of study is apparent. Case-control studies indicate that an identifiable trigger was present in approximately 15% of patients.16,35,36 It is likely that an even larger number of infarcts had a trigger that cannot be identified by the relatively insensitive methods currently available. Hence, triggering plays a role in a significant number of cardiac events. If its mechanisms were better understood, efforts to design therapy to sever the link between a potential trigger and its pathologic consequences would be greatly facilitated, and many coronary events might be prevented.

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