Circadian Variation and Triggers of Onset of Acute Cardiovascular Disease

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Direct events often precipitated 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.

A quote from the original description of myocardial infarction published by Obraztsov and Strazhesko in 1910.1

Coronary occlusion takes place irrespective of the physical activity being performed or the type of rest taken.

A quote from a study of the role of effort in precipitating myocardial infarction published by Master in 1960.2

The conflicting views presented above—the earlier assertion that the onset of myocardial infarction is frequently triggered by external events and the currently accepted view of Master—that infarct onset is generally unrelated to the day’s activities—must be reexamined in light of new information. The major advances in the understanding of mechanisms and treatment of coronary artery disease accomplished during the past decade have provided a new basis on which to examine the onset of myocardial infarction and sudden cardiac death. The recognition of silent myocardial ischemia and its precipitants, the identification of endothelial dysfunction, the rediscovery of coronary thrombosis, and the lysis of obstructive thrombus by thrombolytic therapy have not only produced immediate gains in treating coronary artery disease but have also generated knowledge that may contribute to prevention. This review will summarize the accumulated data that, together with new information about circadian variation of disease onset, suggest that daily activities trigger onset of most cases of myocardial infarction and sudden cardiac death.

History

The proposal by Obraztsov and Strazhesko1 in 1910 that activities frequently trigger infarction was challenged in the 1930s when studies of larger numbers of patients revealed that, in many instances, infarction occurred without an obvious precipitating event. A lively controversy developed with investigators for3-5 and against6 the view that triggers were frequent. The debate ended with widespread acceptance of the conclusion of Master,2 based on retrospective questionnaires, that activities are of little importance in triggering onset.

This viewpoint has prevailed for the past 3 decades, even though it is based on studies conducted without the benefits of modern methods of epidemiologic investigation, without enzymatic diagnosis of myocardial infarction, and without the insight provided by recent advances in the understanding of the pathogenesis of myocardial infarction. Data obtained with these new techniques indicate that the original proposal by Obraztsov and Strazhesko may be correct and that—just as the causative role of coronary thrombosis was rediscovered in the early 1980s—it will be rediscovered that daily activities frequently trigger the onset of coronary thrombosis.

Epidemiologic Evidence of Morning Increase of Events

The present proposal that daily activities are of importance in triggering coronary thrombosis is based, in part, on epidemiologic findings that the events caused by coronary thrombosis—myocardial infarction and sudden cardiac death—do not occur randomly throughout the day but that they occur in a prominent circadian pattern with a morning increase in frequency (Figure 1).

Myocardial Infarction

Objective evidence that myocardial infarction is at least three times more likely to begin in the morning than in the late evening was obtained from the Multicenter Investigation of Limitation of Infarct Size (MILIS)7 (Figure 1) and from the Intravenous Streptokinase in Acute Myocardial Infarction (ISAM) study.8 Both studies determined the onset of myocardial infarction objectively on the basis of the time of first appearance of creatine kinase in the plasma. Their finding is supported by a larger number of studies9-12 that used onset of pain as a marker of time of myocardial infarction.
onset. The earlier studies received limited attention because the reported morning increase in incidence was thought to be simply the result of delayed reporting of onset of myocardial infarction that actually began during the night while the patient was sleeping.

Several features of this morning increase were recently explored. Hjalmarson et al\textsuperscript{11} have found that the morning increase is blunted or abolished in subgroups of patients with characteristics such as advanced age, diabetes, smoking history, and prior infarction, while Goldberg et al\textsuperscript{12} have reported that the increase in incidence occurs in the first 4 hours after awakening.

**Sudden Cardiac Death**

Because of the close relation between myocardial infarction and sudden cardiac death, identification of the increased morning incidence of myocardial infarction led to efforts to determine the time of occurrence of sudden cardiac death. The apparently simple task of determining time of occurrence is even more difficult for sudden cardiac death than for myocardial infarction because of 1) the difficulty, in certain situations, of determining whether or not a sudden cardiac event is actually the cause of death, 2) the occurrence of unwitnessed deaths for which the determination of time of death, as well as cause of death, is uncertain, 3) the increased likelihood that such unwitnessed deaths will occur at night, and 4) the large number of subjects needed to detect a morning increase. These methodologic problems were solved in studies of two large databases—mortality records for Massachusetts for 1983\textsuperscript{13} and the Framingham Heart Study.\textsuperscript{14}

Results of examination of death certificates of 2,203 individuals who experienced out-of-hospital sudden cardiac death in Massachusetts in 1983 showed a circadian rhythm of occurrence remarkably similar to that observed for myocardial infarction\textsuperscript{15} (Figure 1). The time of sudden cardiac death was then examined in the Framingham Heart Study population.\textsuperscript{14} The frequency of definite or possible sudden cardiac death in this well-characterized population showed a prominent circadian variation similar to that observed in the death certificate study.

A number of prior studies of time of death support the conclusions of the Massachusetts Death Certificate Study and the Framingham Heart Study, although no single study features their combination of size and specificity of diagnosis.\textsuperscript{15,16}

**Stroke**

Characterization of the time of stroke onset has also been plagued by the problem of determining time of onset of events detected when the patient awakens. However, when such events are considered to have occurred randomly during the 8 hours before awakening, there remains a prominent increase in the interval from 6:00 AM to noon similar to that observed for myocardial infarction and sud-
FIGURE 2. Bar graphs of variation during a 24-hour period of eight physiologic processes possibly contributing to the increased morning frequency of disease onset shown in Figure 1. Systemic blood pressure and heart rate measured intra-arterially in five normotensive ambulant subjects; coronary blood flow velocity measured by Doppler ultrasonic flow probe in 21 dogs; whole blood viscosity measured by Ostwald-capillary-viscometer in eight normal male volunteers; platelet aggregability measured by in vitro platelet aggregometry in 15 normal male volunteers; tissue-type plasminogen activity (tPA) measured by spectrophotometric assay in six normal volunteers (four male, two female); plasma cortisol measured by competitive protein binding method in six normal male volunteers; plasma epinephrine measured by a radio isotope method in 15 normal male volunteers. See text for discussion. Data adapted with permission.
den cardiac death. The time of stroke onset is remarkably similar to that of myocardial infarction and sudden cardiac death (Figure 1).

The epidemiologic data presented in Figure 1 are likely to underestimate the true magnitude of the morning increase in disease onset because, in these databases, onset time is not adjusted for variable time of awakening and variable work schedules. It is far more likely as suggested by the study of Goldberg et al., that the onset of disease is more closely related to the activity cycle of the individuals than to the absolute time of day.

Timing of Transient Myocardial Ischemia

Data indicating the increased morning incidence of onset of the relatively infrequent cardiovascular disasters—myocardial infarction, sudden cardiac death, and stroke—have been supported by information about the much more frequent and more easily studied disorder of transient myocardial ischemia. With improved techniques of ambulatory electrocardiographic monitoring, Selwyn et al., Schang and Pepine, Cohn, Stern and Tzivoni, and others have clearly established that, in the absence of anti-ischemic therapy, most patients with stable angina exhibit episodes of transient myocardial ischemia with ST segment depression (70–90% of which are clinically silent) during routine out-of-hospital activities.

With episodes of transient ischemia occurring that frequently and with continuous Holter monitoring eliminating the possibility of bias resulting from unobserved periods, the timing of episodes of transient ischemia has been possible with great accuracy. These studies have consistently shown a peak incidence of episodes occurring between the hours of 6:00 AM and 12 noon (Figure 1). Furthermore, Rocco et al. were able to adjust the timing of episodes for wake time and show that the increase in frequency occurs in the first 4 hours after awakening and beginning the day’s activities, a finding similar to that reported for myocardial infarction onset.

Triggers of Transient Myocardial Ischemia

A number of studies have investigated the cause of transient ischemia, the results of which may contribute to improved understanding of the cause of myocardial infarction and sudden cardiac death. The parallel morning increases in transient ischemia and these catastrophic cardiac events suggest that the generally reversible event of transient ischemia may, in the presence of a vulnerable plaque, trigger the onset of the irreversible events of infarction and sudden death, although transient ischemia and the irreversible events may be merely associated and not causally related.

Investigations of the possible triggers of transient ischemia have attempted to identify activities or pathophysiologic processes that occur before individual episodes or that have a temporal distribution similar to that of the ischemic episodes. Barry et al. have shown that when potential mental, as well as physical, causes of ischemia are considered, over half of transient ischemic episodes are preceded by possible triggering activities. Furthermore, normalization of a triggering activity for the time spent engaged in the activity, revealed a high likelihood of occurrence during increased physical or mental stress.

Studies of the mechanism by which an activity triggers transient ischemia have led to considerable controversy over the relative contribution of decreases in myocardial oxygen supply (due to transient vasoconstriction or platelet aggregation causing decreased coronary artery blood flow) and of increases in myocardial oxygen demand (as determined by increases in heart rate and systemic arterial pressure). The view that transient ischemia is due to decreases in coronary artery flow is supported by in vitro observations that an artery with atherosclerotic changes shows an exaggerated vasomotor sensitivity to a number of normally occurring substances such as norepinephrine, histamine, and serotonin and a paradoxical vasoconstrictor response to acetylcholine. Patients with coronary disease also have abnormal coronary endothelial function that may lead to paradoxical vasoconstriction in response to a number of stimuli that produce coronary vasodilatation in normal individuals. Angiographic studies in patients have shown that, in the presence of atherosclerosis, dynamic exercise, handgrip, exposure to cold, and infusion of acetylcholine produce coronary vasoconstriction, when vasodilatation would be the normal response. A decrease in regional coronary blood flow may also result from passive mechanical collapse of the epicardial coronary artery distal to a fixed critical stenosis.

Careful dissection of the supply-demand issue by study of the ischemic threshold suggests that both increased demand and decreased supply are frequent causative factors. Quyumi and coworkers recently reported in patients with stable angina that exercise performance was worse in the morning and at night at times when forearm vascular resistance (and presumably coronary vascular resistance) was highest.

The mechanism of transient ischemia produced by mental stress has also been examined. Verrier et al. showed that in dogs with a partially obstructed coronary artery, coronary vascular resistance increases 2–4 minutes after anger, leading to an additional 35% reduction in flow. Deanfield et al. found that in patients with stable angina, a regional reduction in coronary flow developed after performing mental arithmetic. Thus, although myocardial oxygen demand rises after mental stress, as indicated by increases in systolic blood pressure, the ischemia that ensues also results from a primary decrease in coronary blood flow.

Cigarette smoking has caused a decrease in myocardial blood flow (decreased uptake), indicating that vasoconstriction may be a mechanism by which it triggers myocardial ischemia.
The response of ischemic episodes to various pharmacologic regimens may also provide indirect evidence of the mechanisms causing the ischemic process. Episodes of out-of-hospital ischemia, both silent and symptomatic, in patients with stable angina are significantly reduced or prevented by β-blockers, supporting the etiologic role of increased myocardial oxygen demand. Nifedipine, a calcium channel blocker that causes reflex increases in heart rate, when used alone may not be as effective in reducing episodes of ambulatory ischemia as diltiazem, which causes a reduction in heart rate. The anti-ischemic efficacy of nifedipine is increased significantly, however, by the addition of a β-blocker that reduces the heart rate.

Concerning the role of platelets in stable angina, metoprolol has reduced significantly the frequency and duration of ischemic episodes without affecting the morning surge in platelet aggregability, and ticlopidine, a potent inhibitor of platelet activity, has been ineffective in reducing episodes of transient ischemia. These studies suggest that platelet aggregation plays only a small role in ambulatory episodes of transient ischemia, although it may have a significant role in unstable angina and thrombus formation.

In summary, it appears likely that episodes of ischemia in patients with stable angina during ambulatory activities are often caused by a combination of transient coronary vasoconstriction and transient increases in heart rate or systemic arterial pressure, or both, although episodes may less frequently be due to either mechanism alone. With either mechanism, the high frequency of triggering by mental stress or physical activity is important. Clarification of this triggering phenomenon may lead to improved means of prevention, not only of transient ischemia, but of the related conditions of myocardial infarction and sudden death.

**Autopsy and Angiographic Data Pertinent to Onset of Myocardial Infarction and Sudden Cardiac Death**

Investigations of the triggers of myocardial infarction and sudden cardiac death are also aided by recent advances in understanding the pathologic basis of these disorders. In 1980, DeWood et al convincingly showed that occlusive coronary artery thrombosis is the cause of most Q wave myocardial infarctions, and although sudden cardiac death is ultimately an electrical event, approximately one third of the subjects have a fresh, occlusive coronary thrombus at autopsy examination. Davies and Thomas have presented data indicating that even the two thirds of cases of sudden cardiac death without occlusive thrombus demonstrable at autopsy frequently have a nonocclusive thrombus in the coronary artery that may have been a site for platelet aggregate formation during life that caused death by temporary proximal occlusion or distal embolization. In patients with rest pain and unstable angina, coronary angiographic and angioscopic findings indicate that nonocclusive thrombus is frequently present. Thus, the occurrence of coronary artery thrombosis appears to be a common, essential link in the onset of most cases of myocardial infarction, sudden cardiac death, and unstable angina.

Valuable autopsy and angiographic data are also available concerning the cause of the thrombus. Serial histologic sections of arteries occluded by thrombus have revealed that, in most cases, the thrombus formed over a ruptured atherosclerotic plaque. This pathologic finding was recently supported by angiographic studies in patients demonstrating the presence of an out-pouching of contrast media indicative of plaque rupture in patients who have undergone successful thrombolysis.

Two mechanisms of plaque rupture have been proposed. Constantinides has advanced the concept that the rupture occurs from the lumen into the plaque, whereas Barger et al have proposed that rupture may occur from the plaque into the lumen. The latter theory is based on the presence of extensive vasa vasorum in atherosclerotic plaques. Because these vessels may originate upstream to a coronary stenosis, under certain conditions, their pressure could exceed that in the coronary lumen distal to the stenosis, leading to explosive rupture of the plaque into the lumen.

Although autopsy studies generally reveal severe atherosclerotic stenosis at the base of a fatal coronary thrombus, angiographic evidence indicates that in many patients surviving a myocardial infarction, the degree of stenosis is relatively mild, and thrombus accounts for most of the obstruction to blood flow. Brown et al reported that the degree of “original” stenosis in patients with myocardial infarction observed after treatment with streptokinase was less than 60% in two thirds of the cases. Little et al recently studied the extent of prior stenosis at sites in the coronary arteries that subsequently became totally occluded. In two thirds of the patients with mild-to-moderate coronary disease, the site of occlusion had less than a 50% stenosis on the preinfarction angiogram. Haft et al have also described “catastrophic” progression of coronary lesions, which presumably results from episodes of thrombosis. These findings may explain the absence of prior symptoms in many patients presenting with acute myocardial infarction or sudden cardiac death and support the suggestion made in 1986 by Oliver that attempts to identify and modify triggers of thrombus formation may have great clinical benefit.

**Morning Increase of Physiologic Processes That May Trigger Cardiac Events**

A coronary atherosclerotic plaque is exposed to a number of systemic physiologic processes that could, if the plaque were vulnerable, cause disease onset. Many of these processes increase in intensity in the morning as shown in Figure 2. Such increases could, alone or in combination, account for the
morning increase in cardiac disease onset (Figure 1) through a variety of mechanisms.

The arterial pressure surge, which is accompanied by a heart rate increase, could cause plaque rupture. The coronary arterial tone increase could worsen the flow reduction produced by a fixed stenosis. The increase in blood viscosity, increased platelet aggregability (resulting from assumption of the upright posture), and an insufficient countervailing increase in circulating tissue-type plasminogen activator activity could produce a state of relative hypercoagulability. Such a thrombotic tendency could increase the likelihood that an otherwise harmless mural thrombus overlaying a small plaque fissure would propagate and occlude the coronary lumen. The increased serum cortisol levels, although decreasing during the period of increased disease onset, could increase the sensitivity of the coronary arteries to the vasoconstrictor effects of catecholamines, which have a prominent surge after assumption of the upright posture.

Although a 24-hour periodicity of disease onset (Figure 1) and physiologic processes (Figure 2) is well established, the degree to which the disease periodicity results from a true, endogenous circadian rhythm or from the daily rest-activity cycle is only partially characterized. Cortisol secretion, for example, is well known to be an endogenous circadian process not dependent on daily activity, whereas the increase in morning platelet aggregability is abolished if the subject remains at bedrest.

The rest-activity cycle seems to be a major determinant of disease onset because adjustment for time of awakening shows that infarction onset and increases of transient ischemia follow awakening, but such adjustment could also align the population for their endogenous circadian rhythms. Also, an interaction between circadian and rest-activity cycles may exist; for example, assumption of the upright posture leading to sympathetic activation may be more likely to cause intense vasoconstriction when endogenously controlled cortisol levels are high.

Although attention has focused on the morning as the time of peak incidence of disease onset, similar physiologic processes probably trigger disease onset at other times of the day. The peak morning incidence of infarct onset and sudden death probably results from the synchronization of the population for triggers in the morning, whereas a secondary evening peak in infarct onset observed in the MILIS data may result from synchronization of the population for an additional trigger such as the evening meal. For other periods of the day, exposure of the population to potential triggers is random, and no other prominent peaks of incidence are observed.

A summary of the types of physiologic change likely to occur in patients with atherosclerosis during several potentially triggering daily activities is presented in Table 1. These activities may be more likely to cause adverse effects in patients than in normal subjects because as noted above, paradoxical vasoconstriction may occur in coronary arteries afflicted with atherosclerosis. The effects of daily activities on the sympathetic nervous system, systemic arterial pressure, and heart rate are well characterized, but the response of the coagulation system to these activities is more complex and less well understood. The conflicting results reflect in part the choice of model and technique: in vivo, ex vivo, or in vitro.

Also, unusual mechanisms of disease onset may occur in only a minority of the population, such as postural hypotension, which has been suggested as a trigger of stroke onset, causing decreased perfusion. Other possible triggering changes are those associated with acute infectious diseases.

Ability of Agents That Block Potential Triggering Processes to Prevent Myocardial Infarction and Sudden Cardiac Death

The theories advanced above are indirectly supported by the demonstrated efficacy of aspirin therapy and \( \beta \)-adrenergic blockade in preventing myocardial infarction and sudden cardiac death. Aspirin, which presumably acts primarily as an antplatelet agent, is thought to reduce the occurrence of sudden death and myocardial infarction by preventing coronary thrombosis.

\( \beta \)-Adrenergic blocking agents have prevented myocardial infarction and sudden cardiac death even though these agents do not have potent antithrombotic or antiarrhythmic properties. A clue to mechanism is provided by the observations in the MILIS and the ISAM databases that \( \beta \)-blockade eliminated the morning peak in the incidence of myocardial infarction onset. In addition, in the Beta Blocker Heart Attack Trial, a morning increase was found in sudden cardiac death in the placebo group but not in the group randomly assigned to \( \beta \)-blockade therapy, suggesting that the beneficial effect was achieved by blockade of the morning surge in sympathetic activity. \( \beta \)-Blockade, but not a short-acting calcium blocker, has attenuated the morning increase in silent myocardial ischemia. It has been suggested that the \( \beta \)-blockers may prevent rupture of atherosclerotic plaques, just as they are considered to exert a beneficial effect in dissecting aneurysms preventing rupture of the aortic wall (personal communication, Dr. William H. Frishman). With increased knowledge of triggering mechanisms, it is likely that the impressive gains already achieved by aspirin and \( \beta \)-blockade therapy can be increased.

General Theory of Triggering of Coronary Thrombosis

Although incomplete, the available data permit formulation of a general hypothesis regarding the manner in which daily activities may trigger coronary thrombosis. The hypothesis presented in Figure 3 is proposed for the sake of the knowledge that its confirmation or rebuttal may generate. It adds the concept of triggering activities to the general
Triggering of Coronary Thrombosis

scheme of the role of thrombosis in the acute coronary syndromes advanced by Davies and Thomas,51 Falk,58 Fuster et al,96 Willerson et al,97 and Badimon et al.98

It is proposed that the initial step in the process leading directly to coronary thrombosis is the development, with advancing age, of what can be termed a "vulnerable atherosclerotic plaque." Plaque vulnerability is defined functionally as the susceptibility of a plaque to rupture. Development of such vulnerability is a poorly understood process but is presumably a dynamic, potentially reversible disorder caused by changes in the constituents of the plaque, its blood supply through vasa vasorum, or the functional integrity of the overlying endothelium.

The theory that onset of thrombosis is unrelated to daily activities would presumably attribute disease onset solely to changes in the plaque, and the diagram would therefore lead directly from the plaque to coronary thrombosis. In the present formulation, however, it is proposed that onset may frequently begin when a physical or mental stress triggers a hemodynamic change sufficient to rupture a vulnerable plaque. (If such a trigger does not occur during vulnerability, the plaque may change and become nonvulnerable.)

The rupture in the plaque may be major or minor, depending on factors such as the amount and type of collagen exposed.98 A major plaque rupture produces a thrombogenic focus sufficiently intense to cause occlusive coronary thrombosis leading directly to myocardial infarction or sudden cardiac death. A minor rupture leads only to a mural thrombus that fails to produce symptoms or leads to unstable angina or non-Q wave myocardial infarction. Again, at this point external activities may lead to occlusion of the lumen. For example, an activity causing a coagulability increase may trigger growth of the thrombus, or a stimulus to vasoconstriction may lead to complete occlusion of an already compromised lumen leading to infarction or sudden death.

Because normal individuals and even patients with coronary artery disease are constantly exposed
to potentially triggering activities that do not produce coronary thrombosis, development of plaque vulnerability is probably the rarest event in the chain of causation described above.

An inverse relation probably exists between the degree of plaque vulnerability and the intensity of the triggering stimulus required to produce rupture. For instance, an elderly individual with a severe fixed stenosis in a coronary artery and an extremely vulnerable plaque may develop thrombosis with only a minor stress, whereas a young individual with only a luminal irregularity may require a major stress (such as heavy lifting producing markedly increased arterial pressure) to trigger plaque rupture and coronary thrombosis. As yet, no data exist to support these hypothetical mechanisms.

Various mixtures of triggering mechanisms may account for thrombosis. For example, the combination of physical exertion (producing a minor plaque rupture) followed by cigarette smoking (producing an increase in coronary artery vasoconstriction and a relatively hypercoagulable state) may be needed to cause disease onset. Thus, the onset of infarction or sudden death may, in some cases, be the result of the unfortunate simultaneous occurrence of several events each by itself of little consequence but catastrophic when occurring together.

**Significance**

The primary immediate value of recognizing the circadian variation of acute onset of cardiovascular disease is the emphasis that can be placed on pharmacologic protection during the morning hours for patients already receiving anti-ischemic therapy. But even complete elimination of the morning increase in onset of myocardial infarction and sudden cardiac death by effective therapy would prevent only a small fraction of the total morbidity and mortality caused by these disorders. Although the incidence of disease onset is greatest in the period from 6:00 AM to noon, most infarcts and sudden deaths occur at other times of the day, and their prevention requires a broader approach. For this reason, the primary significance of the recognition of circadian variation of disease onset is the support it provides for the broader concept that the onset of coronary thrombosis at any time of the day is frequently triggered by activities of the patient. This concept provides a number of clues to the mechanisms of disease onset—clues that suggest a value of studies ranging from the epidemiologic to the molecular levels.

On the epidemiologic level, studies must be conducted in which patients who experience a nonfatal myocardial infarction and witnesses to a sudden cardiac death are interviewed to determine whether or not the event had an identifiable trigger. Because potentially triggering activities occur frequently without producing an event, the studies must be controlled for the frequency of potential triggers at times when an event did not occur.

The certainty with which an activity can be identified as a trigger will also vary in individual cases. In a patient whose plaque is only slightly vulnerable, the activity required to produce disease onset may be extreme, and the activity can be recognized as a trigger by its intensity. Other features that may aid in recognizing an activity as a trigger are its occurrence immediately before the event, its ability to produce physiologic changes likely to trigger thrombosis, and its absence as part of the patient’s routine activity. However, in a patient with an extremely vulnerable plaque, even nonstrenuous, routine, daily activities may be sufficient to trigger the cascade leading to infarction or sudden death. In such instances, identifying the triggering activity may be impossible even though it was present. Thus, the group of patients with identifiable triggers will be a subset of those in whom external triggering actually occurred.

On the clinical level, increased study of the relation between daily activities and potentially triggering physiologic responses, such as the eight processes presented in Figure 2, could clarify the
manner in which these and other processes cause disease onset.

On the basic science level, a need exists for complete characterization of the control mechanisms of potentially adverse physiologic changes. When these mechanisms are understood more fully, it may be possible to eliminate unnecessary surges in arterial pressure, vasoconstriction, and coagulability that contribute to disease onset. Further study is also needed of the factors determining plaque vulnerability and of the possibility that reduction of plasma cholesterol may exert its beneficial effect by reducing the susceptibility of a plaque to rupture as well as by preventing the development of stenotic lesions.

A more complete understanding of triggering mechanisms should permit progress in the prevention of most cardiac deaths that occur unexpectedly in an out-of-hospital setting. The means of prevention would not be to eliminate potential triggering activities—an undesirable and unattainable goal—but to design regimens that can be evaluated in randomized studies for their ability to sever the linkage between a potential triggering activity and development of a catastrophic coronary thrombosis.

**Summary**

Information obtained during the past decade suggests the need to reexamine the possibility that the onset of myocardial infarction and sudden cardiac death is frequently triggered by daily activities. The importance of physical or mental stress in triggering onset of coronary thrombosis is supported by the findings that 1) the frequencies of onset of myocardial infarction, sudden cardiac death, and stroke show marked circadian variations with parallel increases in the period from 6:00 am to noon, 2) transient myocardial ischemia shows a similar morning increase, and episodes are often preceded by mental or physical triggers, 3) a ruptured atherosclerotic plaque, often nonobstructive by itself, lies at the base of most coronary thrombi, 4) a number of physiologic processes that could lead to plaque rupture, a hypercoagulable state or coronary vasoconstriction, are accentuated in the morning, and 5) aspirin and β-adrenergic blocking agents, which block certain of these processes, have been shown to prevent disease onset.

The hypothesis is presented that occult circadian coronary thrombosis occurs when 1) an atherosclerotic plaque becomes vulnerable to rupture, 2) mental or physical stress causes the plaque to rupture, and 3) increases in coagulability or vasoconstriction, triggered by daily activities, contribute to complete occlusion of the coronary artery lumen.

Recognition of the circadian variation—and the possibility of frequent triggering—of onset of acute disease suggests the need for pharmacologic protection of patients during vulnerable periods, and provides clues to mechanism, the investigation of which may lead to improved methods of prevention.

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