

Cardiology Rounds

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Circadian rhythm and the triggering of acute coronary syndromes

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Despite the frequency of the acute coronary syndromes of myocardial infarction (MI), sudden cardiac death, and unstable angina, relatively little is known of the events that transform a patient with chronic, stable coronary atherosclerosis into a patient with an acute life-threatening illness. While epidemiologic studies have traditionally focused on the role of chronic risk factors in promoting atherosclerosis and disease onset over a period of years, several recent observations have opened the broad field of acute risk and triggering to study. First, Q-wave MI is now recognized to be preceded by coronary thrombosis, which is in turn associated with plaque fissuring.^{1,2} Second, the demonstration that plaque disruption and thrombosis frequently occur at the site of a previously mild stenosis suggests that the transformation occurs acutely.³ Third, the circadian variation in frequency of MI, sudden cardiac death, and unstable angina, indicates that events occur non-randomly and may be frequently triggered by external activities.⁴

History of the triggering concept

The concept of stressors such as physical exertion or psychological stress as triggers of acute cardiovascular disease has strong historical roots. The 18th century surgeon John Hunter said that his life was in the hands of any scoundrel who chose to annoy him.⁵ After emerging from a rancorous hospital board meeting, Hunter, who suffered from angina pectoris, collapsed and died.

Obratsov and Strazhesko, in their 1910 description of the clinical features of acute MI, stated that activities frequently triggered infarction onset.⁶ Their view was challenged in the 1930s as studies of larger numbers of patients revealed that in many instances, infarction occurred without an obvious precipitating event.^{7,8} The view that activities are of minor importance in triggering onset has prevailed until recent challenges based on modern epidemiologic investigation and large data sets.

Morning increase of cardiovascular events

The proposal that daily activities are important in triggering MI and sudden death is based, in part, on epidemiologic findings that acute coronary syndromes occur in a prominent circadian pattern with a morning increase in frequency.

Myocardial infarction

The epidemiologic finding of a morning increase in MI was an unexpected finding from the Multicenter Investigation of Limitation of Infarct Size (MILIS). In 849 patients with confirmed MI, a marked variation in time of onset of infarction was present. A maximum of 45 infarcts occurred between 9 AM and 10 AM, and a minimum of 15 occurred between 11 PM and midnight.⁹

These results are now supported by a larger number of studies.¹⁰⁻¹² For example, in 3339 patients enrolled in the Thrombolysis in Myocardial Infarction (TIMI II) Study,¹² there was a higher frequency of onset of infarction in the morning, with 34.4% of episodes occurring between 6 AM and noon versus 15.4% occurring between midnight and 6 AM (Figure 1). Subgroup analysis has also revealed different patterns of onset that provide insight into mechanism. For example, patients with congestive heart failure appear to have a more prominent secondary evening peak than do those without reduced



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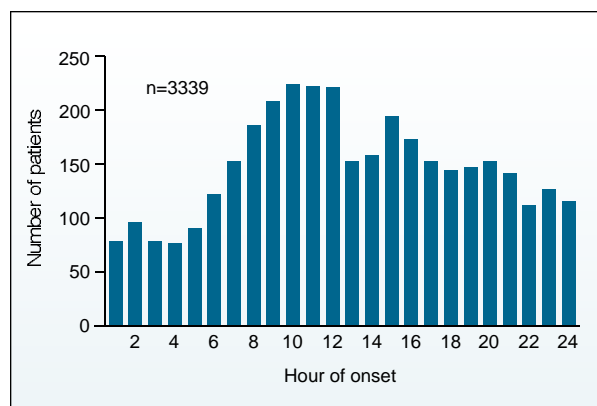
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Figure 1: The hourly frequency of the onset of MI as determined by the onset of pain symptoms in the TIMI II Study. A prominent circadian rhythm is present.



Adapted from Tofler et al² with permission of the *J Am Coll Card*.

left ventricular function.¹⁰ This may be due to a greater activation of sympathetic nervous system throughout the 24 hours in these individuals.

The morning peak in frequency is less apparent on the weekends than on weekdays. While this may reflect the greater variability in time of awakening and onset of activity during the weekend, it is also consistent with the hypothesis that the stress of the work week contributes to the morning peak in cardiovascular events. Goldberg et al¹³ demonstrated that the increased morning incidence of infarction occurs in the first four hours after awakening and onset of activity, supporting the role of activity rather than merely time of day in onset of infarction. In several analyses, including MILIS, there has also been a suggestion of a smaller secondary evening peak of infarction.^{9,10}

Transient myocardial ischemia

Several investigators have reported a morning peak in transient myocardial ischemia, both in symptomatic and asymptomatic episodes.¹⁴⁻¹⁷ An epidemiologic advantage of the studies of transient ischemia over those of MI and sudden cardiac death is that continuous 24-hour monitoring of myocardial ischemia overcomes the problem of lack of observation during the night.

To test the hypothesis that the morning increase in transient myocardial ischemia was related to time of awakening rather than to the time of day, Rocco et al¹⁸ studied 32 patients with angina in whom time of awakening was known. When their data were replotted with time of awakening considered to be time zero, the early morning increase of ischemia was even more striking, and the peak activity was found to occur in the first two hours after rising. This observation was confirmed by Parker and colleagues,¹⁵ who found that delaying the time of arising and onset of morning activity deferred the time of peak ischemia.

In addition to physical activity triggering transient myocardial ischemia, Barry et al¹⁹ investigated the relationship between a patient's perceived level of mental activity and ST depression during daily life. Although most ischemic episodes occurred during activities classified as "usual" physical or "usual" mental activity, when the duration of ST depression was divided by the total time spent in each category, it was

found that transient ischemia was more likely to occur as the intensity level of mental activity increased. Mental activities appear to be as potent as physical activities in triggering daily life ischemia.

Unstable angina

Patients with unstable angina are a heterogeneous group with differing pathophysiology. Behar and colleagues found the time of onset of instability to be maximal during the 6 AM to noon period. Recently, Cannon²⁰ found a similar morning peak in frequency in patients with unstable angina and non-Q-wave infarction enrolled in the TIMI III Study and Registry.

Sudden cardiac death

A circadian variation has been found for sudden cardiac death that parallels that of MI. The evidence that sudden cardiac death has an increased incidence in the morning was initially obtained from mortality reports of the Massachusetts Department of Public Health.²¹ The findings of a morning peak were then confirmed by analysis of the well-characterized Framingham Heart Study population.²² While for most cases of definite or possible sudden cardiac death, the exact time of death was known, for some it was necessary to estimate the interval in which the death occurred. In such instances, the probability of death was evenly distributed over the estimated interval. The time of occurrence of definite sudden cardiac death exhibited a prominent circadian variation with a peak in the morning and a low frequency during the night, as would be expected from the requirement that the death be witnessed. However, this circadian variation persisted when patients with possible sudden cardiac death (particularly those with unwitnessed deaths between midnight and 6 AM) were added to the analysis. The hourly risk of sudden cardiac death was at least 70% greater between 7 AM and 9 AM than the average risk during the remaining 22 hours of the day.

More recently, Levine and coworkers²³ identified a morning peak of sudden cardiac death in out-of-hospital cardiac arrests in the City of Houston Emergency Medical Services. Using documentation from semi-automated defibrillators in the Berlin emergency care system, Arntz et al²⁴ found a primary peak of frequency of ventricular fibrillation between 6 AM and noon, whereas asystolic episodes were more evenly distributed throughout the day. A primary arrhythmic event is more likely to occur in the morning since increased adrenergic activity at that time may increase electrical instability.

Most studies of ventricular ectopy indicate a prominent peak during daytime hours and a trough at night.²⁵ Twidale et al²⁶ observed that the peak incidence of sustained symptomatic ventricular tachycardic episodes in 68 patients occurred between 10 AM and noon. Although epidemiologic studies of sudden cardiac death have consistently found a morning peak, they are limited by their reliance on eyewitnesses to determine the timing of sudden cardiac death. The implantable cardioverter/defibrillator (ICD) provides a new opportunity to firmly establish the timing of malignant tachyarrhythmias, the most common cause of sudden cardiac death.²⁷ In an analysis of 483 patients who had an ICD implanted between 1990 and 1993, a prominent circadian

pattern of ventricular tachyarrhythmias was demonstrated with a peak between 9 AM and noon (21.8% of total episodes during the three-hour period).²⁸

Role of coronary atherosclerotic plaque

To better understand the underlying mechanism of the morning peak in these events, insights may be gained from autopsy and angiographic data into the role of plaque rupture and thrombosis. In 1980, DeWood and colleagues convincingly demonstrated that occlusive coronary artery thrombosis is the cause of most Q-wave MIs.¹ With the use of serial histologic sections, Constantinides and Davies found that in the majority of cases, the thrombus had formed over a ruptured atherosclerotic plaque.^{29,30}

Vulnerability to rupture is inversely related to the thickness of the fibrous plaque and directly related to the size of the lipid pool. The fibrous cap is often thinnest and weakest at its junction with the nearby intima.³¹ There is also angiographic evidence that in many patients surviving an MI, the degree of stenosis is relatively mild prior to the acute infarction. Obstructive thrombus accounts for the majority of the abrupt interruptions to coronary flow. Little et al³ studied the extent of prior stenosis at sites in the coronary arteries that subsequently became totally occluded. In two-thirds of patients, the site of occlusion had less than 50% stenosis on the preinfarction angiogram. These findings may explain the absence of prior symptoms in many patients presenting with acute MI, and indicate that attempts to identify and modify triggers of thrombus formation may have great clinical benefit.

Morning increase in physiologic processes that might trigger infarction (Figure 2)

Physiologic studies suggest that both plaque rupture and occlusive thrombosis may be more likely to occur in the morning.

Plaque rupture

The likelihood of plaque rupture may be increased by the 20-30 mmHg rise in systolic blood pressure that occurs during the morning hours.³² The parallel increase in heart rate,³² besides increasing myocardial oxygen demands and predisposing to transient ischemia, may also alter the rheologic properties at the site of a plaque and predispose to rupture. An increase in coronary arterial tone described in the morning

could worsen the flow reduction produced by a fixed stenosis, and potentiate plaque rupture.³³ Panza and colleagues have demonstrated that forearm vascular resistance, as determined by plethysmography, is higher in the morning than at other times of the day.

Occlusive thrombosis

The likelihood of occlusive thrombosis is also increased in the morning. Platelet hyperreactivity in the morning has been described^{34,35} which is due primarily to assumption of the upright posture; resumption of the supine posture led to a lower aggregability. It is likely that a sympathetic surge contributes to the increase in aggregability, since assumption of the upright posture is accompanied by an increase in plasma levels of epinephrine and norepinephrine. An epinephrine-stimulated release of platelets from the spleen into the circulation may also be a contributor to the increased platelet activity.

Thrombosis may also be potentiated in the morning by an increase in blood viscosity³⁶ and a nadir of fibrinolytic activity.³⁷ The reduced morning level of tissue plasminogen activator activity,³⁸ could enable an otherwise harmless mural thrombus overlying a small plaque fissure to propagate and occlude the coronary lumen. Elevated levels of plasma catecholamines and cortisol may further potentiate cardiovascular events in the morning. The degree to which the disease periodicity results from a true, endogenous rhythm or from a daily rest-activity cycle remains to be fully characterized. Cortisol has an endogenous rhythm independent of daily activity. Although serum cortisol levels are falling during the period of increased disease onset, they are increased above basal levels.³⁹ This increase could enhance the sensitivity of the coronary arteries to the vasoconstrictor effects of catecholamines,⁴⁰ which have a prominent surge after assumption of the upright posture.³⁵

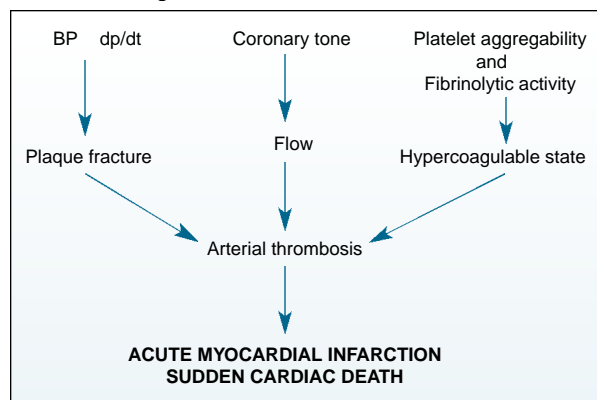
The adrenergic nervous system and platelet hyperreactivity

Support for the role of the adrenergic nervous system and platelet hyperreactivity playing an etiologic role in the morning predilection for acute coronary syndromes is provided by the efficacy of beta-blockers and aspirin in blunting the morning peak in events. Beta-adrenergic blocking agents, which inhibit the morning adrenergic activation, have been most convincingly shown to blunt the morning peak of ischemia, infarction and sudden death.⁴

The Physicians' Health Study⁴¹ found that aspirin reduces the overall incidence of myocardial infarction by 44%. In a detailed analysis of this beneficial effect, Ridker and colleagues found that aspirin exerted a selective effect — a 59% reduction — during the morning interval when platelet activity is increased. These findings indirectly support the hypothesis that the morning increase in platelet reactivity may contribute to the acute precipitation of events.

A contributory role for circadian changes in fibrinolysis is also suggested by data from Kurnik that efficacy of thrombolytic therapy is reduced in the morning hours.⁴² Decousus⁴³ also reported a circadian variation in the efficacy of a constant intravenous infusion of heparin so that activated partial thromboplastin times were at their lowest level in the morning hours. Interestingly, a recent analysis of the TIMI III population²⁰ showed that prior use of neither beta-blocking drugs nor aspirin modified the circadian rhythm of onset of unstable

Figure 2: Potentially adverse physiologic changes occurring in the morning



angina. This may reflect a preferential reduction of MI by these agents and possibly a diminution of disease severity to that of unstable angina. While the data for calcium channel blockers are less convincing, a recent analysis of the Danish Verapamil Infarction Trials (DAVIT I and II)⁴⁴ suggested that verapamil is associated with a preferential reduction in morning sudden cardiac death.

Physiologic processes at other times of the day

Although attention has focused on the morning as the peak period of disease onset, it is likely that similar physiologic processes trigger disease onset at other times of the day. The secondary evening peak at about 8 PM may result from synchronization of the population for an additional trigger — the evening meal. Meals have been associated with a reduction in the threshold for myocardial ischemia.⁴⁵ In addition, a lipid-rich meal has been demonstrated to produce a prothrombotic increase in factor VII levels.⁴⁶

Many of the physiologic changes that occur in the morning may also occur following potential triggering activities, such as physical exertion, anger and cold exposure. All these stressors are associated with an increase in adrenergic activity. In individuals with atherosclerosis, an increase in coronary vascular resistance and vasoconstriction may occur in response to these stressors, while the response of the normal endothelium is one of dilation.⁴⁷ In the presence of normal endothelium, stress-induced increases in prostacyclin and tPA production may balance any prothrombotic changes caused by increases in platelet activation. This balance may be tipped unfavorably in individuals with coronary artery disease as they have diminished fibrinolytic response to physical exercise compared with healthy subjects.⁴⁸ A reduced tPA response to exercise has been associated with increased risk of subsequent cardiovascular events in patients with stable angina.⁴⁹ The ratio of plasma thromboxane A₂ to prostacyclin production following exercise is also greater (i.e., the response was more prothrombotic) among patients with coronary artery disease than among normal subjects (1.9 vs 0.1).⁵⁰

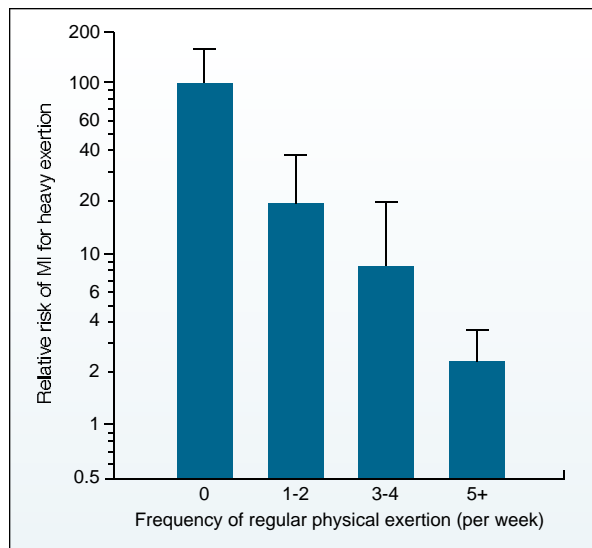
Triggers of infarction and sudden cardiac death

Physical activity

Almost half (48.5%) of the 849 patients with MI enrolled in the MILIS study⁵⁷ reported one or more possible triggers, including moderate physical activity (14.4%), and heavy physical activity (8.7%). Sumiyoshi and colleagues reported similar findings. In TIMI II, moderate or marked physical activity was reported to occur at onset of myocardial infarction in 18.7% of patients.¹² Although these and other descriptive studies support the popular view that physical exertion can trigger a heart attack, methodological problems exist such as recall bias, lack of information in fatal cases, and lack of appropriate controls.

These limitations were addressed in the Myocardial Infarction Onset Study, a multicenter investigation of over 1700 patients in which each subject was used as his own control. Using the case-crossover analytic technique of Maclure and Mittleman,^{51,52} the relative risk of a potential trigger causing infarction can be estimated as the ratio of the observed frequency of the activity during a designated hazard period (e.g., within one hour of onset of symptoms of MI) to

Figure 3: Modification of the relative risk of MI by usual frequency of heavy exertion. Sedentary individuals experienced an extreme relative risk (107), whereas those who exerted themselves 5 or more times per week had only a doubling in risk over that of baseline.



From Mittleman et al.⁵² Reprinted with permission of the *N Engl J Med*.

the expected frequency (from control information). The control information can be gained from an estimate of the usual annual frequency of the potential trigger or the frequency during the control period on the day prior to infarction. Using this study design, there was a relative risk of 5.9 of infarction occurring in the one hour following heavy physical activity (more than 6 METS).⁵²

Among sedentary individuals who exercised less than once per week, there was a hundred-fold increase in relative risk of infarction in the hour following heavy physical exertion. However, there was only a doubling of risk among individuals who regularly exercised five or more times a week (Figure 3). Willich et al found similar results in the TRIMM study.⁵³

While these data indicate that heavy exertion can trigger infarction, they are also consistent with a protective effect of regular exertion, both in reducing the relative risk of infarction following exertion, and in reducing the absolute risk of infarction, as shown by other investigators. In TIMI II, patients who were engaged in physical exertion at the time of their infarction were less likely to have a vessel with significant stenosis following thrombolytic therapy than those whose event occurred at rest.¹² A New Zealand study also showed that patients with exertion-associated infarction had a lower in-hospital mortality than did those whose infarction occurred at rest or in bed.⁵⁴ While these findings reflect, in part, the modifying effect of patient age on frequency of exertion, they also are consistent with the role of physical exertion in generating hemodynamic and hemostatic forces that trigger plaque disruption and occlusive thrombosis in the absence of severe prior coronary narrowing.

Siscovick and colleagues⁵⁵ have demonstrated that sudden cardiac death is more likely to occur following heavy physical exertion than during sedentary behavior. In men with low levels of regular activity, the relative risk of cardiac arrest during exercise, as compared with other times, was 56 (95%

CI, 23-131). The risk among men at the highest level of regular activity was also elevated but only by a factor of 5. Vouri⁵⁶ reported that the risk of sudden cardiac death during cross-country skiing was 4.5 fold higher than the risk during sedentary activities. In this study, the relative risk of sudden death was even greater for strenuous competitive exercise than for nonstrenuous exercise.

Psychosocial triggers

Despite numerous anecdotes linking emotional stress to the precipitation of MI or sudden cardiac death, there has been relatively little systematic study of this relationship in patients. In the MILIS Study⁵⁷ of nonfatal MI, 18.8% of the patients reported a possible emotional trigger. Using case-crossover methodology, it has been possible to investigate the relative risk associated with episodes of anger.

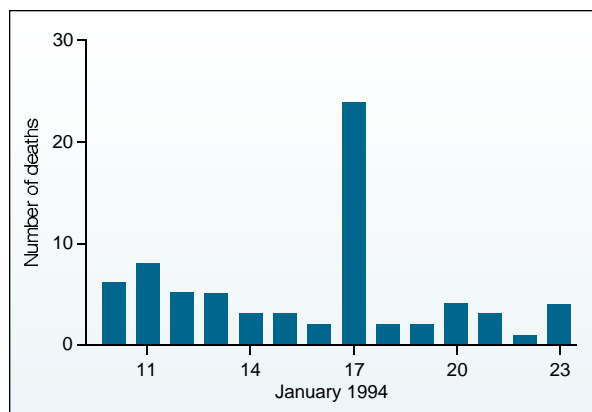
In the Onset study, 2.4% of patients reported episodes of anger (\geq level 5 on an anger scale) in the two-hour period before infarction. The relative risk of MI in the two hours after such an episode of anger was calculated at 2.3 (95% CI, 1.7-3.2).⁵⁸ These data support evidence for psychological stress as an acute trigger for MI. Reich and colleagues⁵⁹ found a presumed psychological trigger in 21% of 117 patients with life-threatening arrhythmias, the most common being anger (15%). The long QT syndrome provides a striking example of a condition in which emotional stress can precipitate ventricular arrhythmia and sudden death.⁶⁰

Most investigations of the etiologic role of psychological stress in cardiovascular disease have focused on chronic risk. These studies have yielded varying results, although depression and the hostility component of the type A personality are most closely linked to increased cardiovascular risk. Grief reactions and depression following bereavement may have a major effect on cardiac mortality. In a cohort of middle-aged widowers, a 40% increase in the mortality rate was observed in the first six months following bereavement.⁶¹ More than half of the deaths were attributed to cardiovascular causes. Depression following MI also has a significant effect on mortality. Frasure-Smith⁶² found that MI survivors with high levels of psychological stress, as assessed by questionnaire, had a three-fold increase in cardiac mortality (mainly due to sudden death) compared with controls with low levels of psychological stress.

The 1991 Iraqi war provided an opportunity to study the effect of psychological stress on cardiovascular events in Israeli civilians. During the initial week of missile attacks on Israel, 20 people developed an acute infarction in the area served by one hospital, compared to eight during a control period.⁶³ More recently, Leor et al⁶⁴ found an increased relative risk of nontraumatic cardiovascular death following the 1994 Los Angeles earthquake compared to baseline (Figure 4). These studies indicate that both acute and chronic psychological stress may increase the risk of infarction and sudden death.

A relationship between hemodynamic response to mental stress and acute disease onset has not been convincingly demonstrated in humans, although a recent Finnish study⁶⁵ indicated that a greater diastolic blood pressure response to mental stress was correlated with a greater extent of carotid atherosclerosis.

Figure 4: Significant increase in the number of cases of sudden cardiac death on January 17, the day of the Northridge Earthquake.



From Leor et al.⁶⁴ Reprinted with permission of the *N Engl J Med*.

Sexual activity

Patients with cardiovascular disease often have a fear of sexual intercourse. Since sexual activity consists of intense periods of physical activity, emotional arousal, and even psychological stress, concerns about the occurrence of infarction and sudden cardiac death are appropriate. Of 858 patients evaluated in the Myocardial Infarction Onset Study, 79 (9%) reported sexual activity in the 24 hours prior to the infarction, and 27 (3%) reported sexual activity in the two hours preceding onset of symptoms. The relative risk of infarction occurring in the two hours after sexual activity was 2.5 (95% CI, 1.7-3.7). In this population, sexual activity was a likely contributor to the onset of infarction in 0.9% of cases.⁶⁶

The relative risk of triggering onset of infarction was not significantly different among those with prior cardiac disease than those without prior disease. The relative risk of sexual activity as a trigger was reduced in individuals who had regular physical activity. Since the absolute hourly risk of infarction is very low, patients and spouses should be reassured that the absolute risk increase caused by sexual activity is also extremely low.⁶⁷

Other potential triggers

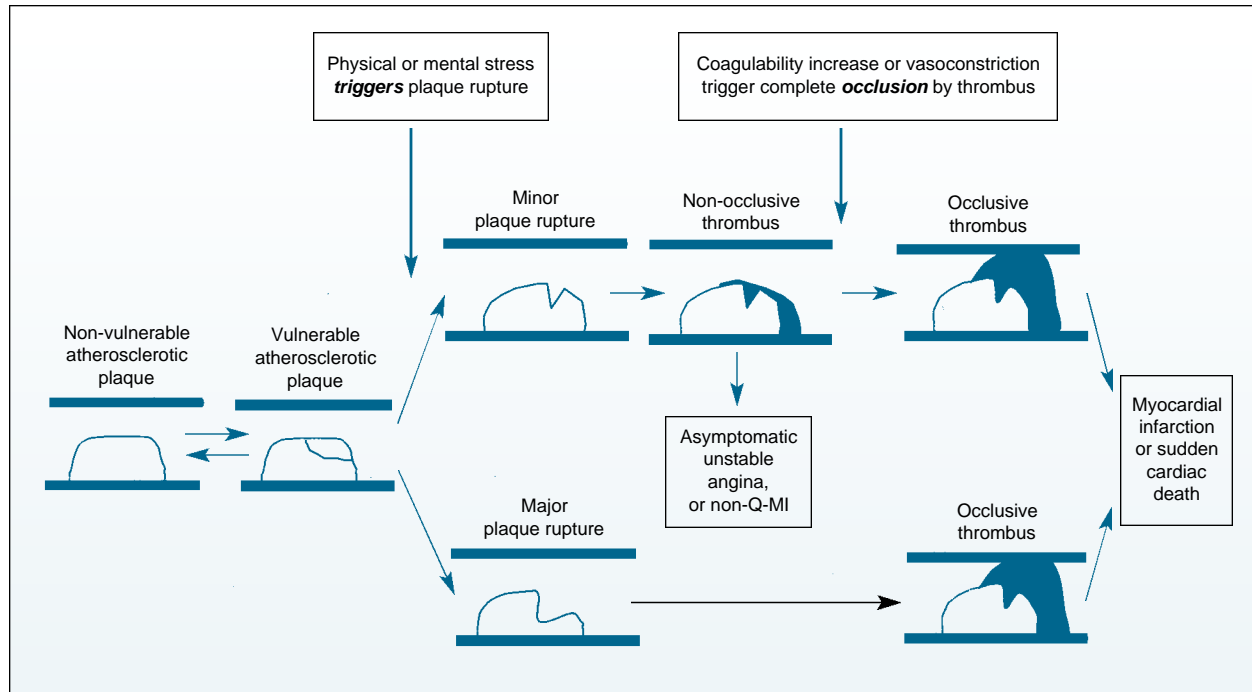
A peak of risk of cardiovascular events in the winter months has been recognized.⁶⁸ While the cause of this seasonal variation is likely to be multifactorial, there is evidence to suggest that respiratory infection may trigger infarction.⁶⁹ The secondary evening peak in infarction that has been described has also led to speculation that a lipid-rich evening meal may transiently increase coagulability and the risk of infarction. These and other potential triggers require further investigation.

General theory of triggering of coronary thrombosis

The information on triggering can be incorporated (Figure 5) into a hypothesis of the progression of coronary artery disease as advanced by Davies, Fuster, Falk, Willerson, and others.^{30,70-73}

Onset may occur when a vulnerable plaque disrupts in response to stressors that produce transient pressure surges or vasoconstriction. If plaque disruption is major, with extensive exposure of collagen and atheromatous core contents to the

Figure 5: Illustration of a hypothetical method by which activities such as heavy physical exertion and emotional stress may trigger acute coronary syndromes. See the text for more detailed discussion. Reprinted with permission of *J Am Coll Cardiol*.⁴



lumen, it may lead immediately to occlusive thrombosis with infarction or sudden cardiac death. Alternatively, and far more commonly, the disruption may be minor and lead to nonocclusive thrombosis. In this latter scenario, the patient may be asymptomatic or develop unstable angina or non-Q-wave infarction. The lesion may gradually heal with smooth muscle cell proliferation and a greater degree of stenosis. On the other hand, a further increase in coagulability or vasoconstriction may lead to occlusive thrombosis, infarction, and sudden cardiac death.

The initial step in the process is the development of a vulnerable atherosclerotic plaque. As normal individuals and even patients with coronary artery disease are constantly exposed to potentially triggering activities that do not produce coronary thrombosis, it is likely that development of a vulnerable plaque is the rarest event in the chain of causation described above. The characteristics of a vulnerable plaque include the presence of a lipid-rich plaque, a thin fibrous cap, and increased macrophage activity with elaboration of metalloproteinases.^{73,74} An inflammatory response, which may be associated with elevated systemic markers of inflammation such as C-reactive protein, is now recognized to play an important role in weakening the fibrous cap.⁷⁵ Recent positive results with HMG-CoA reductase inhibitors suggest that these agents may be able to stabilize plaque, returning a previously vulnerable plaque to a nonvulnerable state.⁷⁶

The future

Studies ranging from the epidemiologic to the molecular level need to be done to better characterize the triggers and the characteristics of a vulnerable plaque. Currently, practical options to modify triggers are limited. While adverse stimuli (such as cigarette smoking) can be avoided, stressors such as

anger and sudden physical exertion are largely unavoidable, but are modifiable. More success may therefore be gained through efforts to interrupt the link between a stressor and the cardiovascular event by nonpharmacologic and pharmacologic means. Data from the Onset study, showing that individuals who exercise regularly have a reduced relative risk of infarction triggered by physical activity compared with sedentary individuals, further support the benefit of regular exercise. Beta-blockers and aspirin may prove particularly useful. By stabilizing plaque, lipid-lowering therapy may also render plaques less vulnerable to the physiologic effects of potential triggers. In addition, the design of antihypertensive and anti-ischemic dosage regimens that provide 24-hour coverage, with particular activity during the morning period of increased risk, are likely to be beneficial. Stress management techniques to reduce the impact of stressful environmental events and to better regulate the stress response hold promise.^{77,78} It is also important to recognize and appropriately treat depression in patients following infarction.

From a population standpoint, recognition that stressors may trigger infarction and sudden death provides a further rationale for public access to defibrillation at locations where large numbers of individuals may be exposed to such stress. This includes airport terminals and on aircraft.⁷⁹ In concert with efforts to better understand triggers and identify individuals at increased risk, the development of diagnostic methods such as magnetic resonance imaging to identify a vulnerable plaque prior to rupture remains an important future goal of investigation. While many advances have occurred in recent years, a more complete understanding of triggering mechanisms and plaque vulnerability should permit further progress in the prevention of the acute coronary syndromes.

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