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Triggering of Acute Coronary Syndromes

J. Müller-Nordhorn, S. N. Willich

External triggers including physical activity and emotional stress or rare events such as earthquakes may precipitate the onset of acute coronary syndromes. Circadian, weekly, and seasonal variations in coronary syndromes have also been observed. Furthermore, changes in the environment appear to play an important role. Triggering events probably result in the rupture of vulnerable coronary plaques via internal pathophysiological mechanisms. Appropriate preventive measures are needed in order to protect patients, particularly during vulnerable periods. *J Clin Basic Cardiol* 2000; 3: 73–9.

Key words: triggers, environment, pathophysiology, prevention, coronary syndromes

Plaque rupture and subsequent thrombosis at the site of the plaque rupture is the most common underlying pathophysiological mechanism of acute coronary syndromes [1]. The clinical manifestations of acute coronary syndromes are sudden cardiac death, acute myocardial infarction and unstable angina. Approximately 90 % of cases of non-fatal myocardial infarction and many cases of sudden cardiac death are caused by the rupture of a coronary atherosclerotic plaque [2]. Plaque rupture may be precipitated by external stresses or 'triggers' imposed on coronary plaques [3].

It is important to differentiate between intrinsic long-term changes of coronary plaques, internal triggering mechanisms and external triggers (Figure 1). Intrinsic long-term changes consist of progressive lipid accumulation of the core and degradation of the fibrous cap by proteolytic processes and inflammation [4, 5]. An increased vulnerability of the plaque and a proneness to rupture are the consequences. External triggers probably activate internal triggering mechanisms such as biomechanical and hemodynamic stresses and changes in platelet aggregability and blood viscosity; they may thus determine the actual time of coronary plaque rupture [2]. External triggers include physical activity, emotional stress, environmental changes and other factors. Circadian, weekly and seasonal variations of coronary events have also been observed.

A number of studies have examined the relationship between external triggers and the onset of acute coronary syndromes. For example, the MILIS (Multicenter Investigation of Limitation of Infarct Size) Study [6] showed that 50 % out of 849 patients reported possible triggers preceding the event. The following main triggers were experienced by the patients: emotional upsets (19 %), moderate physical activity (14 %), and heavy physical activity (9 %). Sumiyoshi et al. [7] found that among 416 patients admitted to the National Heart Center of Japan, 53 % reported that their infarct occurred during moderate to heavy exertion, emotional stress, or

excitation. Smith et al. [8] showed that out of 186 patients interviewed within 72 hours after admission for myocardial infarction, 40 % reported either emotional upsets, strenuous exercise or a sudden change in position, usually in the morning after awakening.

In this article, we will review the evidence for the frequency and importance of external triggers of acute coronary syndromes and their pathophysiological consequences and propose implications as to better preventive strategies.

External triggers of plaque rupture

Physical activity

Physical activity may trigger the rupture of coronary plaques resulting in acute coronary syndromes [7, 9, 10]. Several studies of patients with acute coronary events have established that in approximately 5 to 14 percent of cases, heavy exertion precedes the onset of symptoms [11]. In the TRIMM (Triggers and Mechanisms of Myocardial Infarction) Study [9], 1194 patients in Germany were interviewed during their

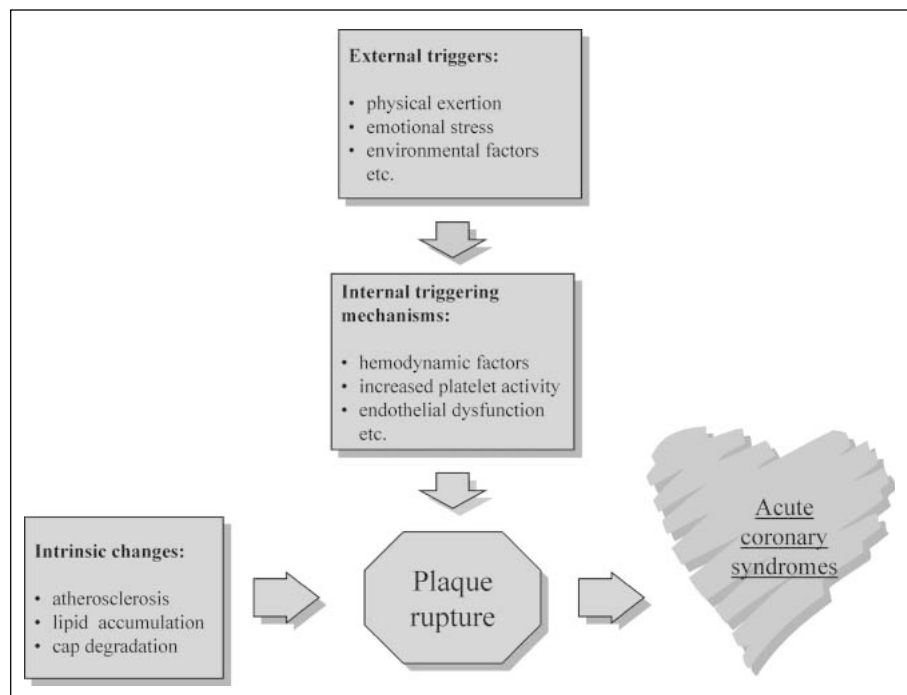


Figure 1. Model of triggering of acute coronary syndromes (see text for details)

hospital stay for acute myocardial infarction, focusing on the hours prior to the acute event. Exposure to possible triggers in patients was compared firstly with matched controls and secondly, in a case-crossover analysis, with the patient acting as his/her own control [12]. In the case-crossover analysis, the frequency of physical exertion in the hours preceding the onset of symptoms was compared to the usual frequency of such exertion over the year prior to the infarction. Heavy physical exertion at the onset of myocardial infarction was reported by 7.1 % of patients, compared to 3.9 % in the control group. The increase in relative risk associated with physical exertion during and in the one-hour period after the acute event was approximately two-fold (RR 2.1; 95 % CI: 1.1, 3.6). Figure 2 shows the different odds ratios of various physical activity states among patients compared with controls [13]. A significant difference ($P < 0.01$) in the relative risk of persons engaging in regular heavy exertion at least four times per week, compared to those exercising fewer than four times per week could be detected as well (RR 1.3 and 6.9, respectively). The risk of myocardial infarction associated with strenuous exercise is therefore particularly increased in individuals with a rather sedentary lifestyle. Similar in design to the TRIMM Study, the Onset Study [10] interviewed 1228 patients in the United States about their activities at the advent of acute myocardial infarction. Heavy physical exertion was reported by 4.4 % of the patients, the induction time usually being less than one hour and symptoms beginning during the activity. The estimated relative risk of myocardial infarction in the hour after heavy physical exercise was 5.9 (95 % CI: 4.6, 7.7). The relative risk ranged from as high as 104 in patients who exercised less than once per week on average, to 2.4 in patients who exercised more than five times per week. Higher levels of habitual physical activity were therefore associated with a lower relative risk during exertional activities. The inherent problem of studies investigating activities preceding acute coronary syndromes is their retrospective nature. Patients may have a tendency to overestimate the amount of physical activity as well as of other possible triggers; recall bias can not be excluded.

Acute physical exertion as a trigger in the subgroup of sudden cardiac deaths is difficult to assess, as a history of the hours preceding the event can usually not be obtained from the patient [14]. Second-hand information from the family

and other witnesses is often incomplete and not reliable. Patients who have been successfully resuscitated can be interviewed, but they may not be representative for the whole group of sudden cardiac death patients. In addition, their memories may be obscured by the experienced traumatic event. Patients with an implantable cardioverter are another potential source of information, but selection bias is difficult to eliminate. Physical fitness is associated with a lower risk of sudden cardiac death, similar to myocardial infarction. In a prospective British cohort study [15], 7735 middle-aged men from 24 British towns with and without preexisting ischaemic heart disease were followed for 8 years. Physical activity was assessed with questionnaires. During this time period, 488 major cardiac events occurred, of which 117 (24 %) were classified as sudden cardiac deaths. Regular exertion was inversely associated with an increased risk of sudden cardiac death ($P < 0.05$) in men without preexisting ischaemic heart disease.

Physical activity is a double-edged sword for patients with coronary disease. Acute exertion is associated with a marked risk of triggering acute coronary syndromes, particularly if performed by untrained individuals with coronary heart disease. But although the relative risk associated with acute heavy exertion may be high, the absolute risk is relatively small [16]. Regular physical activity, on the other hand, has a beneficial effect and reduces mortality from coronary heart disease in the long-term perspective [17].

Emotional stress

Acute coronary syndromes may also be triggered by emotional stress. Studies indicate that approximately 4 to 18 percent of cases of myocardial infarction are immediately preceded by emotional stress [11]. Especially episodes of anger have been reported to trigger acute events. The Onset Study [18] showed a two-fold increased relative risk of acute coronary syndromes in the two hours after an emotional outburst of anger (Figure 3). Anger was assessed by the Onset anger scale, which is a single item, seven-level and self-reported scale, and by the state anger subscale of the State-Trait Personality Inventory. 39 out of 1623 patients (2.4 %) were identified with episodes of anger in the two hours prior to the onset of myocardial infarction. Regular users of aspirin ($P < 0.05$) had a significantly lower relative risk than nonusers (1.9 versus 2.9 %, respectively). The patients of the TRIMM Study were more likely to report emotionally upsetting events as possible triggers of myocardial infarction than the controls ($P < 0.05$). In addition to this subjective reporting, objective unusual life events such as death of a family member or friend etc. were evaluated. The cumulative frequency of these life events during the weeks prior to myocardial infarction was similar in both groups. The patient group showed a greater tendency to report stress at work than the control group, but this was not statistically significant [9].

Personality structures predisposing to acute coronary events are type A behavior, and anxiety [19]. The evidence provided by several prospective studies on the relationship between depression and acute coronary syndromes is inconsistent. Components of type A behavior that increase the risk of acute coronary syndromes are hostility, cynicism and anger [20]. A prospective study by Kawachi et al [21] in 1994 with a cohort of US health physicians suggested an increased risk of sudden cardiac death associated with phobic anxiety.

Other possible triggers

Other possible triggers of acute coronary events include sexual activity, war threats and earthquakes. They often combine unusual emotional and physical stress, but other factors may play a role as well.

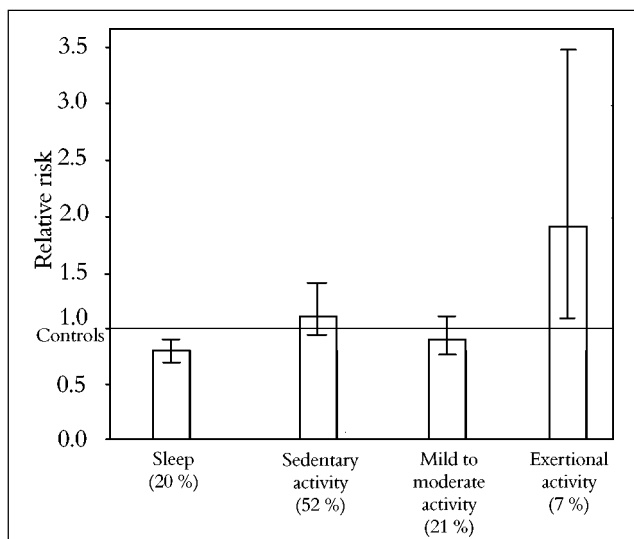


Figure 2. Physical activity at the onset of myocardial infarction. Adjusted odds ratios of physical activity states among patients with myocardial infarction compared with controls. Redrawn after [13]

Sexual activity occasionally serves as a trigger of myocardial infarction, unstable angina and sudden cardiac death. The Onset Study, for example, showed a 2.5-fold increased relative risk of acute coronary syndromes in the two hours after sexual activity [22]. But as sexual activity only contributed to about 0.9 % of cases, the authors concluded that the absolute risk was extremely low. Furthermore, the relative risk was not increased in patients with a previous history of acute coronary syndromes, and regular exercise appeared to prevent triggering. A number of cardiac deaths have been reported under the new drug Viagra (Sildenafil), which is taken as a treatment for male erectile dysfunction. As their risk profile is similar, patients with impotence may also suffer from coronary heart disease, e.g. they are more likely to be older and to have other underlying diseases such as hypertension, diabetes, etc.. Apparently a combination of nitrates and other cardiovascular drugs with Viagra can lead to an irreversible drop in blood pressure resulting in myocardial infarction and death in men with preexisting coronary heart disease [23]. Another possible explanation is that men, who are no longer used to regular sexual activity, suddenly engage again in a potentially strenuous activity. But further evaluation of the reported deaths is still needed.

Acute stress such as is caused by earthquakes or war threats can result in acute coronary syndromes as well. Suzuki et al [24] examined patients with acute myocardial infarctions after the most severe earthquake ever to occur in Japan (Hanshin-Awaji district) in January 1995. The number of patients increased by about 3.5-fold during the first four weeks after the earthquake. The mean post-traumatic stress disorder reaction index score indicated a severe stress level. The proportion of women with acute myocardial infarction was significantly higher than in the preceding years; their mean score on the stress disorder index was considerably higher than in men. The authors concluded that after an earthquake, severe emotional stress can trigger acute myocardial infarctions, esp. in women.

Sudden cardiac deaths increased significantly during the Northridge earthquake in California in January 1994 [25]. The number of deaths rose from a daily average of 4.6 (± 2.1 SD) to 24 on the day of the earthquake (Figure 4). The week after the earthquake showed an unusual low incidence of sudden cardiac deaths (2.7 ± 1.2 per day); this suggests that stress may precipitate cardiac events in people who are predisposed to such events.

The effect of war threats on the incidence of acute coronary syndromes has been observed in the Israeli civilian

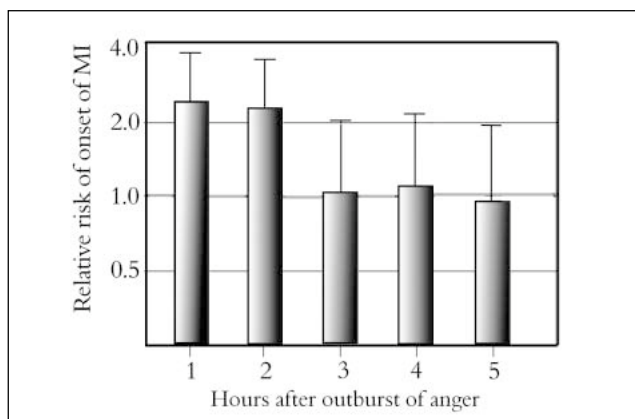


Figure 3. Relative risk of myocardial infarction in the hours following an outburst of anger. The error bars indicate the 95 % confidence intervals; the dotted line represents the baseline risk. Redrawn after [18]

population during the first days of the Gulf war in 1991 [26] (Figure 5). A 58 % increment in mortality largely due to an increase in mortality from cardiovascular diseases could be observed on the day of the first strike on Israeli cities [27]. Female mortality showed a more pronounced increase with 77 % than male mortality with 41 %.

Environmental factors and smoking

Air pollution as an environmental factor has been consistently associated with increased cardiovascular mortality. For example, in the December 1952 smog disaster in London a substantial increase in cardiovascular mortality was reported [28]. Several studies have documented associations between short-term increments of air pollutants, esp. inhalable particles smaller than 10 microns in diameter (PM10) and sulphur dioxide, and cardiovascular hospital admissions [29]. But as different methods for evaluation have been used, a comparison of the results proved to be difficult. The multinational European Community funded APHEA (Air Pollution of Health: European Approach) project in 10 different European countries and 12 European cities [30] investigated the relationship between air pollution and mortality from specific causes using a standard statistical method. A time series analysis with the application of the Poisson regression to the counts of daily number of deaths from selected causes over several years was performed. Possible confounding factors were taken into account. A positive relationship between increased daily air pollution and inci-

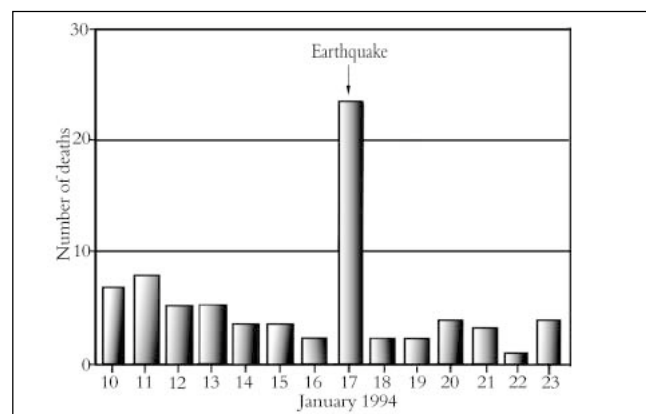


Figure 4. Daily incidence of sudden cardiac deaths associated with an earthquake. A major earthquake occurred in Northridge, California, on January 17, 1994. Redrawn after [25]

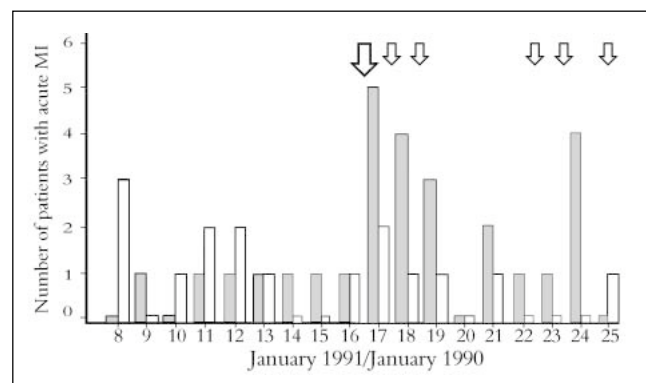


Figure 5. Daily incidence of acute myocardial infarction associated with war threat in a Tel Aviv population from 8th to 25th January 1991, compared with the same period in 1990. Large arrow = beginning of the Gulf war; small arrows = missile attacks on Israel. Redrawn after [26]

dence of acute coronary syndromes has been observed by a considerable number of European cities participating in the APHEA trial [31–35] as well as by a number of other trials outside Europe [29, 36–39]. Major pollutants responsible for the increased incidence were particles (PM₁₀), sulphur dioxides and ozone esp. in summer; despite levels being around or below national and international guidelines.

Peters et al [40] hypothesized that inflammation of the peripheral airways caused by pollution might increase blood coagulability via an acute-phase reaction. Plasma viscosity was measured as part of the WHO MONICA (Monitoring trends and determinants in cardiovascular disease) Augsburg survey during the winter of 1984–85. Daily mean concentrations of air pollution were recorded by the Bavarian air-quality network in Augsburg. Plasma viscosity were assessed in 324 people during a 13-day period, where high concentrations of sulphur dioxide (mean 200 micrograms/m³) and total suspended particles (mean 98 micrograms/m³) were reported. In the remaining time period of the survey, plasma viscosity of a further 2932 people was measured. The odds ratio for plasma viscosity above the 95th percentile of the distribution in the 13-day time period was 3.6 (95 % CI: 1.6, 8.1) for men and 2.3 (95 % CI: 1.0, 5.3) for women.

As to smoking, there is some evidence suggesting that smoking is not only a long-term risk factor for coronary heart disease, but may be a potential trigger for the development of an acute coronary thrombus as well. Burke et al. [41] examined the coronary arteries of 113 patients with sudden cardiac death. 59 men had developed an acute coronary thrombus and in the remaining 54 men, narrowing of the coronary arteries by an atherosclerotic plaque without acute thrombosis could be detected. 75 % of men with an acute thrombus were smokers compared to 41 % of those with stable plaques ($P < 0.001$).

The significance of the circadian, weekly and seasonal variation

The circadian variation

The presence of a circadian variation in the onset of acute coronary events was originally proposed by Muller et al. [42]. Based on numerous reports, the circadian pattern with an increased morning risk and a trough during the night is now well established [43–46]. A meta-analysis, performed by Cohen et al. [47] in 1997, concluded that approximately 1 of every 11 acute myocardial infarctions and 1 of every 15 sudden cardiac deaths are attributable to the morning excess risk. The TRIMM Study [9] demonstrated a two- to three-fold increased risk of acute coronary syndromes in the three hours after awakening ($P < 0.01$) (Figure 6). Two major prospective studies, the ISAM (Intravenous Streptokinase in Acute Myocardial Infarction) Study [48] and the ISIS-2 (Second Intravenous Streptokinase and Infarct Survival) trial [49] which included 1,741 and 12,163 patients, respectively, confirmed the morning peak of coronary events. It was often argued that the morning peak was due to the fact that patients slept through the onset of symptoms, and only reported them after awakening. The MILIS Study [42] used serial creatinine kinase levels from 703 patients and extrapolated from the results, in order to define the onset time of the event. Again, a marked morning peak could be shown and an artefact due to increased reporting in the morning seems unlikely.

Some studies [50–52] described a second peak of acute coronary events in the afternoon or evening. For example, a Swedish study by Hansen et al. [53], including 10,791

patients, observed a bimodal circadian variation with a peak in the morning (0600 A.M. and 1200 A.M.) and a second peak in the evening (0600 P.M. and 1200 P.M.). A New Zealand Study, the ARCOS Study [54], which was done in collaboration with the WHO MONICA Project ($n = 4983$ patients), demonstrated both an afternoon peak and a secondary morning peak in the subgroup of sudden cardiac death patients. The observed difference in circadian patterns may reflect different life styles and/or rest activity patterns.

The combination with other triggers of acute coronary syndromes, such as physical activity or emotional stress, appears to increase the morning risk even further. Krantz et al. [55] showed that during the morning, ischaemic versus non-ischaemic periods were more likely to occur with high levels of activity ($P < 0.001$). High physical activity triggered ischaemia to a lesser but still significant extent in the afternoon ($P < 0.05$), but not in the evening ($P < 0.04$).

The circadian variation affects all types of coronary syndromes. Sudden cardiac deaths have an approximately three-fold increase in relative risk during the morning [56]. The CAST (Cardiac Arrhythmia Suppression Trial) [57] showed that sudden cardiac deaths occurred most frequently within 2 h after awakening. Esp. ventricular fibrillation and ventricular tachycardia as causes of sudden cardiac death followed the circadian pattern, whereas electromechanical dissociation and asystole were quite evenly distributed throughout the day [50, 58]. The circadian variation is also observed in unstable angina and non-Q-wave acute myocardial infarction ($P < 0.001$), as demonstrated by Cannon et al. [43].

Beta-adrenergic blocking agents and aspirin appear to reduce the incidence of myocardial infarction in the morning. The Physicians' Health Study [45], a randomized placebo-controlled trial, compared the incidence of myocardial infarction in 22,071 US males taking either aspirin or placebo. Aspirin was associated with a 59 % reduction in the incidence of infarction during the morning hours, compared with a 34 % reduction for the remaining hours of the day. A number of studies [42, 48, 53] showed the absence of a circadian variation with beta-blocking agents. The importance of these findings is that appropriate pharmacological protec-

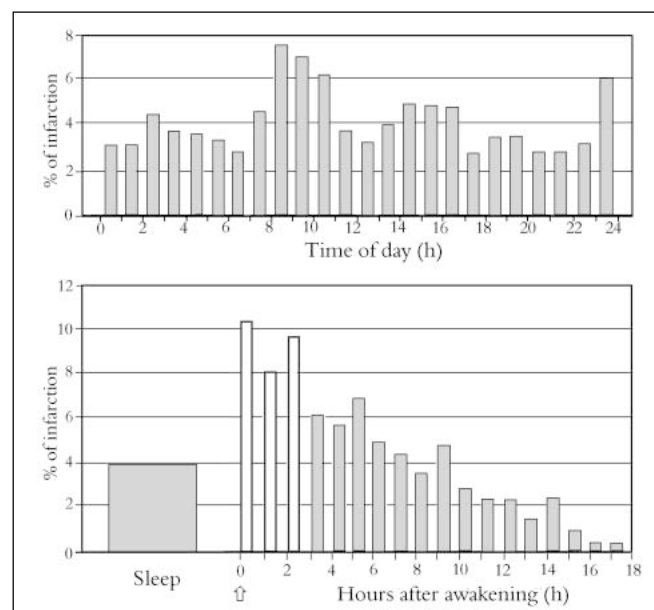


Figure 6. Circadian variation in the onset of myocardial infarction. The upper panel shows the unadjusted circadian pattern of myocardial infarction ($P < 0.01$); the lower panel the circadian pattern adjusted for time of awakening. Redrawn after [9]

tion can be directed at the morning hours for patients with coronary heart disease [59]. The absence of a circadian pattern in the subgroup of patients with diabetes in the ISIS-2 (Second International Study of Infarct Survival) Study ($n = 12,163$ patients) suggests an involvement of the autonomic nervous system [49]. The findings of Behar et al. [44], on the other hand, did not confirm the absence of a circadian variation in diabetic patients, only in patients with peripheral vascular disease and those having suffered from a stroke.

The inhibition of fibrinolytic activity in blood peaks in the morning and this inhibition may favor the development of an arterial thrombus [60]. A Japanese study with 244 patients with acute myocardial infarction described a resistance to thrombolytic treatment following a circadian pattern similar to myocardial infarction [52] ($P < 0.05$), with a phase difference of about 2 hours. Similarly, Kurnik [61] claimed that there is a circadian variation in the ability of the tissue-type Plasminogen Activator to rapidly open coronary arteries, with the highest efficacy between noon and midnight. In a study of Winther et al. [62] with healthy male subjects, assuming the upright position in the morning significantly increased platelet aggregation and produced only a moderate increase in fibrinolytic activity. Compared to exercise, assuming the upright posture increased platelet aggregation to similar levels, but exercise was also associated with a higher protective fibrinolytic activity.

The weekly variation

The weekly profile shows that the risk of acute coronary syndromes is greater at the beginning of the week than on the other days [46, 63]. The New Zealand ARCOS trial [54] found an increased incidence not only on Mondays, but also during the weekend for surviving patients, and a Saturday high (18.6 %) for sudden cardiac deaths. In a study conducted by the Augsburg MONICA center, 5596 patients were analyzed in a regionally defined population between 1985 and 1990 [64]. Patients with myocardial infarction ($n=2636$) demonstrated a significant weekly variation ($P < 0.01$) with a peak on Monday, whereas patients with sudden cardiac death ($n=2960$) were evenly distributed throughout the week. Information on working status was available for 2075 patients out of the 2636 patients with myocardial infarction. The weekly variation in the incidence could only be seen in the working population, with a 33 %-increase in relative risk on Mondays ($P < 0.05$) (Figure 7). The weekly pattern was observed in all patients out of the working population, irrespective of age, sex, cardiac risk factors, prior cardiac medication and infarct characteristics.

The seasonal variation

Myocardial infarction occurs more frequently in the winter months than in summer months and, generally, on colder days the year around [46, 65, 66]. Analysing a total of 259,891 cases of acute myocardial infarction reported to the second National Registry of Myocardial Infarction (NRM-2), Spencer et al. [67] confirmed the seasonal variation with increased incidence in winter. Approximately 53 % more cases were reported in winter than during the summer months. The same seasonal pattern was seen in men and women, in different age groups and in 9 of 10 geographic areas.

Pathophysiology

Physical exertion, emotional stress and the other possible triggers of coronary plaque rupture syndromes may lead to a change in the hemodynamic and biomechanical parameters

as well as to an alteration of the platelet and coagulation system [68, 69]. The activation of the sympathetic nervous system by stress of any kind increases the cardiac output with a higher blood pressure and pulse rate via the secretion of catecholamines. Greater circumferential and flexion stresses on vulnerable plaques are the consequence. Circumferential stress depends, according to Laplace's Law [2, 70], on the arterial blood pressure and the vessel radius and is inversely related to the thickness of the vessel wall. Following Laplace's Law, mild and moderate lesions are more likely to rupture than the more severe ones; this is confirmed by 60–70 % of acute coronary syndromes evolving from mildly to moderately obstructive atherosclerotic plaques [4]. Flexion stress with axial bending and stretching of the coronary arteries [2] is associated with heart contractions.

Platelet activity, leading to thrombosis at the site of the ruptured plaque, appears to be increased by acute physical exertion; especially in patients with prior myocardial infarction [71] and in sedentary individuals [72], but not in healthy volunteers. Emotional activity [73] and smoking, similarly, lead to a higher platelet aggregability. Aspirin does not prevent the enhanced platelet activity in smokers [74]. Increased catecholamine secretion and shear stress during periods of stress are probably responsible for the activation of the platelet system [75]. The benefit of regular dynamic exercise appears to be caused by an improved cardiac output and stroke volume. This leads to a decreased activation of the sympathetic nervous system with lower levels of plasma catecholamines and a lower pulse rate and rate-pressure product at rest and during comparable levels of physical exertion. Regular exercise also has a favourable effect on the lipid profile, causes an inhibition of platelet aggregability [76] and increases the endogenous fibrinolytic response to venous occlusion.

The higher morning incidence of acute coronary events is presumably also caused by an activation of the sympathetic system in the morning [77]. Elevation of coagulation factors with a greater tendency to clot during cold weather may in part explain the higher mortality from myocardial infarction in winter. A study by Yeh et al. [78] measured coagulating factors including antithrombin III, prothrombin time, activated partial thromboplastin time, fibrinogen, plasminogen and the factors VII and VIII in 2877 subjects. A statistically significant increment of all parameters, except prothrombin time, could be shown on days with a mean temperature < 20 degrees C compared to days with a mean temperature > 20 degrees C.

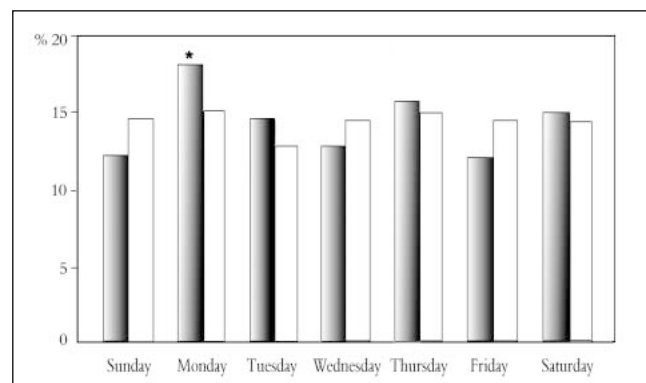


Figure 7. Weekly variation in the onset of myocardial infarction in a working ($n = 884$) and a non-working population ($n = 1191$) (1985–1990); ■ = working ($n = 884$), □ = non-working ($n = 1191$) * $p < 0.05$. Redrawn after [64]

Implications for prevention

External triggers in acute coronary syndromes were identified in previous studies in up to 50 % of all patients. Reduction or elimination of triggers could, therefore, play a major role in the prevention of acute events. But whereas certain triggering activities are comparatively easy to avoid, others such as emotional stress or sexual activity belong to human life and it is neither desirable nor feasible to control them. Pharmacological protection of the population at risk during vulnerable periods will be one of the key issues in the future. Medication such as beta-blockers and aspirin has already been shown to lower the increased morning risk. Health education about the risks associated, for example, with sudden, strenuous exercise in untrained individuals or with smoking has to be given more emphasis as well. But it has to be taken into account that knowledge about potential triggers might increase anxiety in patients and result in a reduction of activities and in a potential loss of quality of life. It is of note, that regular physical activity is not only of long-term protection, but also reduces the risk of acute strenuous exercise.

A vulnerable plaque is a "time bomb" with potential catastrophic consequences. To avoid or at least delay plaque rupture by developing appropriate preventive strategies is essential in reducing incidence and mortality of coronary syndromes. Behavior modification and pharmacological interventions appear equally important.

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