CHAPTER 1

Sudden cardiac death: epidemiology, circadian variation, and triggers

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\textit{Curr Probl Cardiol} 2011;36:56-80
ABSTRACT

Sudden cardiac death (SCD) remains a major health issue accounting for over 5% of annual mortality in the Western World. There are several causes of SCD, most commonly coronary artery disease. Although identifying the prodrome of SCD has attracted considerable interest, a large proportion of patients die before any medical contact is established. SCD onset seems to follow a circadian pattern, most likely due to exposure to endogenous and exogenous triggers. The aim of the present report is to review the current knowledge of epidemiology, patterns of onset, and triggers of SCD and present directions for future research with a focus on coronary artery disease.

INTRODUCTION

Sudden cardiac death (SCD) remains a major health issue accounting for a significant percentage of all cardiac deaths. Furthermore, the lack of warning symptoms in SCD seems to preclude the opportunity for preventive treatment. A thorough knowledge of epidemiology, circadian variation, and possible triggers is essential for optimizing the possible treatment strategies to lower the incidence of SCD.

EPIDEMIOLOGY OF SUDDEN CARDIAC DEATH

Definition and incidence of sudden cardiac death

The World Health Organization (WHO) definition of SCD is sudden and unexpected death witnessed within 1 hour of symptom onset.\(^1\)\(^2\) If unwitnessed, subjects should have been seen alive and symptom free within 24 hours of symptom onset. Furthermore, noncardiac causes of sudden death should be excluded. However, not all population studies assessing the incidence of SCD have used the WHO definition. Some included all patients dying within 24 hours of symptom onset. Such variability in definition may affect assessment of incidence in population studies.

Several researchers have attempted to estimate the incidence of SCD. The prospective Oregon Sudden Unexpected Death Study\(^3\) evaluated that by assessing the Multnomah County population (n=660,486) for one year. They estimated the incidence of SCD to be 53/100,000. SCD accounted for 5.6% of annual mortality in that series. A prospective study in the Maastricht area of the Netherlands with a study population of 132,762
inhabitants and a follow-up of 4 years, showed an incidence for SCD of 90-100/100,000⁴ and 18.5% of deaths were attributed to SCD. However, in this study the 24 hour definition of SCD was used, and the incidence may therefore be an overestimate. In addition, it is important to note that both studies included survivors of cardiac arrest in these estimates. The survival rate was 8% in the Multnomah County population and 6.2% in the Maastricht study. These and additional studies⁵,⁶ taken together, estimated the incidence of SCD in Europe and the U.S. to be in the range of 50-60/100,000. This equals approximately 180,000-250,000 cases per year in the U.S.⁷ There is evidence that other geographical areas have different SCD incidence rates than those observed in Europe and the U.S. For instance, the incidence of SCD tends to be lower in China and Japan.⁸,⁹

The incidence of SCD is affected by age and sex. The Maastricht study was not suitable to observe those trends, because patients older than 75 years were excluded. In the Oregon study, however, clear age and sex trends were observed (Figure 1). Approximately 25% of SCD cases occur before the age of 65 years. Among the population <35 years a small peak is observed in the age group of 0-5 years, due to sudden infant death syndrome.¹⁰ The major peak occurs in the age group of 75-84 years, and is mainly due to coronary artery disease (CAD). Overall, 43% of the cases were females.

The incidence of SCD over time has followed the incidence of overall CAD. An analysis of the Framingham Heart Study cohort and offspring demonstrated a decline in SCD of 49% in 1990-1999 compared with 1950-
1969. However, the global burden of CAD and therefore SCD will probably increase the coming decade, because of ageing and increasing incidence of CAD in the developing world.7,12

**Causes of sudden death**
Although cardiac causes of nontraumatic sudden death exceed other causes by far, there are other causes of sudden death – most common pulmonary embolism. Cardiac causes of sudden death can be divided into 3 categories. The cardiac cause most commonly associated with sudden death is CAD and accounts for approximately 80% of SCD causes.3,7 It is believed that there is an acute and a chronic mechanism by which CAD can result in SCD.7,13 The acute mechanism is plaque rupture and acute occlusion of one or more coronary arteries. This causes myocardial ischemia. Myocardial ischemia leads to intercellular uncoupling and decreases intercellular conduction, thus providing circumstances leading to re-entrant circuits.14 The chronic mechanism is scarred myocardium due to ischemic cardiomyopathy after one or more myocardial infarctions. Both of these mechanisms can lead to ventricular fibrillation and death. Cardiomyopathies comprise approximately 10-15% of SCD victims, mainly dilated cardiomyopathies, hypertrophic cardiomyopathies, arrhythmogenic right ventricular dysplasia, and myocardial infiltrative disease (sarcoidosis, amyloidosis).7 It is likely, however, that there is some overlap between CAD and the cardiomyopathies, since they can co-exist in any single individual. The final 5-10% of SCD is caused by the more rare cardiac syndromes with structural or electrical abnormalities, such as coronary anomalies, congenital heart disease, long QT syndrome, and Brugada syndrome.7 This final category also comprises subjects with sudden unexplained death, also known as idiopathic ventricular fibrillation (IVF) or sudden arrhythmic death syndrome. About 4.1% of sudden cardiac deaths are unexplained.15 These unexplained death cases may be caused by unidentified genetic disorders, although family history seems to be a reliable predictor in only a minority of sudden unexplained death cases. Remarkably, unexplained death occurs relatively more frequently in young women than in young men.16 The exact cause of this phenomenon remains to be determined.17

**Risk factors for sudden cardiac death**
Several factors have been shown to be risk factors for SCD. Although CAD is the major cause of SCD, analysis of the Framingham Heart Study cohort demonstrates that only a minority of CAD presents as SCD.18 Percentages of CAD presenting as
SCD vary between 13% in women aged 35-64 years, and 20% in men aged 65-94 years. In addition, the risk of SCD is very low once CAD is diagnosed and treated. Bardy et al. found an annual overall mortality of only 2% in a cohort of 7,001 patients with previous anterior wall myocardial infarction. The median follow-up was 37.3 months. Death could be attributed to noncardiac causes in 37.8% of cases, thus actual mortality from SCD seems to be even lower than 2%. However, it is important to note that SCD may be caused by CAD without any clear antecedent evidence in a substantial number of cases; up to 50% of victims dying of SCD are unaware of prior CAD. Furthermore, it is known that pathological diagnosis of acute myocardial infarction is difficult when death occurs within 6 hours of the ischemic episode. Biochemical and histological evidence of myocardial necrosis needs time to develop. In addition, even though the known existence of CAD in subjects seems to be a poor predictor for SCD, this does not hold true for specific subgroups of CAD patients. Patients with a previous myocardial infarction and arrhythmia risk markers (i.e. inducible nonsuppressible ventricular tachyarrhythmia on electrophysiologic study) do have a high risk of SCD, estimated at about 30%. The efficacy of prophylactic ICD implantation to prevent SCD in those patients was first demonstrated in the Multicenter Automatic Defibrillator Implantation Trial (MADIT I). Another known risk factor for SCD is severe left ventricular dysfunction. Currently, severe left ventricular dysfunction – whether in the presence or absence of CAD – is the most reliable predictor for SCD and, in addition, is relatively easy to assess. The first report identifying left ventricular ejection fraction as a strong predictor for SCD in post-infarction patients dates back to 1983. That this finding still holds true was confirmed by a more recent study reporting a 21 percent increase in the risk of SCD or cardiac arrest with resuscitation for each 5 percentage point decrease in left ventricular ejection fraction. Left ventricular ejection fraction has also shown to be a strong predictor for SCD in patients with nonischemic cardiomyopathy. It is important to note, however, that even though left ventricular function predicts SCD, only a small part of SCD is explained by left ventricular dysfunction. Stecker et al. demonstrated only 30% of SCD can be explained by severe left ventricular dysfunction. In a substudy of the Oregon Sudden Unexplained Death Study, Stecker and coworkers retrospectively analyzed all cases in which left ventricular function was assessed prior to the occurrence of SCD. Severe left ventricular dysfunction comprises the
main indication for implantation of an implantable cardioverter-defibrillator (ICD).\textsuperscript{1,23} In order to estimate the effectiveness of ICD implantation in preventing SCD, one could study the hypothetical situation in which all patients dying of SCD would have been examined before their death. Stecker and coworkers concluded that, even after excluding other causes of SCD such as long QT syndrome and Brugada syndrome, up to 65\% of SCD cases would not have been prevented by using current ICD implantation criteria.\textsuperscript{27}

Third, functional impairment in chronic heart failure, as is measured by the New York Heart Association (NYHA) classification, has shown to be a predictor of SCD. Interestingly, NYHA class II and III patients are at higher risk of SCD than pump failure, while NYHA class IV patients are more likely to die of pump failure than SCD.\textsuperscript{23,28} Still, absolute SCD mortality rates among class IV patients are higher, due to increased overall cardiac mortality.

Fourth, diabetes has been identified as an independent predictor of SCD. In a large prospective Parisian cohort, diabetes was a predictor of SCD.\textsuperscript{29} Adjusted for other variables, the relative risk for SCD was 2.2 for patients with diabetes. Even though the initial cohort included 7,746 men, there were only 118 cases of SCD, and consequently the calculated relative risk was based on only 9 patients with diabetes in the SCD group. It has been suggested that the tentative association between diabetes and SCD is caused by either ‘diabetic cardiomyopathy’ or a prolonged ventricular repolarization, as is measured by the corrected QT (QTc) interval. QTc prolongation in diabetes seems to be associated with cardiac autonomic neuropathy and has been demonstrated in diabetics without any evidence of ischemic heart disease.\textsuperscript{30} In an other study, QTc prolongation was an independent predictor of mortality in patients with type 1 diabetes.\textsuperscript{31} The QTc interval has also shown to be a risk factor for SCD, independent of diabetes.\textsuperscript{32,33} When corrected for other variables, a QTc interval of more than 440 milliseconds was associated with a 2.3 times higher risk for sudden death compared with a QTc interval of 440 milliseconds or less in patients without a history of symptoms of pump failure or an ejection fraction less than 40\%.\textsuperscript{32}

Finally, several researchers have pointed out the existence of an association between low socioeconomic status and SCD.\textsuperscript{34,35} Whether this association is independent or mediated by higher exposure to other risk factors of SCD, such as CAD, is unclear.
Sudden cardiac death: epidemiology, circadian variation, and triggers

Part 1 – Symptom onset

Patterns in onset of sudden cardiac death

Circadian variation in sudden cardiac death

Circadian patterns have been the subject of considerable interest in cardiovascular disease including both SCD as well as myocardial infarction.\textsuperscript{36,37} Cohen and coworkers\textsuperscript{37} analyzed 19 studies on the pattern of incidence of SCD. In their meta-analysis, including 19,390 patients, a morning excess in the incidence of SCD was found. Between 6:00 and 12:00, 30.1% of SCD events occurred; the incidence of SCD was 29% higher in the morning than during the rest of the day (relative risk 1.29; 95% confidence interval [CI] 1.26 – 1.32). An elegant method of studying the circadian variation of SCD was performed by Arntz et al.\textsuperscript{38} They analyzed automatic external defibrillator recordings of patients with out-of-hospital SCD used by emergency medical personnel during resuscitation attempts. The exact time of onset of unconsciousness was determined by bystander interview. The main result of this analysis, including 703 patients, is shown in Figure 2. A clear morning peak in the incidence of SCD is visible between 6:00 and 12:00. Furthermore, a secondary peak can be identified between 15:00 and 19:00. When patients were divided into subgroups based on age, the secondary peak was not observed in the >65 years subgroup (in contrast to the ≤65 years subgroup). This might be related to the fact that younger people have a

\textbf{Figure 2.} Onset of sudden cardiac death throughout the day in 703 patients. A primary peak can be identified between 6:00 and 12:00 (36% of patients; P<0.0001) and a secondary peak between 15:00 and 19:00. Reprinted with permission.\textsuperscript{38}
different lifestyle than older people. For instance, younger people <65 years, generally work, while older people do not. Support for this hypothesis was presented by a recent Greek study. In a retrospective analysis of 2,665 cases of SCD no significant morning peak was found. In contrast, they found a peak in the incidence of SCD between 20:00 and 24:00. The authors argue that this discrepancy with previous studies might be explained by the fact that Greek workers sleep during their lunch break and start working again later in the afternoon. In an other study, however, no differences in age groups were observed. Furthermore, the circadian pattern does not seem to be influenced significantly by gender and initial cardiac rhythm. Finally, it is important to note that patients with obstructive sleep apnea seem to be at highest risk of sudden death between midnight and 6:00 in the morning. Gami and coworkers found a relative risk of 2.57 (95% CI 1.87 – 3.52) during this time period.

**Figure 3.** Relation between wake up time and sudden cardiac death onset. The incidence of sudden cardiac death is significantly increased in the first 3 hours after awakening compared with the rest of the day (n=84; relative risk 2.6; 95% confidence interval 1.6 - 4.2). Reprinted with permission. Copyright © 1992, Elsevier.

**Wake up time**

An important question relates to whether the increase in the incidence of SCD is related to just the morning period or, more specific, to the time of awakening. There are only a few studies assessing this question. Willich and coworkers demonstrated a clear relationship between the incidence of SCD and wake up time in a small population (n=84) of SCD patients (Figure 3). A similar trend has been observed in patients with myocardial infarction.
Other patterns

The incidence of SCD seems to follow a circadian pattern, but other time patterns can be observed as well. In the previously mentioned Greek study,\textsuperscript{39} a significant weekly pattern in the incidence of SCD was found, with a low incidence on Sunday and a peak on Monday ($n=2,665$; $P<0.005$). This weekday distribution was less pronounced in patients older than 65 years, suggesting a relationship with employment status. In the incidence of myocardial infarction, weekly distribution with a peak on Monday is well established.\textsuperscript{44,45} Studies assessing seasonal distribution of SCD are rare and inconclusive. As is the case in myocardial infarction, some studies find peak incidences in winter months.\textsuperscript{46,47} A large study\textsuperscript{46} assessing the seasonal incidence of SCD between 1985 and 1996 in Los Angeles County ($n=222,265$) found a statistically significant increase in SCD during December and January compared with other months. Although there was an inverse correlation between temperature and SCD, SCD tended to peak around Christmas and New Year, suggesting a potential role for overindulgence, holiday stress, and increased delay to seek medical attention as well. The hypothesis that SCD peaks on Christmas and New Year, irrespective of seasonal influences, was confirmed by a more recent American study, assessing 53 million deaths over 26 years on a nationwide level.\textsuperscript{48} However, the study conducted in Greece\textsuperscript{39} found a peak incidence in July and August, which may be explained by an increase in the population caused by tourism and migration towards areas with poorer medical facilities (e.g. seaside).

TRIGGERS OF SUDDEN CARDIAC DEATH

General theory

Muller and colleagues investigated potential triggers of acute coronary syndromes and published several reviews on this topic.\textsuperscript{49-52} Therefore, it is no surprise that this research group contributed significantly to the development of a general theory that explains how acute coronary syndromes, which are often the cause of SCD, can be triggered. The theory developed by Muller et al.\textsuperscript{50,51} is shown in Figure 4. Acute coronary syndromes such as unstable angina pectoris and myocardial infarction are caused by disruption of a vulnerable atherosclerotic plaque in the coronary arteries. Therefore, any triggering factor of acute coronary syndromes must promote plaque disruption. There are three general causes of plaque disruption:\textsuperscript{50}

1. Hemodynamic forces – shear stress – arterial pressure and cardiac contractions;
2. Increased vascular tone – loss of vasodilator substances as nitric oxide or excessive secretion of vasoconstrictor substances such as endothelin-1;
4. Triggers of acute coronary syndromes mainly influence the first two mechanisms of plaque disruption. In addition, increased coagulability promotes total occlusion after a minor plaque disruption. Intra-plaque factors are largely independent of triggering factors and are estimated to account for about one third of acute coronary syndromes. To date, several endogenous and exogenous triggers have been identified, accounting for about 20% of acute coronary syndromes (Table 1).

Endogenous triggering factors
Endogenous triggering factors of SCD are internal physiologic processes that alter neural, hormonal, and metabolic processes in a circadian pattern. Examples of potential endogenous triggering factors are heart rate, blood pressure, coagulation, and vascular tone. All these processes are known to display circadian variation. Physiological processes that display circadian variation are thought to be regulated by central and peripheral circadian clocks. Circadian clock genes are expressed throughout the body. For instance, a micro-array study showed that ≥ 8-10% of the genes expressed in mouse heart are under circadian control. The molecular clock mechanism is summarized in Figure 5. Yamashita et al. demonstrated circadian gene expression of cardiac K+

| Table 1. Endogenous and exogenous triggers of sudden cardiac death |
|--------------------------|--------------------------|
| **Endogenous** | **Exogenous** |
| Blood pressure | Physical activity |
| Heart rate | Mental stress |
| Sympathetic drive | Emotional stress |
| RAAS activity | Anger |
| Catecholamine levels | Natural disasters (e.g. earthquake) |
| Vascular tone | Unnatural disasters (e.g. war) |
| Cortisol levels | Change of posture |
| Hemostasis | Sexual activity |
| Platelet aggregation | |
| t-PA levels | |
| PAI levels | |
| Hematocrit | |
| Nadir levels of medication during peak levels of exposure to triggers |

PAI, plasminogen activator inhibitor; RAAS, renin-angiotensin-aldosterone system; t-PA, tissue-type plasminogen activator
channels in rats that reflected changes electrophysiological characteristics.\textsuperscript{57}

Whether or not circadian variation in cardiac gene expression is related to the circadian variation of arrhythmias and SCD in humans remains to be determined.

**Blood pressure and heart rate**

Due to 24-hour ambulatory blood pressure monitoring, it is known that normotensive and uncomplicated hypertensive subjects display a circadian pattern in blood pressure and heart rate.\textsuperscript{58,59} This circadian variability is characterized by a low blood pressure and heart rate during the night, and highest blood pressure and heart rate in the mid morning. The mean daytime blood pressure is about 10-20\% higher than the mean nighttime blood pressure, and heart rate increases 10-20 beats per minute in the morning (Figure 6). In the elderly, these differences can be even more pronounced as a result of loss of elasticity in the arteries.\textsuperscript{60,61}

The mechanisms responsible for these patterns include autonomic nervous system and renin-angiotensin-aldosterone system (RAAS) activity. During rapid eye movement (REM) sleep, the sympathetic drive is activated and REM sleep occurs more
frequent in the morning hours\textsuperscript{61,62}. Furthermore, renin activity has shown to exhibit a circadian pattern with an early morning peak (6:00-8:00 hours) that is independent of posture and dietary influences.\textsuperscript{63,64} These observations also explain the early morning increase in the catecholamine levels of adrenaline and noradrenaline, as is displayed in Figure 6. The early morning heart rate and blood pressure surge increases the hemodynamic stress on any vulnerable atherosclerotic plaque, and can thus be regarded as a potential triggering factor for SCD and acute coronary syndromes. This adverse situation is further amplified by increased sympathetic activity and plasma catecholamine concentration. However, it is important to notice that the mechanism of plaque rupture due to arterial pressure is theoretical and hard to prove in vivo. Still, increased systolic blood pressure, measured by 24-hour ambulatory blood pressure monitoring, has definitely shown to be a predictor of cardiovascular events.\textsuperscript{65} Finally, of special interest regarding the incidence of SCD is the finding that increased sympathetic activity lowers the threshold for ventricular fibrillation.\textsuperscript{66,67}

\textbf{Figure 5.} (A) Central en peripheral molecular clocks. Peripheral molecular clocks are present throughout the body and are thought to be synchronized by the central circadian clock, the suprachiasmatic nucleus (SCN) of the hypothalamus. The SCN is the only circadian clock that is directly influenced by light through the retino-hypothalamic tract (RHT). (B) Molecular clock mechanism. The molecular clock mechanism consists of self sustained transcriptional and translational feedback loops with a period of approximately 24 hours. Transcription of ‘circadian locomotor output cycles kaput’ (CLOCK) and ‘brain and muscle arylhydrocarbon receptor nuclear translocator-like protein-1’ (BMAL1) genes creates CLOCK (C, oval), BMAL1 (B), and NPAS2 (N) transcription factors. These transcription factors form heterodimers and activate the period (Per) and cryptochrome (Cry) genes by binding to E-box elements in their promoters. Translated Per (P) and Cry (C, diamond) protein heterodimerize, translocate to the nucleus, and inhibit CLOCK and BMAL1 mediated transcription. The combination of ubiquitin mediated degradation of Per and Cry protein and inhibition of transcription of Per and Cry genes relieves inhibition and causes the cycle to start over again. Reprinted with permission.\textsuperscript{56}
Vascular tone
In 1992, Quyyumi et al.\textsuperscript{68} found vascular resistance to be higher in the morning hours while ischemic threshold was lower. It is very likely that this is at least partially the consequence of high plasma catecholamine levels. In addition, plasma cortisol level has a circadian variability with a peak in the morning; irrespective of daily activity.\textsuperscript{50,69} High cortisol levels may increase the sensitivity of the coronary arteries to the vasoconstrictive effects of catecholamines.\textsuperscript{69}

Hemostasis
Several studies have found evidence for an increased coagulability during the morning.\textsuperscript{70} For instance, Tofler et al.\textsuperscript{71} found increased platelet aggregability during the hours 6:00 to 9:00 in the morning. This association was not found when subjects remained supine and inactive, suggesting a potential role for the change of posture in the morning. Moreover, further analysis of activation-dependent platelet surface markers by Andrews et al.\textsuperscript{72} revealed that the increase in platelet aggregation is not accompanied by increased platelet activation. This may be explained by the observation that assuming an upright position causes an increased platelet count and hematocrit, which is probably caused by increased plasma epinephrine levels.

Fibrinolytic activity was evaluated by Andreotti et al.\textsuperscript{73} who found that fibrinolytic activity is reduced in the morning. Tissue-type plasminogen activator (t-PA), the major component of the fibrinolytic system, was reduced in the morning, reaching lowest values at 6:00 hour. At the same time, the activity of the fast-acting inhibitor of fibrinolysis, plasminogen activator inhibitor (PAI), was increased. These and other\textsuperscript{74} findings identify a stronger

![Figure 6. Circadian patterns of blood pressure (BP), heart rate (HR), plasma adrenaline, and plasma noradrenaline. *For scaling purposes, noradrenaline values are 3.5 times reduced. Reprinted with permission.\textsuperscript{59}](image-url)
tendency towards thrombosis during the morning hours compared with the rest of the day which may result in SCD.

**Inadequate treatment of endogenous triggers**

Endogenous triggers are particularly suitable for treatment in patients at risk of SCD. In patients with known CAD, for instance, it is important that pharmacologic therapy is adequate during the morning hours. It is suggested that medication usually subscribed in patients with CAD (statins, angiotensin-converting enzyme inhibitors, aspirin, and β-blockers) act by modulating triggers. In fact, Ridker et al. demonstrated in the Physicians Health Study that alternate day aspirin intake can abolish the circadian variation in acute myocardial infarction. In addition, Mulcahy et al. found that morning ischemic episodes in patients with CAD were abolished when using β-blockers. However, it is usual that patients take their medication once they get up in the morning. Most likely, this is not hazardous with aspirin, but other trigger modulating medication may have suboptimal blood levels in the relatively dangerous morning hours. Twenty four hour ambulatory blood pressure recordings provide a helpful tool in assessing circadian variation in blood pressure and pharmacodynamics of antihypertensive medication throughout the day.

**Exogenous triggering factors**

Exogenous triggers are thought to be associated with acute coronary syndromes and SCD since at least one century. Most potential exogenous triggers have a final common pathway. They carry out their adverse effects through emotional or physical stress, thus activating the sympathetic nervous system and releasing catecholamines.

**Physical activity**

On a theoretical basis, physical activity seems to be an obvious potential trigger of SCD and acute coronary events. Indeed, physical activity activates the sympathetic nervous system, causes release of catecholamines, and increases arterial pressure and myocardial oxygen demand. In an autopsy series, Burke et al. found that in patients where exertion preceded SCD, plaque rupture occurred significantly more frequent than in patients at rest before dying of SCD. Thompson et al. reported a 7 times higher rate of SCD among joggers compared with the average SCD rate. The relative risk of SCD and acute coronary syndromes when performing physical activity seems to be dependent on physical condition. Maclure calculated the relative risk of heavy physical exercise compared with light activity or no activity at all in different subgroups, using the case-crossover design (Table
Several other authors have found the association between physical activity and acute coronary syndromes or SCD.\textsuperscript{50,81} In practice however, the incidence of heavy physical activity in triggering SCD seems to be limited. In a recent substudy of the Oregon Sudden Unexpected Death Study, Reddy et al.\textsuperscript{82} demonstrated that 80% of patients (n=304) were asleep or were performing light activities prior to experiencing sudden cardiac arrest. Only 13% of patients were performing moderate activities (e.g. walking for exercise, gardening) and 5% of patients were performing heavy activity (e.g. sports as jogging, tennis). This finding is in accordance with a meta-analysis from 2005.\textsuperscript{83} This meta-analysis by Čulić et al. included 17 studies on possible external triggers of acute myocardial infarction. Ten studies included data about heavy physical activity: in 643 of 10,519 patients (6.1%) heavy physical activity was reported prior to acute myocardial infarction. In this regard however, it must be remembered that regular physical exercise has many beneficial effects, including limiting atherosclerosis disease progression.\textsuperscript{84}

### Mental stress

Mental stress has also been associated with a variety of cardiovascular conditions, including Takotsubo cardiomyopathy, acute coronary syndromes, and SCD. In the previously mentioned meta-analysis, Čulić et al.\textsuperscript{83} found that as many as 6.8% of patients were experiencing any kind of emotional stress (particularly anger in 2.1% of cases) prior to acute myocardial infarction onset. The role of mental stress in exacerbating CAD was also demonstrated by Barry et al.\textsuperscript{85} who studied ST-segment depression in 28 patients with documented CAD, using ambulatory electrocardiographic monitoring and diary records. Remarkably, 22% of ischemic events occurred at high levels of mental stress and low physical activity. A ‘unique opportunity’ to study mental stress as a trigger of SCD is offered by natural and unnatural disasters, such as earthquakes and wars.

<table>
<thead>
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<th>Condition (usual exercises / week)</th>
<th>Relative risk of MI</th>
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<tr>
<td>&lt; 1</td>
<td>107</td>
</tr>
<tr>
<td>1 – 2</td>
<td>19.4</td>
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<tr>
<td>3 – 4</td>
<td>8.6</td>
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<td>≥ 5</td>
<td>2.4</td>
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Table 2. Relative risk of MI in the first hour after heavy physical activity in different subgroups based on physical condition

MI, myocardial infarction

The research group of Kloner in Los Angeles published several articles about the effects of the 2004 Northridge earthquake in this area. In one of their studies they clearly show that SCD was increased during the day of the earthquake (Figure 7). Remarkably, during the six days after the earthquake, the number of SCD cases was below average. This observation suggests that the earthquake was a source of great mental stress, thus causing SCD in numerous patients who otherwise would have reached the ‘triggering threshold’ for SCD a few days later due to other causes. Similar results were found in the Israeli population on the days of Iraqi missile attacks during the Gulf war in January 1991. Finally, a more contemporary example of the effects of unnatural disasters on SCD was presented by Stuckler et al. They recently calculated that a banking crisis coincides with a 6.4% (95% CI: 2.5% to 10.1%; P<0.01) increase in cardiovascular disease mortality in developed countries, using data from 1960 to 2002.

Change of posture
In the previous sections of this article, several explanations of the possible morning increase in SCD and acute coronary syndromes were reviewed. Some researchers have argued that the act of standing up after awakening contributes to the morning increase in SCD. A systematic review of 23 studies on this topic is available. Two
important consequences of change of posture are an increase of hematocrit of 1.3-4.6% (based on 11 studies) and a loss of plasma volume of 7-17% (i.e. 200-640 mL; based on 15 studies). This hemoconcentration is caused by redistribution of blood to the lower part of the body, causing higher hydrostatic pressure and subsequent transvascular loss of plasma to the interstitial fluid compartment. The resulting increased blood viscosity may contribute to the morning increase in acute coronary syndromes. Furthermore, some of the morning changes in blood coagulability, as described earlier, might be caused by change in posture. However, evidence on this topic is limited and further research is needed to draw conclusions.

**Sexual activity**

Sexual activity is considered a separate category of trigger, because it includes physical activity as well as emotional activity. Sexual activity is decreased in a large proportion of patients with known CAD, mostly because of anxiety. Muller et al.\(^9^0\) interviewed 858 patients who were sexually active in the year prior to nonfatal acute myocardial infarction onset. Of these patients, 9% reported sexual activity in the hour prior to acute myocardial infarction onset, and 3% in the 2 hours prior to myocardial infarction. This represents a relative risk of 2.5 (95% CI 1.7 – 3.7). In patients with prior myocardial infarction, the relative risk was 2.9 (95% CI 1.3 - 6.5). Regular exercise was associated with a lower risk. Because the absolute risk of myocardial infarction is very low and sexual intercourse is a relatively infrequent event, the anxiety should be taken away in most cases. Although there are no reports assessing the risk of SCD during sexual activity, it is presumed to be similar to the risk of myocardial infarction.

**FUTURE DIRECTIONS**

Although several large prospective studies have been conducted, it is still not possible to identify the large group of asymptomatic individuals prior to their fatal cardiac event as up to 50% of patients dying of SCD as a result of CAD are unaware of prior CAD.\(^2^0\) Future progress should come from improvements in risk stratification and targeted ICD implantation in individuals at high risk of SCD. In addition, implantable devices which can track ST-segment shifts and changes in rhythm with patient feedback mode are being tested.\(^9^1\) Such a strategy appears promising in high risk patient subsets. Prevention of SCD in a broad, less defined population is unfeasible. Due to the low incidence of SCD in such a population – even with very accurate testing – the number of false positives will be high.

In patients with (asymptomatic) CAD,
endogenous as well as exogenous factors may trigger SCD and acute coronary syndromes. Future preventive strategies should focus on minimizing exposure to exogenous triggers and treating exposure to endogenous triggers. Exposure to endogenous triggers can be reduced with medication in susceptible individuals, particularly during the morning hours. Exogenous triggers can often be modified by lifestyle changes. Kloner argued, for instance, that the act of waking up can be made less hazardous by taking the time to get out of bed and stand up, perhaps combined with soft music instead of a loud alarm. This is not a proven therapy yet, but is worth more research. Finally, specific pharmacological treatment might be beneficial in preventing trigger mediated SCD or acute coronary syndrome. Mittleman et al. demonstrated that regular aspirin users had a significantly lower risk of anger triggered myocardial infarction compared with nonusers. With the intention to provide a framework for future research, Tofler and Muller also identify strategies for ‘triggered acute risk prevention’. To implement such strategies in clinical practice is a major future challenge.

**CONCLUSIONS**

In conclusion, SCD is still an important cause of death and seems to be greatly influenced by triggers. More research is warranted on risk stratification, identification of potential triggers, and targeted prevention of exposure to those triggers in individuals at risk of SCD.
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REFERENCES


24. Multicenter Post Infarction Research Group. Risk stratification and survival after


46. Kloner RA, Poole WK, Perritt RL. When throughout the year is coronary death most likely to occur? A 12-year population-based analysis of more than 220,000 cases. *Circulation* 1999;100:1630-4.


51. Muller JE, Tofler GH, Stone PH. Circadian variation and


78. Kloner RA. Natural and unnatural triggers of myocardial infarction. *Prog...*


