



Review

Emotional triggering of cardiac events

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ABSTRACT

Psychological factors may contribute not only to the evolution of coronary atherosclerosis and long-term risk of coronary heart disease, but also to the triggering of acute cardiac events in patients with advanced atherosclerosis. Evidence for emotional triggering of cardiac events derives both from population-based studies of hospital admissions and sudden deaths following major traumas such as earthquakes and terrorist incidents, and from individually based interview studies with survivors of acute coronary syndromes (ACS). The latter indicate that acute anger, stress and depression or sadness may trigger ACS within a few hours in vulnerable individuals. The psychobiological processes underlying emotional triggering may include stress-induced haemodynamic responses, autonomic dysfunction and parasympathetic withdrawal, neuroendocrine activation, inflammatory responses involving cytokines and chemokines, and prothrombotic responses, notably platelet activation. These factors in turn promote coronary plaque disruption, myocardial ischaemia, cardiac dysrhythmia and thrombus formation. The implications of these findings for patient care and ACS prevention are outlined.

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1. Introduction

Cardiovascular disease is one of the main causes of serious illness, and a major cause of death and reduced quality of life. The costs of cardiovascular disease, including healthcare costs, the price of unpaid care and loss of earnings, were estimated at €169

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billion in 2003 (Leal et al., 2006). Coronary heart disease (CHD) is the largest single cause of death in Europe, accounting for 21% of male and 22% of female deaths (Allender et al., 2008). It is also the leading cause of death in people aged less than 75 years (20% male and 19% female deaths). However, death rates have been declining for the past three decades in many countries, due primarily to improvements in risk factor profile, and also to increased survival following acute coronary events. This means that the prevalence of diagnosed CHD in the population has been rising. Recent figures from the USA indicate that 6.5% of the population have a history of heart attack (myocardial infarction) or angina pectoris (Anon., 2007).

There is an extensive literature relating psychosocial factors with the development of CHD (Everson-Rose and Lewis, 2005; Kuper et al., 2005). The condition underlying CHD is coronary atherosclerosis, a progressive process of arterial wall thickening due to lipid deposition, inflammation and smooth muscle infiltration (Hansson, 2005). The psychosocial factors implicated in both atherosclerosis and CHD include low socioeconomic status (SES), chronic stress exposure, particularly in the work place, and aspects of the social environment such as social isolation and low social support. In addition, emotional factors including depression, anxiety, anger and hostility are thought to contribute to the development of CHD (Suls and Bunde, 2005; Steptoe, 2006). This research has been primarily concerned with long-term aetiology, and with demonstrating that exposure to psychosocial risk factors promotes accelerated atherosclerosis and higher rates of CHD incidence. There is, however, another way in which emotional factors might contribute to cardiovascular disease, and this is through the stimulation of acute cardiac events such as myocardial infarction (MI), unstable angina, or sudden cardiac death. Such cardiac events typically occur in people with advanced coronary atherosclerosis. The emotional factors involved in these situations are not necessarily the same as those implicated in long-term aetiology, since they act over a much shorter time scale. The purpose of this review is to summarize the evidence for emotional triggering of cardiac events, and to outline the psychophysiological processes that stimulate the pathological responses underlying acute coronary syndromes (ACS, comprising myocardial infarction and unstable angina) or sudden cardiac death.

2. Acute cardiac events

It used to be thought that acute MI occurred as the end product of a passive process of lipid accumulation in the coronary artery wall, when the vessel walls became so thick that the artery was completely blocked. However, it is now recognized that atherosclerosis is an active inflammatory disease in which the accumulation of oxidized lipoprotein, macrophageous foam cells and smooth muscle cell proliferation leads to the development of fibrous plaque (Steptoe and Brydon, 2007). The key pathophysiological events underlying ACS are the disruption of coronary plaque, and subsequent development of a thrombus (internal clot) in the artery. Plaque rupture is the commonest type of plaque disruption, accounting for some 70% of fatal acute myocardial infarctions and sudden cardiac deaths (Naghavi et al., 2003). Rupture occurs when the fibrous cap of the plaque is mechanically disturbed or degraded by the action of matrix metalloproteinases released by macrophages, enzymes that degrade the cap's extracellular matrix, rendering it weak and prone to rupture. In other cases, injury is due to plaque erosion, when thrombus is superimposed on a plaque that is intact except for the loss of the endothelial cells layer. Vulnerable plaques are characterized by active inflammation, macrophage accumulation and activated T-cells, a thin fibrous cap with a large lipid core, and endothelial

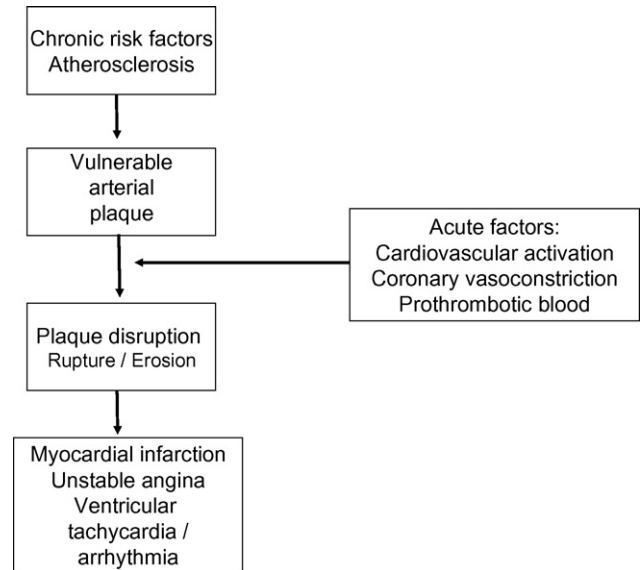


Fig. 1. Sequence of pathophysiological events leading to acute coronary syndromes and ventricular tachyarrhythmias.

denudation coupled with platelet aggregation (Hansson, 2005). A number of biomarkers of atherosclerotic plaque instability and rupture have been proposed, notably Interleukin-6 (IL-6), IL-18, and monocyte chemoattractant protein-1 (MCP-1), but the clinical utility of such measures is uncertain at present (Koenig and Khuseyinova, 2007).

However, it is also known that episodic plaque disruption is a relatively common event that only occasionally provokes an acute coronary syndrome. Other factors apart from plaque disruption are necessary for an ACS to occur. Fig. 1 outlines the combination of pathophysiological factors that lead to acute ischaemic events. It is thought that in addition to vulnerable plaque, three other factors may be present. The first is cardiovascular or haemodynamic activation, with acute increases in heart rate and blood pressure leading to disturbed blood flow across the disease vessel, stimulating endothelial shear stress (Chatzizisis et al., 2007). Autonomic nervous system responses may stimulate cardiovascular activation, while also provoking potentially life-threatening ventricular tachyarrhythmias (Kokolis et al., 2006). Second, coronary vasoconstriction may occur, disrupting blood flow and promoting plaque rupture. The third factor is the presence of procoagulatory and antithrombotic factors in the blood. After plaque rupture, the local balance between prothrombotic and thrombolytic factors will determine whether occlusion of the artery takes place.

This sequence of events may occur spontaneously, or be triggered. A trigger is a stimulus or activity that produces the acute physiological or pathophysiological changes that initiate a cardiac event. Generally speaking, the focus in trigger studies is on stimuli that occur within 1–2 h before the onset of an ACS, though some studies suggest that longer periods up to several weeks may be relevant (Tofler and Muller, 2006). Triggers may take many forms, including physical exertion, heat and cold stress, infection, and use of substances such as cocaine (Kloner, 2006; Čulić, 2007). The focus in this article is on the possible role of acute negative emotional states. The study of emotional triggers presents particularly thorny methodological issues, as described below.

3. Methods of studying emotional triggers

It is difficult to study emotional triggering of cardiac events prospectively, since the occurrence of acute MI or sudden cardiac

death cannot be anticipated in advance. Studies of emotional triggering are therefore typically retrospective, and involve two broad strategies. The first is to study the impact of emotionally stressful events such as natural disasters, terrorist attacks, industrial disasters and sporting events on admissions for ACS or the occurrence of sudden cardiac death. The advantage of this population-based approach is that the stimulus is timed objectively, and the occurrence of ACS can be contrasted with comparison periods. The second method is to study individual patients after they have suffered a cardiac event, asking them about their experiences in the period before symptom onset. This allows precise information to be collected about the person's emotions. Both these methods have strengths and limitations, and will be briefly illustrated here.

4. Population-based studies

4.1. Earthquakes

Earthquakes are devastating and very stressful experiences, and their effects on acute cardiac events have been studied in several countries (Bhattacharyya and Steptoe, 2007). Unfortunately, results have not been completely consistent. The most thorough analyses were carried out in the aftermath of the Northridge Earthquake that took place in the Los Angeles area in January 1994. A postal survey of more than 100 hospitals showed that admissions for acute MI increased from 149 in the week before to 201 in the week after the earthquake (Leor and Kloner, 1996). This was reinforced by a study of the coroners' records for Los Angeles County, which found that sudden deaths from cardiac causes increased from an average of 4.6 per day in the week before to 24 on the day of the earthquake (Leor et al., 1996). Only three of these cases were associated with unusual physical exertion. A later analysis of all deaths in Los Angeles County confirmed the increase CHD mortality, and showed that there was no increase in deaths from other cardiovascular diseases or from non-cardiovascular causes (Kloner et al., 1997), suggesting a specific triggering effect.

Studies of the Hanshin-Awaji earthquake in 1995 in the Kobe region of Japan showed similar results, with a large increase in the number of patients admitted for acute MI on the day of the earthquake (Suzuki et al., 1995). By contrast, the 1989 Loma Prieta earthquake in the San Francisco Bay area did not lead to any increase in ACS admissions (Brown, 1999). One explanation may be the timing of these earthquakes. Both the Northridge and Hanshin-Awaji quakes struck early in the morning on a winter day, while the Loma Prieta earthquake occurred on the afternoon in October. There is a greater susceptibility to acute MI in winter months, and the early morning of weekdays may be particularly dangerous (Barnett and Dobson, 2005).

4.2. War and terrorism

A few studies have examined the impact of war and terrorist acts on acute cardiac events. Meisel et al. (1991) documented an increase in the incidence of acute MI and sudden death in the Tel Aviv area during the initial phases of the Gulf War in 1991. This was confirmed by a national survey in Israel which showed a 58% increase in mortality on the day of the first missile strikes of the Gulf War that was largely attributable to acute MI and sudden cardiac death (Kark et al., 1995). Studies of other war zones have produced mixed results, but the quality of data collected under such difficult circumstances is very variable (Dumitrascu et al., 1993; Mihatov et al., 1995).

The terrorist attack in New York City on September 11, 2001 (9/11) has also been studied. Perhaps surprisingly, there was no

increase in cardiac death or admissions to acute coronary care in New York City following 9/11 (Chi et al., 2003a,b). One study of admissions to a hospital in Brooklyn observed an increase in the proportion of cardiac admissions for acute MI and tachyarrhythmias compared with unstable angina in the 2 months following 9/11 (Feng et al., 2006). The authors argued that the stress of the terrorist attack resulted in the development of more severe forms of acute heart disease, though not an increase in absolute incidence. More recently, Holman et al. (2008) showed in a US national survey that the incidence of cardiovascular ailments diagnosed by physicians increased by more than 50% in the 3 years after 9/11, after statistical adjustment for earlier cardiovascular and mental health. It is uncertain whether this represents acute triggering, or the impact of more chronic stress due to persistent worries about terrorism.

4.3. Sporting events

Major sporting events can be very stressful for supporters, so might theoretically act as triggers for cardiac events. An important match in the European soccer championship in 1996 between France and the Netherlands ended with a penalty shoot out (sudden death) which the French won. Cardiovascular mortality following this exciting match was analyzed in the complete Dutch population aged 45 or more (Witte et al., 2000). There was a relative risk of death from acute MI or stroke of 1.51 (95% confidence intervals 1.08–2.09) on the day of the match for men compared with the 5 days on either side, with no effect on women. An increase in hospital admissions for acute MI in England on the day of the 1998 World Cup match against Argentina has also been described (Carroll et al., 2002); again, this match involved a penalty shoot out, and England lost. Other studies have been less consistent, but have not all involved such crucial matches and tight finishes for a national team (Brunekreef and Hoek, 2002; Katz et al., 2005). Wilbert-Lampen et al. (2008) recently conducted a very thorough analysis of cardiac events in the Munich area during the 2006 World Cup. The incidence of cardiac emergencies was substantially increased among German men on the days the German team played, with a lesser rise among women. Effects were particularly marked during the 2-h after the start of matches. The circumstances surrounding these deaths are not known, and it is possible that physical exertion, emotional stress and alcohol consumption all contributed to triggering.

4.4. Problems of interpretation

The evidence from these population-based studies of emotional triggering is rather mixed. A limitation of these studies is that the circumstances surrounding each cardiac event are not well defined, and analyses typically take place weeks, months or even years after the trauma. Information about how the individuals who were affected actually experienced the trauma is seldom collected, making it difficult to rule out alternative explanations of associations between disasters or traumatic incidents and ACS onset. For example, apart from the emotional stress of these situations, cardiac health could be affected by concomitant behaviours such as vigorous physical exertion (e.g. escaping from disaster zones), heavy eating and drinking (sporting events and festivals), exposure to toxins and pollutants (war and terrorist settings), and disruption of primary care and emergency services which might otherwise have prevented acute cardiac events. These limitations are not surprising, since findings typically come from opportunistic retrospective investigations of situations in which the health services had more immediate priorities such as treating injuries and saving lives.

5. Individual emotional triggers

The first large scale project to evaluate emotional triggers in individuals was the Multicenter Investigation of Limitation of Infarct Size (MILIS) study, which involved 849 patients interviewed within 18 h of acute MI. 18% reported emotional upset in the period immediately before symptom onset (Tofler et al., 1990). In the Triggers and Mechanisms of Myocardial Infarction (TRIMM) study, 35% of patients reported either emotional upset or stress within the hours before acute MI (Willich et al., 1991). Other studies have reported much lower levels of emotional triggers (Behar et al., 1993). In a meta-analysis of 17 studies, Čulić et al. (2005) concluded that 6.8% of patients report emotional stress preceding the onset of MI.

However, there are two serious problems with the interpretation of studies that simply enquire about the occurrence of triggers. First, patients' reports can be affected by their attempts to make sense of their predicament, and by their beliefs about the causes of heart disease. Stress is frequently mentioned both by patients and healthy adults as a major cause of heart disease (French et al., 2001), and these opinions may affect recall of the trigger period. Second, control time periods are not tested. If emotional stress occurs frequently in a patient's life, its association with ACS onset may be coincidental. Control groups are difficult to select, since there can be healthy volunteer biases, and control individuals may be less likely to agree to participate on stressful days.

These issues have led to the development of case-crossover designs, in which the critical time period (the trigger period) is compared with control time periods on a within-person basis (Maclure and Mittleman, 2000). For example, a patient might be questioned about emotional stress in the 2-h before symptom onset, and also about the same 2 h period that occurred 24 h earlier (pair-matched interval approach). By comparing hazard and control periods, the relative risk that an episode of emotional stress is followed by an ACS can be computed. This method has the advantages that self-matching eliminates selection and individual reporting biases, and that any differences in chronic cardiovascular risk profile between cases and controls are also eliminated, reducing the risk of residual confounding.

5.1. Anger

Acute anger is the emotional trigger of ACS that has been studied most extensively. In the Determinants of Myocardial Infarction Onset Study (Onset), 2.4% of patients reported being very angry or furious in the 2-h before their acute MI (Mittleman et al., 1995). The odds of ACS onset following acute anger relative to no anger in the pair-matched analysis were 4.0 (95% confidence intervals 1.9–9.4). This association was independent of age, sex, cardiovascular risk factors, and the use of beta-blockers, but was more common in lower SES patients (Mittleman et al., 1997). A similar result was reported in the Stockholm Heart Epidemiology Program (SHEEP) study (Moller et al., 1999).

We carried out a similar study in London with a clinical cohort of 295 ACS patients selected for their ability to recall the onset of symptoms, and excluding individuals with co-morbid conditions that might have affected mood and emotion (Strike et al., 2006a). 17.4% reported episodes of acute anger in the 2-h before symptom onset, including arguments with neighbours, family conflict and anger during commuting. The odds of an ACS starting after anger compared with no anger in the pair-matched analysis were 2.06 (CI 1.12–3.92). A wider definition of anger was used in this study than in previous work, and this is why the overall incidence of anger was higher. As in the Onset study, anger triggering was more common in lower SES patients, and was not related to cardiovascular risk

factors, having a previous MI, or to the presence or absence of premonitory symptoms.

5.2. Acute stress

Acute work stressors were assessed as possible triggers in the SHEEP study (Moller et al., 2005). It was found that stressors such as having high-pressure deadlines in the previous 24 h were associated with substantial increases in risk (odds ratio 6.0, CI 1.8–20.4), in comparison with the period 24–48 h before the MI. Other studies have assessed more general emotional stress. For example, emotional upset in the 2-h before symptom onset was reported by 4.4% in a German study, with a relative risk in a case-control analysis of 2.7 (CI 1.1–6.6) (Willich et al., 1993). Stress resulting from exposure to heavy traffic has also been evaluated (Peters et al., 2004); the odds of MI following exposure to traffic in the hour before symptom onset were 2.92 (CI 2.22–3.83).

5.3. Acute depression

Depression is relevant both to the long-term development of CHD and to prognosis following cardiac events (Steptoe, 2006). In our recent study, we enquired about the occurrence of episodes of acute depression and sadness in the 2-h before onset of cardiac symptoms (Steptoe et al., 2006). Episodes of depression or sadness were reported by 18.2% of patients, and in the case-crossover analysis, the odds of ACS following depressed mood were 2.50 (CI 1.05–6.56). When analyses were limited to episodes of severe depression or sadness, the odds were greater (5.08, CI 1.07–47.0). Triggering by depressed mood was not related to the clinical severity of the ACS or the extent of underlying disease, but was more common in lower SES patients, and in those who had experienced severe life stress in the previous 4 weeks.

5.4. Problems of interpretation

The data from patient interview studies is rather consistent in suggesting that a proportion of ACS patients experience acute emotional distress in the 2-h before symptom onset, and that the pattern is more common in lower SES groups. However, the case-crossover design does not completely overcome the methodological problems of studying emotional triggers (Strike and Steptoe, 2005). Reporting biases cannot be completely eliminated. Even though the same patients provide information for hazard and control periods in case-crossover designs, they may selectively report emotional experiences in the presymptomatic period, since this will be more emotional salient than the control period. The control period is also more distant in time, so recall may not be as accurate as for the hazard period. No studies have yet been published that attempted to verify patients' reports by obtaining information from witnesses to symptom onset.

6. Psychobiological processes underlying acute triggering

Psychological stress elicits a range of physiological responses that are potentially relevant to the triggering of ACS. Some of these responses occur both in healthy individuals and in patients with advanced coronary atherosclerosis, while others are present only in people with diseased coronary vessels. Fig. 2 outlines five categories of physiological response to acute stress, and the possible effects that these might have in people with advanced coronary artery disease.

First is the widely studied haemodynamic response, which includes increases in blood pressure, heart rate and cardiac output, coupled with regional changes in blood flow that promote

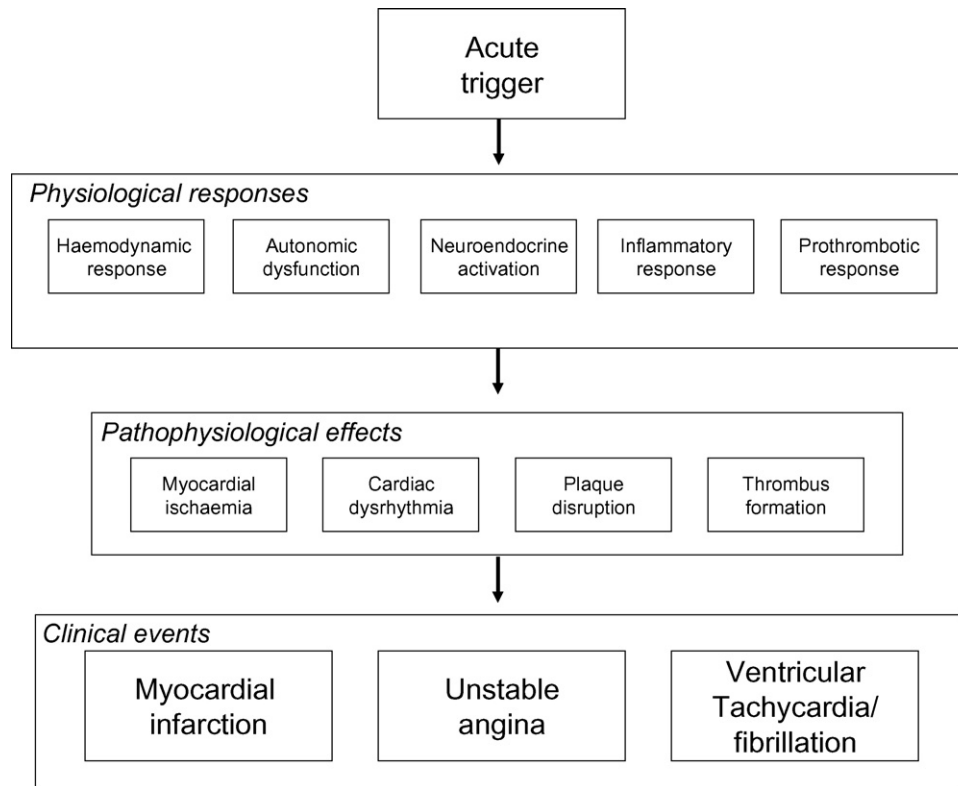


Fig. 2. Hypothesized links between acute emotional triggers and clinical cardiac events, mediated through physiological responses and their pathophysiological consequences. Adapted from [Bhattacharyya and Steptoe \(2007\)](#).

preferential energy supply to working muscle in the voluntary musculature and myocardium ([Hjemdahl, 2007](#)). There is evidence that haemodynamic responses are altered in cardiac patients, with larger or more enduring pressor responses ([Strike et al., 2004](#)). Additionally, a proportion of patients with advanced coronary atherosclerosis show coronary artery vasoconstriction instead of the normal vasodilatation in response to stress. In a study of 26 patients who carried out mental arithmetic during coronary catheterization, the blood flow through regions of high stenosis was reduced by an average of 27%, so stress accentuated the already impaired blood flow to heart muscle ([Yeung et al., 1991](#)). [Boltwood et al. \(1993\)](#) reported that anger-provoking tasks elicited marked coronary vasoconstriction in patients with CHD, a finding that is consistent with the clinical triggering literature described in Section 5.1.

Haemodynamic responses to stress are stimulated in part through the second component, namely autonomic dysfunction. Both sympathetic activation and parasympathetic withdrawal not only influence pressor responses, but can also stimulate malignant arrhythmias and the threshold for ventricular fibrillation. Reduced parasympathetic activity, indexed by decreased heart rate variability, is a predictor of CHD in population studies, death in patients following acute MI, and of sudden cardiac death ([Thayer and Lane, 2007](#)). Heart rate variability is also reduced by acute mental stress, with more prolonged responses in people of lower SES ([Steptoe et al., 2002](#)). Depression has been associated with reduced heart rate variability in patients with ACS ([Carney et al., 2001](#)).

Autonomic dysfunction is closely associated with the third component, namely neuroendocrine activation. Acute stress induces increases in hypothalamic–pituitary–adrenocortical activity and in catecholamine levels. There is a particularly large increase in noradrenaline spillover from the heart during mental

stress, reflecting sympathetic stimulation of the myocardium ([Esler et al., 1989](#)).

The fourth component of the acute physiological stress response that is relevant to triggering is activation of inflammatory processes. Inflammatory markers such as IL-6 and tumour necrosis factor (TNF) α increase following emotional stress, although responses take 60–90 min to become measurable in the circulation ([Steptoe et al., 2007](#)). Inflammatory cytokines, chemokines and other molecules are intimately involved in advanced atherosclerosis and in thrombus formation ([Steptoe and Brydon, 2007](#)). Cytokines released by activated T lymphocytes destabilize plaques by inhibiting smooth muscle cell production of collagen, a protein that lends strength to the plaque's protective fibrous cap, as well as stimulating monocyte release of matrix metalloproteinases that degrade the cap. At the same time, cytokines promote thrombosis by stimulating monocyte production of tissue factor, one of the key initiators of blood coagulation in ACS. They also stimulate hepatic synthesis of fibrinogen, an acute phase protein that plays a pivotal role in blood coagulation, plasma and whole blood viscosity and platelet aggregation. Several of the substances involved in haemostasis and blood clotting also increase in response to emotional stress including fibrinogen, von Willebrand factor, Factors VII and VIII, and fibrin D-dimer ([von Kanel et al., 2001](#)). Platelets are potentially particularly important in the triggering process, since they aggregate at the site of plaque rupture in an attempt to seal off the damaged vessel wall ([Brydon et al., 2006](#)). We have shown that platelet activation is increased during emotional stress, with more prolonged responses in patients with coronary artery disease compared with controls ([Strike et al., 2004](#)).

The combined effect of these physiological responses may be to stimulate plaque disruption, promote thrombus formation, and induce ventricular electrical instability. One product of these

responses is to induce transient reversible myocardial ischaemia which can be assessed by measuring wall motion abnormalities, ST-segment changes on the electrocardiogram, or by observing reductions in ejection fraction. There is a substantial literature on mental stress-induced myocardial ischaemia which can be induced in up to 50% of patients with coronary artery disease (Strike and Steptoe, 2003). Interestingly, transient myocardial ischaemia is stimulated by mental stress at a lower heart rate and rate–pressure product than during physical exercise, suggesting that in addition to haemodynamic activation, coronary artery vasoconstriction and microvascular responses may contribute (Goldberg et al., 1996).

7. Psychophysiological studies of triggering

Fig. 2 summarizes the processes that potentially underlie emotional triggering of cardiac events, but direct evidence is difficult to obtain. Since ACS are unpredictable, there have been few studies that have been able to measure physiological responses at the time of cardiac events. However, in one study, an earthquake happened to occur as 15 patients with suspected coronary artery disease were undergoing Holter monitoring (Lin et al., 2001). Spectral analysis of R–R intervals showed a marked increase in the low to high frequency ratio for about 40 min after the earthquake, indicative of vagal withdrawal. ST-segment depression (indicating transient myocardial ischaemia) was measured in several patients, and was correlated with the increase in low frequency power. Parati et al. (2001) described a single patient undergoing ambulatory blood pressure monitoring during an earthquake in central Italy, who showed a large increase in pressure and in heart rate which persisted for an hour. Other acute effects include increased blood viscosity, fibrinogen and D-dimer levels (Matsuo et al., 1998), and abnormal cardiac sympathetic function as revealed with metaiodobenzyl guanidine imaging (Yamabe et al., 1996). Lampert et al. (2002a) measured 24-h heart rate variability in cardiac patients and matched controls during the week of the 9/11 terrorist attacks. A reduction in high frequency power was recorded during the week of the terrorist attack, again suggestive of vagal withdrawal and a shift in autonomic balance towards the sympathetic nervous system.

Another way of investigating psychophysiological processes is to study patients with implantable cardioverter defibrillators (ICDs). The pattern of discharges of ICDs, indicative of the presence of potentially lethal ventricular arrhythmias, varies with season of the year and time of day in the same manner as ACS (Anand et al., 2007). A diary study of patients with ICDs indicated that spontaneous discharges were associated with reports of increased anger over the day (Lampert et al., 2002b), while an investigation of 200 patients in New York City showed an increase in serious arrhythmias following the 9/11 attacks, with the proportion of patients who experienced tachyarrhythmias more than doubling over the next 30 days (Steinberg et al., 2004). Whang et al. (2005) demonstrated that depressive symptoms predicted ICD discharges in a large cohort of cardiac patients.

The evidence therefore suggests that emotional stress does induce physiological responses in CHD patients that could contribute to triggering of cardiac events. However, this raises the question of whether all patients with advanced CAD are responsive to emotional triggering, or whether it is a characteristic of a subset of individuals with particular psychophysiological vulnerabilities. To date, only one study has addressed this issue, and has demonstrated that patients susceptible to emotional triggering show a distinct pattern of physiological responses to emotional stimuli. This was an experiment that we carried out with 34 male survivors of ACS (Strike et al., 2006b). Fourteen patients reported negative emotions (anger, stress or depression)

in the 2-h before symptom onset, while the remaining 20 men did not. We carried out psychophysiological testing of these patients around 15 months after admission to hospital, when they had long since recovered from the acute phase of CHD. By comparing the trigger and non-trigger groups, we were able to discover whether vulnerability to emotional triggering was accompanied by heightened stress-induced physiological responses. We studied physiological responses to two short standardized mental stress tests—mirror tracing and simulated public speaking. In the light of the pathways outlined in Fig. 2, we monitored haemodynamic responses, platelet activation and inflammatory cytokine responses. The statistical analysis took into account potential confounders such as age, body mass index and medication with aspirin or β -blockers.

We found that both groups of patients responded to tasks with large increases in blood pressure, heart rate and subjective stress. But patients who had experienced emotional triggers of their ACS showed more prolonged systolic blood pressure responses than did the non-trigger group. Even 30 min after tasks were completed, systolic pressure was significantly higher in the trigger group. Additionally, there was a marked difference in platelet activation, as indexed by the proportion of circulating monocyte–platelet aggregates assessed using flow cytometry. The trigger group showed a doubling of monocyte–platelet aggregates following stress and 30 min later, while the non-trigger group did not show any increase in platelet activation. Patients who experienced an emotional trigger therefore appear to have heightened and prolonged biological responses to emotional stimuli. If such responses coincide with plaque disruption, the result might be the development of an ACS.

The results we have published from this study combined patients who experienced intense stress, anger or depression in the 2-h preceding symptom onset (Strike et al., 2006b). However, it is possible that different emotional states induce slightly different patterns of biological response. We have therefore more recently analyzed the patients who reported the three different types of acute emotional response separately. We found that patients who experienced acute depressed mood or sadness during the trigger period had a distinctive pattern of inflammatory response to stress. Concentrations of plasma IL-6 were measured at baseline and then at several time points up to 2 h post-stress. The results are summarized in Fig. 3. It can be seen that patients who experienced depression during the 2-h trigger period showed greater IL-6 responses to laboratory psychophysiological stress 15 months

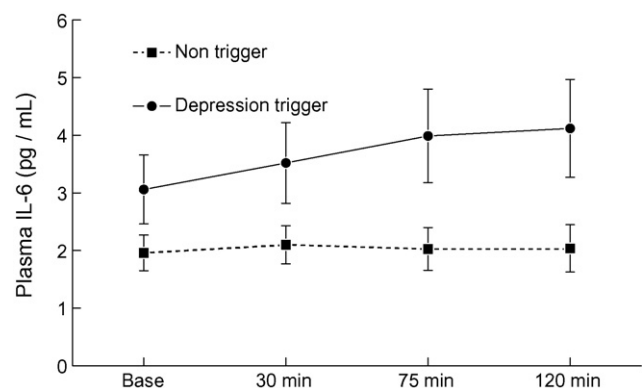


Fig. 3. Mean levels of plasma IL-6 at baseline, 30, 75 and 120 min following stressful tasks in cardiac patients whose ACS had been preceded by depression or sadness (solid line) or no depression or sadness (dashed line). Values are adjusted for age, aspirin use and medication with β -blockers. Error bars are standard errors of the mean.

Table 1
Methods of reducing risk of acute triggering of cardiac events

ACS trigger	Management technique
Reducing exposure to triggers	
Physical exertion	Exercise training programmes
Anger	Anger management programmes
Stress and heightened emotion	Stress management, cognitive behaviour therapy, medication
Alcohol, cocaine use	Public health awareness campaigns, individual treatment
Infectious illness	Influenza vaccination, antibiotic treatment, public health awareness programmes
Precautions in high risk situations	
Festivals/public holidays/sporting events	Improved access to defibrillators, increased medical cover, public health awareness programmes
Natural disasters/industrial and transport accidents/terrorist acts	Programmes to increase public and clinical awareness of triggering, appropriate emergency care
Anniversaries, significant dates	Targeted social support

later, independently of age, body mass and medication. Over the post-stress period, the concentration of plasma IL-6 increased around 35% in the depression trigger group, compared with less than 5% in the remaining patients. Since triggering of ACS can take up to 2 h, it is possible that the enhanced proinflammatory response elicited by sadness or depressed mood in these patients may contribute to plaque disruption and thrombus formation.

8. Clinical implications

There are important clinical implications to understanding the role of emotional stimuli as triggers of ACS that have been considered comprehensively by [Tofler and Muller \(2006\)](#). They have argued that clinical strategies for reducing risk of triggering should complement the management of long-term risk factors. Vulnerability to emotional triggering may place certain types of patient at high risk when they are exposed to interpersonal situations that elicit strong negative emotions. If such individuals could be identified in advance, special procedures could be put in place for their clinical management. [Table 1](#) summarizes some of the procedures that might be relevant not only for emotional triggers, but also for other types of trigger of acute cardiac events. They include methods of reducing exposure to triggers, and procedures that could be put in place in high risk situations. Most methods of reducing risk relate to individual triggers, and include such approaches as physical training to reduce risk of triggering by physical exertion, and anger management for reducing risk of anger triggering. Methods relevant to high-risk situations include public awareness programmes for highlighting the potential dangers of major sporting events, and social support to help patients cope with episodes of extreme sadness and depressed mood, stimulated by bereavement, loss and anniversaries. The use of pharmacological methods requires fuller evaluation, since while some studies suggest that emotional triggering is less common in patients taking β -blockers ([Čulić et al., 2004](#)), others have not found a link ([Mittleman et al., 1995](#); [Strike et al., 2006a](#)).

9. Conclusions

Studies involving a range of different methodologies provide convergent evidence supporting the role of emotional stimuli in the acute triggering of ACS. Emotional triggering appears to be more common in people of lower SES. The pathophysiological processes underlying emotional triggering remained to be fully elucidated, but include processes that may promote plaque rupture, together with a prothrombotic vascular environment that encourages thrombus formation, and neuroendocrine and autonomic processes stimulating rhythm disturbances. Little of this knowledge has been used in clinical management to date, and the development of a systematic approach to risk stratification and prevention is a priority. Little is known about ethnic differences in the occurrence of triggers, and

women have been under-represented in many cohorts. Nonetheless, the study of emotional triggers promises important insights into the timing of acute cardiac events, and opens up possibilities for new methods of clinical management.

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