REVIEW ARTICLE

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Editor's Choice

Emotional stressors trigger cardiovascular events

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SUMMARY

Aims: To describe the relation between emotional stress and cardiovascular events, and review the literature on the cardiovascular effects of emotional stress, in order to describe the relation, the underlying pathophysiology, and potential therapeutic implications. **Materials and methods:** Targeted PUBMED searches were conducted to supplement the authors' existing database on this topic. **Results:** Cardiovascular events are a major cause of morbidity and mortality in the developed world. Cardiovascular events can be triggered by acute mental stress caused by events such as an earthquake, a televised high-drama soccer game, job strain or the death of a loved one. Acute mental stress increases sympathetic output, impairs endothelial function and creates a hypercoagulable state. These changes have the potential to rupture vulnerable plaque and precipitate intraluminal thrombosis, resulting in myocardial infarction or sudden death. **Conclusion:** Therapies targeting this pathway can potentially prevent acute mental stressors from initiating plaque rupture. Limited evidence suggests that appropriately timed administration of beta-blockers, statins and aspirin might reduce the incidence of triggered myocardial infarctions. Stress management and transcendental meditation warrant further study.

Review criteria

Dr. Kloner has extensive experience publishing on this topic and was familiar with the majority of the articles referenced in this manuscript. In addition, targeted PUBMED searches were conducted.

Message for the clinic

The clinician should recognise that mental stress, including certain community-wide events, can precipitate cardiovascular events through plaque rupture. Triggered cardiovascular events might be prevented with traditional cardiovascular medications (aspirin, beta blockers, statins) and by stress management, including transcendental meditation.

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None.

Introduction

Cardiovascular disease accounts for about a third of all deaths annually in the United States, where approximately 935,000 myocardial infarctions (MIs) occur each year, or 1 MI every 34 s (1). Cardiovascular events may occur randomly, but are often triggered by physical exertion or acute mental stressors (2,3). This review describes the differential impact of various community-wide triggers, including earthquakes, acts of war and sporting events, on cardiovascular endpoints. A community-wide trigger that elicits a strong emotional response from the majority of the study population can increase the incidence of major adverse cardiovascular events on a large scale. Pathophysiological mechanisms are presented that link acute mental stress to cardiovascular events through plaque rupture. Finally, therapeutic implications are presented.

Cardiovascular events are triggered

Emotional triggers were acknowledged in the original description of acute MI in 1910 by Obraztsov and Strazhesko (4). An analysis of 849 patients with acute MI identified possible triggers in 48.5%, including physical exertion, emotional upset and sleep deprivation (3). The concept of triggers was advanced with the description of similar circadian patterns in numerous physiological parameters and in adverse cardiovascular events. Waking from sleep and assuming an upright posture precipitates a surge in sympathetic activity which results in a morning peak in blood pressure, heart rate, ventricular contractility, platelet aggregability and other parameters (5,6). In parallel, transient myocardial ischaemia, MI, sudden cardiac death and thrombotic stroke each occur with increased frequency in the morning (2,6,7).

Acute mental and physical stressors are now considered acute risk factors for cardiovascular events (Table 1). Traditional cardiac risk factors, including hypertension and diabetes, increase the long-term risk for atherosclerosis and provide the milieu for future major adverse cardiovascular events. Acute risk factors, described below, increase the short-term risk for plaque rupture, fatal arrhythmias and catastrophic cardiovascular events, especially in patients with pre-existing coronary disease.

Table 1 Triggers of cardiovascular disease

Mental stressors	Physical exertion	Community-wide triggers	Other triggers
1. Emotional upset	1. Heavy physical exertion	1. Wake-up time (morning)	1. Lack of sleep
2. Anger	2. Moderate physical exertion (includes sexual activity)	2. Day of the week (Monday)	2. Overeating
3. Anxiety		3. Seasonal variation (winter)	3. High air pollution
4. Bereavement		4. Blizzards	4. Respiratory infection (flu season)
5. Sadness/frustration		5. Christmas and New Year's holidays	5. Smoking cigarettes
6. Work-related stress (high-pressure deadline)		6. Heat waves	6. Smoking marijuana
7. 'Alarm response'		7. Emotionally charged sporting events	7. Using cocaine
8. Sexual activity (unfamiliar partner, setting)		8. Earthquakes	
		9. Wartime missile attacks	
		10. Other natural disasters	

Acute mental stress as a trigger

Anxiety and acute mental stress can trigger adverse cardiovascular events (8–14). Weekly variation of MI onset reflects stress levels: MIs occur less frequently on Sundays and with 30–33% increased relative risk (RR) on Mondays in working people, correlating with increased stress levels associated with returning to work (15,16). Cardiac death rates also increase by 4.65% during the Christmas and New Year's holidays which may reflect the mental stress associated with party planning, shopping, family gatherings and added financial pressure (17,18). Mental stress, defined in one study as tension, sadness or frustration, more than doubled the likelihood of myocardial ischaemia on ambulatory electrocardiographic monitoring in patients with symptomatic ischaemic heart disease (10). A case-crossover study of 1623 patients with acute MI found that the risk of MI increased in the 2 h after an episode of anger (RR 2.3) (14). The risk for MI increased after the death of a loved one, during the bereavement period (1 day after RR 14.3; 2 days after RR 7.9; 8–28 days after RR 4.8) (19). High job strain, defined as high psychological demands and low decision latitude, increased the risk of recurrent coronary heart disease events (12). Similarly, 'a high pressure deadline at work' increased the risk of MI by sixfold during the next 24 h (20). Firefighters had an increased risk of MI (odds ratio 2.8–14.1) during 'alarm response', defined as 'responses to emergency incidents, including false alarms' (prior to fire suppression) (21). Furthermore, reduction in left ventricular ejection fraction during mental stress testing (induced by such stressors as mental arithmetic and public speaking) predicted cardiac events and event-free survival (22,23).

Community-wide events as triggers of major adverse cardiovascular events

Community-wide events have the potential to increase cardiac death rates within the affected population, provided that the event elicits a strong emotional response and affects the entire population (or the majority of the population). Large earthquakes induce fright and anxiety throughout the affected geographical area and earthquakes increased cardiac death rates in several locations, including Los Angeles, California (24–26), Athens, Greece (27), Hanshin-Awaji, Japan (28–30) and Niigata, Japan (31). The Northridge earthquake in Los Angeles in 1994 caused a 71% increase in deaths because of coronary artery disease on the day of the earthquake and a 35% increase in hospital admissions for MI over the ensuing week (25,26). Moreover, the increase in cardiac admissions and coronary artery disease deaths correlated with the distance from the Northridge earthquake's epicentre (25,26).

Reports on earthquakes precipitated studies of other potential stressors, with mixed results. A community near Tel Aviv, Israel observed a marked increase in acute MI and sudden death in the initial days of the Gulf War (32). This community was not targeted by missile attacks, but could hear the missiles explode in neighbouring communities, causing the residents to fear imminent attacks and death.

In the days following 11 September 2001, there were reports of increased rates of MI (33) and increased rates of ventricular arrhythmias in patients living in (34) and living remotely from New York City (35). However, these three reports were each limited by a small sample size and two of them did not correct for known seasonal variation in ventricular arrhythmias. In contrast, other studies that accounted for seasonal variation and analysed large datasets found no association between the 11 September terrorist attacks and cardiovascular-related hospital admissions and death rates in New York City (36,37).

The riots in Los Angeles in 1992 caused a significant increase in total deaths, and in mortality from violence or trauma. However, no significant increase

was observed in deaths related to atherosclerotic cardiovascular disease in Los Angeles in the days following the 1992 riots (38).

Stock market volatility in Shanghai, China increased death rates from coronary heart disease (39). The authors noted that the population in Shanghai is unique in that it includes many elderly, inexperienced investors who spend large portions of their own money on stocks, then spend their days monitoring market fluctuations in real-time. Conversely, total and cardiac death rates did not increase in Los Angeles during the stock market crash in October 2008 (40).

We hypothesise that the September 11 terrorist attacks, the Los Angeles riots and the October 2008 stock market crash did not effect people intensely enough to precipitate cardiovascular events as they watched the news unfold on television. The relatively large populations studied may have diluted an increase in cardiac event rates from more targeted populations with a more personal connection to these events, including people trapped within the World Trade Center buildings, business owners victimised during the riots and financial investors during the stock market crash.

Sporting events

Sporting events, primarily soccer matches in Europe, have increased cardiac event and death rates (41–47). This was investigated with a prospective analysis of German residents in 2006, when Germany hosted the World Cup soccer matches (41). The incidence of cardiac emergencies increased on days the German team played a match, including an increased incidence of ST elevation MI [incidence ratio (IR) 2.49], combined unstable angina or non-ST elevation MI (IR 2.61), and cardiac arrhythmias causing major symptoms (IR 3.07). On 6 of the 7 days that the German team played a match, there was a significant increase in cardiac emergencies. The degree to which cardiac emergencies increased correlated with the intensity and importance of the game. Moreover, there was a cluster of events with onset of symptoms within 2 h of the start of the match, suggesting a relation to the game.

Similarly, total and cardiac death rates increased by 17–21% ($p < 0.0001$ for total, circulatory, and ischaemic heart disease deaths) in Los Angeles in the days following the Los Angeles Rams' dramatic Super Bowl loss to the Pittsburgh Steelers in 1980 (42). The 1980 Super Bowl drew an emotional response from fans in Los Angeles because the game was played locally (in Pasadena) and the game was very intense, featuring seven lead changes and a number of exciting plays. The Rams were winning to begin the final quarter before the Steelers seized control and won the game. These reports and others (43–47) indicate that sporting events have the potential to elicit strong emotions which can adversely affect cardiovascular event rates. Several factors increase this adverse risk, including hometown game location, losing outcome, high importance of the result and high intensity or drama, such as a shoot-out (41–44).

Some have questioned the validity of these studies and the appropriateness of assuming that patients suffering cardiovascular events actually watched the sporting event (48). Indeed, a few reports found no association between soccer matches and death rates (49–51). The 1984 Super Bowl featuring the Los Angeles Raiders was not associated with an increase in death rates in Los Angeles (42). The 1984 game was not played locally and was not closely competitive (the Raiders won 38 to 9) (42). Cardiac death rates also did not increase in Los Angeles during each of the 2000–2004 Super Bowls, when Los Angeles did not have a professional football team (42). However, sporting events with low drama, low stakes, a small audience or an audience without an emotional connection are not expected to cause widespread stress in the community. Moreover, the temporal relation between symptom onset and the 2006 German World Cup soccer matches suggests that the patients were watching the game (41). Three men were watching exciting televised hockey games in Canada when they suffered ruptured aortic aneurysms (two men died) (52). One of these men underwent emergency surgery. Upon waking from the anaesthesia the man asked, "Who won the game?" (52)

Tako-Tsubo cardiomyopathy

A review of triggers and cardiovascular events would be incomplete without a discussion of Tako-Tsubo cardiomyopathy. Also referred to as stress induced cardiomyopathy or apical ballooning syndrome, Tako-Tsubo cardiomyopathy mimics acute MI with chest pain, ST segment elevation (in 49–82%; involving precordial leads in 84%), mild cardiac troponin elevation (in 86–92% of patients), and is characterised by marked left ventricular contraction abnormalities (usually mid segments) (53–55). By definition, Tako-Tsubo cardiomyopathy does not involve obstructive epicardial coronary artery atherosclerosis (53,54). The degree of acute systolic dysfunction can be severe, but fortunately Tako-Tsubo cardiomyopathy is rare and the majority of cases resolve spontaneously with supportive care. As many as 89% of patients with Tako-Tsubo cardiomyopathy report a precipitating stressful event (53). Precipitating events are most commonly emotional stressors

(including a death in the family, a heated argument, a frightening experience or exhausting work), but also include physical triggers (acute non-cardiac illness, medical/surgical procedure) and exposure to catecholamine and beta-agonist drugs (53–56). An earthquake in Niigata, Japan dramatically increased the incidence of Tako-Tsubo cardiomyopathy to 25 cases in the 4 weeks after the earthquake compared with 1 case in the preceeding 4 weeks and 1 case in the corresponding 8-week periods in the previous 2 years combined (31). Ten cases occurred within hours of the first shock (31). The pathophysiology of Tako-Tsubo cardiomyopathy is thought to be related to catecholamines (53–56) which were remarkably elevated in 13 patients with Tako-Tsubo cardiomyopathy to levels 7–34 times normal values (56). Although the pathophysiology of Tako-Tsubo cardiomyopathy differs from that of acute MI and sudden cardiac death, it provides a striking example of the connection between emotional stress, catecholamine levels and cardiovascular disease.

Pathophysiology linking mental stress to cardiovascular events

Several mechanisms link mental stress to cardiovascular events, including primary ventricular tachyarrhythmias and myocardial oxygen supply demand mismatch with or without plaque fracture. These various mechanisms may exist independently, but also complement each other. This section focuses on catastrophic plaque rupture.

Studies surrounding community-wide events have provided insight into the pathophysiology linking emotional stress to cardiovascular events (Figure 1). The Hanshin-Awaji Earthquake struck Japan in 1995 with an initial shock measuring 7.2 on the Richter scale, followed by 14 days of frequent aftershocks. Patients with previously scheduled, routine appointments at a hypertension clinic during these 14 days were studied (29,30). Compared with baseline data obtained within 11 weeks prior to the earthquake, significant increases were observed after the earthquake in blood pressure and haematocrit. In addition, blood levels of fibrinogen, D-dimer, von Willebrand factor and tissue-type plasminogen activator antigen were elevated, indicating endothelial cell hyperstimulation and enhanced fibrin turnover. Potentiation of these haemostatic factors correlated with patients' stress levels (29,30). An investigation of Holter-monitor data at the time of a large earthquake in Taiwan revealed increased sympathetic activity and withdrawal of parasympathetic activity lasting approximately 40 min after the earthquake (assessed by heart rate and heart rate variability) (57). The surge of sympathetic over parasympathetic activity was especially prominent in the patients who showed significant ST segment depression (27% of patients). Compared with healthy controls and with a group of patients with MIs without an emotional trigger, patients with a stress-associated MI related to World Cup soccer matches had elevated levels of inflammatory and vasoconstrictive mediators including endothelin-1 (58).

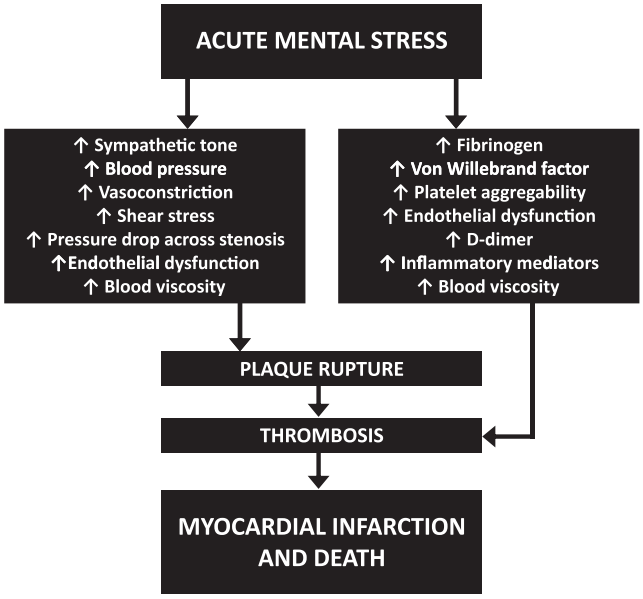

Figure 1 Mechanisms linking acute mental stress to myocardial infarction and death. This figure depicts the pathophysiological changes resulting from acute mental stress that may increase the risk for myocardial infarction and death. ↑ = increases

Additional insight comes from studies employing mental stress testing. Subjecting healthy subjects to four types of mental stressors revealed a correlation between the degree of stress-induced endothelial dysfunction and systemic vascular resistance responses (59). In 15 patients with stable angina, mental stress testing significantly increased the rate-pressure product, plasma epinephrine and norepinephrine levels, and autonomic arousal as measured by changes in skin conductance (60). Mental stress testing was conducted in 34 patients with an average of 15 months after an acute coronary syndrome (61). Fourteen patients had experienced an acute negative emotion prior to symptom onset (trigger group) and twenty patients had not experienced a negative emotion (non-trigger group). Blood pressure and cardiac index increased similarly in both groups in response to mental stress (public speaking). However, compared with the non-trigger group, the trigger group showed delayed recovery of systolic blood pressure and cardiac index and showed significant increases in leucocyte-, monocyte- and neutrophil-platelet aggregates. The authors suggested that some patients with heightened platelet activation in response to stress may be particularly susceptible to emotional triggering of acute coronary syndromes (61).

Two comprehensive literature reviews on haemostasis, coagulation and fibrinolysis expand on these findings (62,63). One review concluded that epinephrine (which becomes elevated with acute mental stress) stimulates the anticoagulant tissue-type plasminogen activator and the procoagulants factor VIII, von Willebrand factor and platelets (62). In the other review (63), the authors concluded that acute mental stress enhances both the coagulation and fibrinolysis systems in healthy individuals, such that the haemostatic equilibrium is preserved. In patients with atherosclerosis, however, stress-induced procoagulant changes predominate over anticoagulant mechanisms. In patients with atherosclerosis, the ability to increase fibrinogen and von Willebrand factor levels in response to acute mental stress is preserved, but endothelial dysfunction may impair the ability to increase tissue-type plasminogen activator activity resulting in impaired clot-dissolving capacity (63). In support of this concept, tissue-type plasminogen activator activity demonstrates circadian variation with markedly lower levels in the morning hours (64).

Collectively, these studies indicate that patients experiencing stressful events undergo adverse physiological changes, including endothelial damage, enhanced coagulation, and increased sympathetic tone, blood pressure, blood viscosity and inflammatory mediators. These physiological changes can cause plaque rupture and manifest as adverse cardiovascular events. Vasoconstriction along with an increase in blood pressure and blood viscosity results in increased shear stress on the vasculature causing endothelial damage with the potential to disrupt vulnerable plaque. In conjunction with a hypercoagulable state, plaque disruption is more likely to cause overlying thrombosis, resulting in MI or sudden cardiac death.

Animal models of plaque rupture demonstrate this concept. In one model (65), spontaneous plaque rupture was rare, but could be induced by administration of phenylephrine which increased blood pressure and caused plaque rupture in 40% of cases. In a similar model (66), apo E knockout mice randomised to stress (electric foot shock and noise stimulation) demonstrated increased blood pressure, heart rate, ejection fraction, maximal systolic flow velocity, norepinephrine and fibrinogen levels compared with the control group. The stress group also demonstrated a significantly higher incidence of plaque disruption, along with altered plaque morphology including decreased fibrous cap thickness, decreased cap-to-core area ratio, decreased collagen content and increased lipid and macrophage contents of plaques.

A human autopsy study supports the plaque disruption concept. First, it is noted that cholesterol expands in volume by up to 45% as it crystallises from a liquid, forming sharp needle-like crystals capable of tearing membranes (67). In a case-control study of autopsies of patients who died with or without an acute coronary syndrome, at sites of plaque disruption, cholesterol crystals with pointed tips were observed perforating the intimal surface with associated thrombus (68). Elevated cholesterol crystal content correlated with plaque disruption, thrombus and clinical symptoms (68).

To summarise, patients with atherosclerosis are susceptible to triggered cardiovascular events because of the presence of vulnerable plaques and impaired endothelial function. Mental stress induces adverse physiological responses that increase shear stress on the vasculature, thus increasing the risk for plaque rupture, especially on vulnerable plaques with high lipid content and a thin fibrous cap. In the setting of endothelial dysfunction, procoagulant changes predominate in response to acute mental stress, thus increasing the risk for intraluminal thrombus.

Implications for therapy

Beyond traditional risk factor modification to prevent the progression of atherosclerosis, therapy targeting the pathways whereby an acute trigger leads to plaque rupture provides an additional opportunity to

intervene and prevent or delay catastrophic cardiovascular events. As acute mental stress affects the cardiovascular system by increasing sympathetic tone, shear stress and coagulation, drugs that target these pathways may prevent the trigger from causing plaque rupture, intraluminal thrombosis and cardiovascular sequelae. In fact, triggered MIs and morning-related MIs, each of which result from increased sympathetic activity, were significantly less likely in patients who had taken beta-blockers, calcium antagonists or nitrates in a prospective analysis of 1384 patients with acute MI (2). In another study of patients with acute MI, patients taking beta-blockers were less likely to report an emotional or physical trigger ($p = 0.08$) (3). Both atenolol and nifedipine prevented mental stress-induced wall-motion abnormalities (60).

Calcium channel blockers reduce overall ischaemic episodes, but do not clearly abolish the intrinsic circadian pattern, suggesting a limited capacity for preventing triggered MIs (69,70). In contrast, beta-blockers abolish the early-morning clustering of ischaemic episodes, suggesting they act by countering the adverse surge in sympathetic activity in the morning hours (71,72). Likewise, aspirin reduced the incidence of MI by 44.8% overall, but by 59.3% in the morning hours (73). Aspirin also abolished the morning increases in platelet aggregability and platelet thromboxane A2 production, suggesting an impact on triggered events (74). Furthermore, patients who used aspirin regularly had a significantly lower risk of MI in the 2 h after an episode of anger (RR 1.4 in aspirin users vs. RR 2.9 in nonusers; $p < 0.05$) (14). Statins and angiotensin converting enzyme inhibitors reduce the incidence of cardiovascular endpoints (75,76) and may work in part by reducing the impact of triggers through their beneficial effects on endothelial function (77,78). Lipid-lowering therapy reduces the progression of mild and moderate atherosclerosis to vulnerable plaques by reducing the plaques' lipid and macrophage content (79). High-intensity statin therapy can even induce regression of atherosclerosis in coronary disease patients (80). Statins stabilise plaque through pleiotropic effects, which include reducing cholesterol volume expansion upon crystallisation, dissolving cholesterol crystals and altering cholesterol crystal structure so that plaque disruption is less likely to occur (81).

Thus, triggered plaque rupture might be prevented by: (i) lipid-lowering therapy to stabilise plaque and prevent the development of vulnerable plaque, (ii) statins and angiotensin converting enzyme inhibitors to improve endothelial function, (iii) beta-blockers to reduce shear stress and (iv) aspirin to inhibit thrombus progression at the site of a ruptured plaque. These medications are prescribed routinely to modify cardiovascular risk factors, but may be especially beneficial in the setting of a cardiovascular trigger. The 'early morning' trigger is predictable, and might be treated by administering long-acting medications before bedtime (82). Certain triggering events are predictable, including high-stakes sporting events, the Christmas holiday and a high-pressure deadline at work, and might be treated with additional prophylactic doses of the aforementioned medications. Other triggering events, like earthquakes and the death of a loved one, are unpredictable. However, their impact on cardiovascular events might be limited if patients are instructed to take an extra dose of medication when they experience an acutely stressful situation. To date there are no large randomised clinical trials that have attempted to test pharmacologic agents specifically for triggering.

Stress management and transcendental meditation

Therapies targeting mental stress may be an alternative strategy to combat the detrimental effects of acute mental stress on the cardiovascular system. In fact, a stress management program reduced the risk of a cardiovascular event over 3 years of follow-up (RR 0.26, $p = 0.04$) (83). This study included patients with coronary artery disease and documented ischaemia and compared stress management training to exercise training and also to usual care. Stress management involved educational sessions on stress and instruction in specific skills to reduce stress, including altering thought patterns and muscle relaxation techniques. Compared with usual care, the stress management group demonstrated improved treadmill times, improved lipid profiles and greater weight loss. Compared with usual care and to exercise training, the stress management group demonstrated less severe wall motion abnormalities, fewer ischaemic episodes during ambulatory monitoring, and fewer cardiovascular events during follow-up (83).

Numerous relaxation, meditation and stress management approaches are used to alleviate stress. One method in particular, transcendental meditation (TM), has been widely studied in the scientific literature with results supporting its usefulness for treating a variety of cardiovascular diseases and risk factors (84). The TM, practiced for 20 min twice a day, induces a state of 'transcendental consciousness' in which mental and physical activity is reduced. This experience is hypothesised to benefit the body's adaptive responses to environmental stressors. The effects of TM on stress responses was investigated by

randomising prehypertensive adolescents to TM or a health education control (85). During a stressful car driving simulation task, the TM group exhibited smaller reactive increases in blood pressure, heart rate and cardiac output, suggesting a reduced sympathetic response to mental stress (85). Meta-analyses indicate that TM reduces stress and anxiety and improves psychological health more so than other relaxation techniques (84). Controlled trials indicate that TM decreases blood pressure and serum cholesterol and reduces dependence on cigarettes, alcohol and drugs (84).The TM has also demonstrated beneficial end-organ effects, including a reduction in carotid artery intima-media thickness, reduced left ventricular hypertrophy, greater exercise tolerance and reduced ischaemia during exercise (84,86). Data pooled from two randomised trials with overall mean follow-up of 7.6 ± 3.5 years show reduced all-cause mortality (RR 0.77; $p = 0.039$) and cardiovascular mortality (RR 0.70; $p = 0.045$) with TM compared with combined control groups (84,87). The cardiovascular benefits of stress management and TM warrant investigation in larger randomised trials. The cardiovascular benefits of psychiatric counselling and antianxiety medications remain unknown (88).

Summary

Acute mental stress, whether caused by job strain or an earthquake, can precipitate plaque rupture, MI and cardiac death. Community-wide events have the potential to increase cardiac endpoints in a large population provided that the trigger affects the majority of the population in a personal and intimate manner, causing an emotional response. Emotional triggers enhance sympathetic output, hypercoagulability and endothelial dysfunction, with the potential to rupture vulnerable plaque, facilitate thrombus formation and manifest as an acute MI. Therapy targeting the pathways whereby an acute trigger precipitates plaque rupture provides an additional opportunity for intervention which might be accomplished by appropriately timed administration of beta-blockers, statins and aspirin. Stress management and TM may improve cardiovascular outcomes by treating mental stress directly and modifying adaptive responses to stress. Cardiovascular mortality could be reduced by preventing acute mental stressors from becoming acute MIs.

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Author contributions

Dr. Kloner designed and Dr. Schwartz drafted the manuscript. Each author, Drs. Schwartz, French, Mayeda, Burstein, Economides, Bhandari, Cannom and Kloner, critically revised and approved the article.

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