Review

Disasters and the Heart: a Review of the Effects of Earthquake-Induced Stress on Cardiovascular Disease

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There is growing evidence that stress contributes to cardiovascular disease. Chronic stress contributes to the atherosclerotic process through increased allostatic load, which is mediated by the neuroendocrine and immune systems (sympathetic nervous system and hypothalamus-pituitary adrenal axis) and related chronic risk factors (insulin resistance syndrome, hypertension, diabetes, and hyperlipidemia). In addition, acute stress can trigger cardiovascular events predominantly through sympathetic nervous activation and potentiation of acute risk factors (blood pressure increase, endothelial cell dysfunction, increased blood viscosity, and platelet and hemostatic activation). Earthquakes provide a good example of naturally occurring acute and chronic stress, and in this review we focus mainly on the effects of the Hanshin-Awaji earthquake on the cardiovascular system. The Hanshin-Awaji earthquake resulted in a 3-fold increase of myocardial infarctions in people living close to the epicenter, particularly in women, with most of the increase occurring in nighttime-onset events. There was also a near doubling in the frequency of strokes. These effects may be mediated by changes in hemostatic factors, as demonstrated by an increase of D-dimer, von Willebrand factor, and tissue-type plasminogen activator (tPA) antigen. Blood pressure also increased after the earthquake, and was prolonged for several weeks in patients with microalbuminuria. (Hypertens Res 2003; 26: 355–367)

Key Words: stress, hypertension, cardiovascular disease, risk factor

Introduction

Recent advances in the field of neuroscience have greatly improved our understanding of how the brain perceives and responds to stress, and how it can affect various target organs such as the brain itself, the cardiovascular system, and the immune system (1). In the field of cardiovascular medicine, it is well known that acute cardiovascular events (acute coronary syndrome and stroke) can be triggered by abrupt emotional or physical stressors such as intense anger or physical exercise (2). In recent years, both animal and human studies have demonstrated that mental and physical stress can also influence chronic disease processes such as hypertension (3–6) and atherosclerosis (2). However, in humans, there are substantial individual variations in the perception of stress and in the subsequent physiologic responses, which means that the consequences are not uniform across all individuals. The recently proposed allostatic load model (described below) can be applied to evaluate these individual differences in the response to stress (1, 7).

Unanticipated catastrophic natural disasters like the Han-
The Hanshin-Awaji earthquake and its sequellae are among the strongest acute and subacute psychological forms of stress, and may be helpful in understanding the cardiovascular consequences of the terrorist disaster of September 11, 2001. Several reports have shown that the incidence of fatal and non-fatal cardiovascular events (both cardiac and cerebral) was increased at the time of the Hanshin-Awaji earthquake (8–12). In this review, based mainly on the findings of the Hanshin-Awaji and other earthquakes, we discuss the effects of this form of stress on cardiovascular risk factors and how it might serve as a model of the more general effects of stress on cardiovascular health.

Earthquake-Induced Cardiovascular Events

Although an increase in coronary heart disease (CHD) deaths following a major earthquake has been reported on several occasions (13–15), the underlying mechanisms have not been fully clarified. The Jichi Medical School Cohort Study (JMS Cohort Study) is a longitudinal study of cardiovascular risk factors started in 1991 in people living in the Awaji-Hokudan district, which is near the epicenter of the Hanshin-Awaji earthquake (16, 17). In the 6 districts in the Awaji Island near the epicenter, CHD events (myocardial infarction and sudden death within 24 h after the onset) and stroke were increased 1.5-times and 1.9-times, respectively, during the 3-month period after the earthquake, when compared with the same period of the previous year (11, 12). The frequency of earthquake-induced CHD death in each district was positively correlated with the earthquake-induced damage to that district.

The estimated duration of the influence of the Hanshin-Awaji earthquake on cardiovascular events differs from those estimated for earthquakes studied previously. In the Athens earthquake (13), the Newcastle earthquake of Australia (14), and the Northridge earthquake of Los Angeles (15), the increase in cardiovascular deaths was limited to a few days. In the Northridge earthquake, after a few days of increased cardiovascular deaths following the earthquake, the subsequent death rate was lower than the baseline rate (18). However, in our study of the Hanshin-Awaji earthquake, the increase in cardiovascular deaths persisted for at least 1 month or more (19). This difference may have been due to the characteristics of the study population and/or the duration of the stressor. In the study of the Newcastle earthquake, CHD death was investigated only in adults aged 70 years or less. However, in our study, more than 30% of the subjects were over the age of 60 years, and more than 90% of subjects who died of cardiovascular events after the earthquake were 70 years or older. Furthermore, our study was only concerned with the most heavily damaged area. Persistent stress resulting from extensive damage to the environment could explain the persistent increase in cardiovascular deaths after the earthquake.

In addition to the increase in cardiovascular deaths, the number of subjects with acute myocardial infarction during the first 4 weeks after the Hanshin-Awaji earthquake was increased by about 3.5-fold (9, 10). The increase was significantly greater in women than men, and the mean post-traumatic stress disorder reaction index score was also significantly higher in women.

Stress Perception and Physiologic Response

As exemplified by the occurrence of an earthquake, extremely stressful experiences can trigger cardiovascular events. Acute major stress and chronic stress (the cumulative load of minor daily stress) could both have long-term consequences. An event is perceived as stressful if it is regarded as being a threat to an individual’s environment, and can induce a variety of negative emotional responses such as fear, anxiety, sadness, anger, hostility, and depression. Fear is likely to have been the predominant psychological reaction during the early stages of the earthquake, because during the 2 weeks after the earthquake, frequent aftershocks occurred. In addition, subsequent earthquake-induced indirect actions from factors such as bereavement, unemployment, poverty, and physical overwork, leading to lifestyle changes in diet, smoking, and exercise could modify these emotional and behavioral responses and have additional influences on the physiological response to stress (Fig. 1). The personality of each subject would modulate these reactions.

Recent clinical studies have shown that negative affects are predictors of hypertension and cardiovascular events (both CHD and stroke) (20–25). A recent study in patients with coronary artery disease showed that mental stress during daily life, including reported feelings of tension, frustration, and sadness, can more than double the risk of ambulatory Holter-ECG monitoring-assessed myocardial ischemia in the subsequent hour (26). Individual susceptibility to cardiovascular stress is determined by genetic factors, development, and experience. Thus, laboratory mental stress induces a more prolonged blood pressure (BP) increase in subjects with a parental history of hypertension than in those without (27). However, genetic factors can only explain a small portion of the individual variability of stress response (28, 29).

Stress and the Allostatic System

Allostasis—the ability to achieve stability through change (30)—has broader boundaries than homeostasis and enables us to respond to changes in our physical state (such as wakefulness, sleep, and postural changes) and to cope with various stressful situations (anger, hunger, extreme temperature, etc.) (1, 7). The major allostatic responses involve the sympathetic nervous system and hypothalamus-pituitary-adrenal (HPA) axis. When these systems are activated, catecholamines are released from the adrenal medulla and the sympathetic nerves, and corticotrophin-releasing hormones
are released from the hypothalamus to mediate the release of corticotrophin from the pituitary, and subsequently the release of cortisol from the adrenal cortex. These allostatic mediator hormones affect cellular physiologic and pathophysiologic response to result in what has been termed allostatic load. The allostatic load triggered by stress is normally shut off as soon as the stress has passed (Fig. 2), and plasma levels of both catecholamine and cortisol return to the baseline level. Overexposure to allostatic load can occur either because of a hyperresponsiveness or a delayed recovery (insufficient shut-off), and hence lead to pathophysiological consequences.
Figure 3 shows 5 different patterns of allostatic load. The most typical pattern of allostatic load is the diurnal variation of rest and activity (Fig. 3A). Early morning activation of the sympathetic nervous system and HPA axis potentiates several sympathetically mediated risk factors (Fig. 1), such as the vulnerability to arrhythmias and the various clinical and subclinical cardiovascular events described below (31).

The second type of allostatic load is hyperreactivity with complete shut-off, which markedly enhances variability (Fig. 3B). An example of this is our finding that the extreme-dipping pattern of nocturnal BP (an exaggerated diurnal variation of BP) is associated with silent and clinically overt stroke in elderly hypertensive patients (32, 33). The marked fluctuation of allostatic load and its induced physiologic response might advance target organ damage and trigger cardiovascular events either through nocturnal ischemia or an enhanced morning BP rise. Another example comes from a recent prospective study (34) in which men characterized by a combination of an exaggerated BP reactivity to acute stressors and hypertensive parents demonstrated a higher resting BP 10 years later, in contrast to men with a smaller reactivity and/or a negative family history.

The third type is the prolonged recovery (incomplete shut-off; see Fig. 3C). The allostatic load of this type may be cumulative and remain consistently high for long periods of time. Thus the delayed response to mental stress that we have observed in normotensive subjects with a family history of hypertension might be one mechanism by which they become hypertensive (27).

The fourth type is lack of adaptation to repeated stressors, resulting in prolonged exposure (Fig. 3D). This has been described in a study of people subjected to repeated-public speaking challenges. Most people show an acute cortisol response during the first exposure, which diminishes with successive trials, but there are others in whom the response persists (35). And during the repeated aftershocks following the Hanshin-Awaji earthquake, the earthquake-induced increase in BP persisted in some people, but in others returned to the baseline level before the earthquake (36).

The last type of allostatic response is an inadequate response by some allostatic systems, which may trigger compensatory increases in others. When cortisol secretion does not increase in response to stress, secretion of inflammatory cytokines (which are counterregulated by cortisol) increases (37), which could advance the atherosclerotic process.

**Stress-Induced Progression of Atherosclerosis**

Many animal and human studies support the concept of stress-induced progression of atherosclerosis as a cumulative burden of allostatic load. Carotid atherosclerosis (measured both as intimamedial thickness and plaque) has been related prospectively to psychosocial cardiovascular risk factors in population studies (38–42) and cross-sectionally to measures of the insulin resistance syndrome (43).

Conversely, the degree of systemic atherosclerosis or silent target organ damage may affect the degree and duration of allostatic load. Figure 4 shows the changes of BP after the earthquake. The acute transient BP increase was comparable in hypertensive patients with and without microalbuminuria (an indicator of silent renal damage), but the BP increase was prolonged in the patients with microalbuminuria (36). The interaction between the acute and chronic effects of allostatic load induced by psychological stress may account for marked individual variation in cardiovascular risk factors (as shown in Figs. 5 and 6) and hence determine cardiovascular prognosis (Fig. 1).

**Stress-Induced Potentiation of Acute Risk Factors**

Risk factors associated with sympathetic nervous activation could be considered as acute risk factors that trigger cardiovascular events (44). In contrast to chronic risk factors that advance the atherosclerotic process—e.g., hypertension, diabetes, dyslipidemia, and smoking—the acute risk factors include: 1) transient BP increase; 2) endothelial cell dysfunction; 3) increased blood viscosity; 4) platelet activation; and 5) imbalance between coagulation and fibrinolysis (augmented procoagulant activity and impaired fibrinolytic activity).

**Thrombosis and Hemostasis**

The formation of a thrombus following the rupture of a coronary atherosclerotic plaque is one of the major mechanisms of acute CHD events such as myocardial infarction and unstable angina. Plaque rupture may be triggered by increased shear stress from a sudden increase of BP and by coronary vasospasm resulting from endothelial cell dysfunction.
Platelet activation plus abnormalities in blood coagulation and fibrinolysis may further facilitate thrombus formation.

Although the pathogenesis of stroke is not necessarily the same as for acute CHD events, it is likely that the same processes contribute to ischemic stroke, and that transient BP increases may trigger hemorrhagic strokes. Increased platelet
activity and imbalance between coagulation and fibrinolysis (hypercoagulability and hypofibrinolysis) are associated with the progression of silent cerebral infarction (a predisposing condition for clinical cerebral infarction) (45) and the onset of ischemic stroke. Increased blood viscosity also contributes to thrombus formation and cardiovascular disease.

The extrinsic pathway of coagulation is activated at the start of cardiovascular events when coagulation factor VII combines with the tissue factor expressed on the injured endothelial cell or subendothelium and is itself activated. This activated factor VII activates factor X, which in turn activates prothrombin to produce active thrombin, a potent thrombogenic substance. Thrombin converts fibrinogen to fibrin, in addition to inducing platelet aggregation and accelerating thrombus formation. At the same time, tissue-type plasminogen activator (tPA) is released from endothelial cells to activate the fibrinolytic system. The tPA converts plasminogen to plasmin, an active fibrinolytic substance, which degrades fibrin to produce the fibrin degradation product, D-dimer. Several factors can be measured to assess the activation of coagulation and/or fibrinolysis. Prothrombin fragment 1 + 2 (F1 + 2) and thrombin-antithrombin complex (TAT) are coagulation markers of activation, plasmin-α2–plasmin inhibitor complex (PIC) is a fibrinolytic marker of both coagulation and subsequent fibrinolysis.

Figures 5 and 6 show the changes of some of these markers of coagulation and fibrinolysis just after the Hanshin-Awaji earthquake in hypertensive patients living near the epicenter (46). The most prominent increase was found in D-dimer levels 1 to 2 weeks after the earthquake, and this increase was higher in the high-stress group (whose housing was completely destroyed or whose family members experienced hospitalization due to earthquake-related injury) than in the moderate-stress group. In the high-stress group, plasma PIC and tPA antigen levels were also increased. Four to 6 months after the earthquake, when the incidence of cardiovascular events returned to the level of the previous year, these indicators of a hypercoagulable state and subsequent fibrinolysis had all returned to the baseline level.

Endothelial Cell Dysfunction

Von Willebrand factor (vWF) is a glycoprotein which is released from endothelial cells by various stimuli, including catecholamines and thrombin, and is widely used as an index of endothelial cell injury. Increases in the blood levels of vWF have been reported in diabetic patients with ischemic heart disease and in hypertensive patients with target organ damage (47, 48). tPA is also released from endothelial cells by catecholamines and thrombin. Increases in plasma tPA antigen levels have been reported to be risk factors for myocardial infarction and stroke (49, 50).

Increases in two endothelial cell-derived factors (vWF and tPA antigens) were observed after the earthquake in the high-stress hypertensive group. There were positive correlations between the levels of these two factors and D-dimer levels after the earthquake (46), suggesting that the endothelial cell dysfunction caused by the earthquake was associated with an increase in fibrin turnover. Moreover, blood viscosity determinants (hematocrit and fibrinogen) were also increased. All of these changes could have contributed to the increase of cardiovascular events following the earthquake.

Mechanism of Activation

The potentiation of the acute risk factors that we observed could be attributed to sympathetic activation resulting predominantly from earthquake-induced stressors. In support of this mechanism, the earthquake-induced BP increase was less pronounced in patients taking α- and β-adrenergic blockers than in those taking other kinds of antihypertensive drugs (36, 51).

There have been some reports that psychological stress and its related sympathetic activation cause platelet hyperactivity, and increases in two of the determinants of blood vis-
coagulation factors (VII, VIII, and fibrinogen) (52–54). This platelet activation has been observed in both healthy subjects and those with advanced atherosclerotic disease (53). In addition, increases of BP induced by psychological stress could augment shear stress-induced platelet activation in patients with atherosclerotic stenoses (55).

There are no experimental data showing that the hormonal mediators of the sympathetic or HPA axis directly trigger a hypercoagulable state. In a study of healthy subjects, the infusion of stress hormones (epinephrine, cortisol, glucagon, angiotensin II, and vasopressin) for 24 h did not affect procoagulant or fibrinolytic factors (56). In vivo, the hypercoagulable state is determined by changes in the coagulation system (leading to thrombin generation) and platelet hyperactivity (leading to microthrombus formation). In this context it is of interest to note that the reduction of acute myocardial infarction by aspirin has been found to be stronger in the morning, particularly during the 3-h interval immediately after waking, a period characterized by sympathetic activation and a risk of infarction twice that of any other comparable time interval during the day or night (57). β-Adrenergic blockade suppressed the early morning rise in plasminogen activator inhibitor-1 (PAI-1) and tPA in patients with chronic coronary artery disease (58). In monkeys, psychosocial stress (72-h exposure of male monkeys to a social stranger) caused a significant increase in the number of injured endothelial cells in the circumsartial areas of the descending thoracic aorta, and this endothelial cell injury was significantly inhibited by β-adrenergic blockers (59) (Figs. 4, 5).

Chronic stress is also associated with changes in hemostatic factors. In a study of healthy women, lower socioeconomic status was associated with increased levels of coagulation factor VII antigen, fibrinogen, and vWF (60). In healthy middle-aged men chronic stress (defined as feelings of fatigue, lack of energy, increased irritability, and demoralization) was positively associated with plasma PAI-1 antigen levels, but was unrelated to tPA levels (61). In addition, levels of coagulation factors (VII, VIII, and fibrinogen) are known to be higher during a period of increased workload (62).

Oxidative Stress

Oxidative stress, a cellular or physiological condition of elevated concentrations of reactive oxygen species that cause molecular damage to vital structures and functions, might be one of the mechanisms involved in the earthquake-induced increase in cardiovascular events. Several environmental factors influence the susceptibility to oxidative stress by affecting the antioxidant status or free oxygen radical generation (63). Regular exercise and carbohydrate-rich diets seem to increase resistance to oxidative stress, and alcohol in lower doses may act as an antioxidant on low density lipoproteins and thereby have an anti-atherosclerotic property. Both cigarette smoke and psychological stress increase oxidative stress (63). Chronic stress can also induce oxidative stress, as assessed by increased plasma superoxide anions and malondialdehyde (64). There is evidence of an association between plasma levels of 60 kDa heat shock protein (HSP60; a specific biological marker of stress) or tumor necrosis factor α (TNF α; a proinflammatory cytokine) with low socioeconomic status (65). The synthesis of HSP60 in mitochondria was found to be stimulated after transient exposure of human endothelial cells to sublethal levels of hydroperoxides, such as H₂O₂ (66).

In addition, oxidative stress is linked to activation of the coagulation system in atherothrombotic disorders. The overall oxidation state of plasma proteins is associated with changes of circulating pro- and anticoagulant markers in healthy subjects (67). The carbonyl content of plasma proteins, which can be taken as an ex vivo index of the overall protein oxidation state due to its correlation with the plasma level of o-tirosine (which is a well-known oxidized product of l-phenylalanine), is positively associated with procoagulant markers such as F1 + 2 and fibrinopeptide A, as well as with the soluble derivative of the endothelial protein thrombomodulin. Vitamin E treatment in vivo partially restores the equilibrium between pro- and anticoagulant pathways (67).

Earthquake-Induced BP Increase

There have been several reports that BP and heart rate are increased at the time of a disaster. In our study of well-controlled hypertensive patients, increases of approximately 18 mmHg in systolic BP and 8 mmHg in diastolic BP were found during the period 2 weeks after the earthquake, when compared with the BP levels before the earthquake (46). In most patients, this increase was transient, and returned to the pre-earthquake baseline level within 4 weeks. A similar time course of BP changes was observed by Saito et al. (51) and by Minami et al. (68) using home BP monitoring. This characteristic of disaster-induced BP increase is important because persistent intense antihypertensive treatment for subjects with high BP at the time of a disaster could result in excessive reductions of BP, as we observed in a patient who had been started on treatment with antihypertensive agents just after the earthquake. She was referred to our clinic because she developed dizziness 3 months later. We discontinued her antihypertensive medication and monitored her ambulatory BP level, which was normal, and her symptoms disappeared (69).

White-coat hypertension, a phenomenon in which ambulatory BP is normal but clinic BP is high, is seen in approximately 20–25% of hypertensive subjects (70). We observed some patients with white-coat hypertension which shifted to a pattern of sustained hypertension (both clinic and ambulatory BP high) after the earthquake. In these patients, the BP increase was still present 2 months after the earthquake, and antihypertensive medication was needed to control it at that time (71). After 1 year of treatment, the 24-h ambulatory BP
decreased to the level before the earthquake. However, the clinic BP remained high, indicating that the white-coat effect can persist in treated patients (72).

Diurnal Variation

Stress-Induced Cardiovascular Events

Stress-induced cardiovascular events also show diurnal variation. Figure 7 compares the diurnal distribution of earthquake-induced cardiovascular deaths in the first 24 h after the earthquake with the diurnal distribution of cardiovascular deaths in the year preceding the earthquake (11, 12). In the year before the earthquake, both CHD events and strokes occurred more frequently in the period from early morning to noon than at other times of day. After the earthquake, cardiovascular deaths during this period were further increased. However, the most prominent increase was observed in the period from midnight to early in the morning. On the other hand, there was no increase of cardiovascular deaths during the active daytime period, from noon to midnight. In this context, it is of interest to note that a previous study of the timing of the onset of acute myocardial infarctions found that 53% of depressed patients, as compared with 20% of non-depressed patients, reported an onset of symptoms between 10 PM and 6 AM (73). Thus, depression or sleep impairment—two closely related conditions—induced by the earthquake may have contributed to these nighttime-onset cardiovascular deaths. Figure 8 shows a possible chronobiological mechanism of the diurnal variation of stress-induced cardiovascular events. Aggravation of acute risk factors, found early in the morning, would be associated with hemorrhagic and ischemic cardiovascular events (31), while imbalance between hemostatic factors and BP level may be involved in the triggering of hemorrhagic cardiovascular events during the period from afternoon to evening (74), as shown in Fig. 8B and C.

Acute Risk Factors

The early morning rise in BP is predominantly determined by α-adrenergic activity (75), is selectively attenuated by α-adrenergic blockers (76, 77), and has been related to increased left ventricular mass (78). Several risk factors for thrombotic events are potentiated early in the morning. These include endothelial cell dysfunction and vasospasm, plasma levels of blood viscosity determinants (hematocrit and fibrinogen), β-thromboglobulin, and platelet factor-4. Aspirin selectively prevents the morning peak of myocardial infarctions (57). A recent study of the diurnal variation of activation markers of coagulation showed that plasma levels of both activated factor VII and F1+2 were higher in the morning than in the afternoon (79). In addition, plasma levels of PIC were decreased, accompanied with an increase in PAI-1 level in the morning (79). This result indicates that fibrinolytic activity is suppressed in the morning. Taken together, these diurnal changes indicate a morning prethrombotic state.

Nighttime Onset of Cardiovascular Events

Approximately 15% of cardiovascular events occur during the night, which is a lower rate than at other time periods. In healthy subjects and hypertensive patients, sympathetic nervous activity is suppressed and parasympathetic nervous activity increased in proportion to the depth of sleep, leading to falls of nocturnal BP (80). During rapid-eye-movement
REM) sleep, bursts of sympathetic activation result in marked BP variations and increase myocardial susceptibility to arrhythmias. Various genetic and environmental factors including psychological and physiological factors that influence abnormal autonomic nervous activity and sleep quality contribute to the non-dipping status (81–90). Although the precise assessment of sleep requires polysomnography, sleep quality can be indirectly assessed using actigraphy, because physical activity increases due to microarousals during sleep (91). We have found a positive association between physical activity during sleep, as assessed by actigraphy, and nocturnal BP fall in healthy adults, and physical activity during sleep was found to be increased in non-dippers (92). Sleep disturbance is an important dimension of post-traumatic stress disorder, as shown by a recent report which demonstrated that subjects affected by Hurricane Andrew showed an increased number of arousals and entries into stage 1 sleep (93). These arousals are associated with sympathetic nervous activation, and transient increases of BP (80). Nocturnal behaviors like nocturia sometimes trigger falls, syncope, or cardiovascular events in elderly subjects, and the sympathetic activation and BP variations associated with these activities are considered to be triggering mechanisms (94). In addition, the ischemic threshold may be decreased during the night (95). Based on these considerations, a possible mechanism for the increased incidence of nighttime-onset cardiovascular events after the earthquake could be an impaired sleep pattern, and subsequent increases in nocturnal activity and microarousals (Fig. 8D).

**Stress-Induced Potentiation of Chronic Risk Factors**

Some recent studies have indicated that chronic psychological stress is associated with increased abdominal fat deposition and increased insulin resistance in humans and non-human primates (96, 97). The activation of the HPA axis might mediate this process. The insulin resistance syndrome is characterized by hyperinsulinemia, activation of the sympathetic nervous system, hypertension, impaired glucose tolerance, dyslipidemia (hypertriglyceridemia and decreased high-density lipoprotein (HDL) cholesterol), and an imbalance between coagulation and fibrinolysis (increased factor VII, and fibrinogen, and tPA-1). One previous paper reported increased levels of cholesterol and triglycerides in the subacute phase a few weeks after an earthquake (98). In contrast, there was no significant worsening in the lipid profile (decreased triglycerides and no changes in total cholesterol or HDL-cholesterol) during the first 2 weeks after the Hanshin-Awaji earthquake (8, 46). Thus, dyslipidemia is unlikely to contribute to the increase in cardiovascular events occurring soon after an earthquake. Finally, there has been one report that in diabetic patients blood glucose control became worse after an earthquake (99).

**Aging, Hypertension, and Target Organ Damage**

Aging, hypertension, and the extent of target organ damage may all influence the allostatic response. Aging increases human sympathetic nervous activity at rest. The failure to turn off the HPA axis and sympathetic activity after stress is a feature of the age-related functional decline in animals. Stress-induced increases of cortisol and catecholamines return to baseline more slowly in some animals with other signs of advanced aging (100, 101), and the negative-feedback effects of cortisol on the HPA axis are reduced in elderly humans (102). Ninety-seven percent of the cardiovascular deaths induced by the Hanshin-Awaji earthquake occurred in subjects aged 60 years or more (11, 12). This highly skewed age distribution indicates that aging is critically important for the triggering of cardiovascular events by environmental...
stress.

We investigated whether the potentiation of acute risk factors after the earthquake is specific to hypertensive patients (46). Four to 6 months after the earthquake, we again measured the plasma levels of coagulation and endothelial cell-derived factors in the same hypertensive patients and normotensive subjects whose plasma samples had been measured just after the earthquake. The increase in vWF in the hypertensive patients persisted even 4–6 weeks after the earthquake, whereas all the other increased factors had returned to baseline. Thus, the earthquake-induced potentiation of coagulation and fibrinolytic activity is transient, and is not specific to hypertensive patients.

Cardiovascular effects of chronic exposure to stress may be more prolonged when target organ damage is present. The increase of BP observed after the Hanshin-Awaji earthquake in older hypertensives who had microalbuminuria persisted for at least 2 months (36). And all of the 3 patients with white-coat hypertension who developed sustained hypertension for several months after the earthquake also had microalbuminuria (71).

Aging is the greatest risk factor for thrombosis, and has adverse effects on three major determinants of thrombosis: 1) impaired microcirculation from increased hematocrit; 2) abnormalities of humoral factors, such as platelet and coagulation activation and hypofibrinolysis; and 3) vascular damage from atherosclerosis. The prethrombotic or hypercoagulable state is a predisposing condition for clinical thrombosis, in the presence of which additional triggering events can easily induce clinically overt cardiovascular events. It is well-known that all the above-mentioned coagulation factors and markers of activation are increased in elderly subjects (103, 104), with decreases in coagulation inhibitors (105), indicating a hypercoagulable state in the elderly. Moreover, it is known that PAI-1, PIC (which reflects generation of plasmin, an active fibrinolytic factor), and D-dimer all increase with aging in normal subjects (106). Therefore, normal aging is associated with hyperfibrinolysis, which balances the hypercoagulable state. However, when accompanied by cardiovascular disease or insulin resistance syndromes such as hyperlipidemia and obesity, plasma PAI-1 levels are increased to inhibit the secondary fibrinolytic activation (107, 108). This imbalance between coagulation and fibrinolytic activities is associated with silent cerebral infarction, which is the most powerful predictor for clinically overt stroke in elderly hypertensive subjects (109). It is thus quite plausible that the intense stress of an earthquake can trigger cardiovascular events in high-risk elderly subjects who are in the prethrombotic state described above.

Conclusions

Earthquakes provide a dramatic example of the effects of acute and catastrophic stress on cardiovascular disease, and how these effects may be mediated both by hemodynamic changes such as BP increases and thrombogenic factors. Some of the results are surprising, such as the observation that the increases in both the perceived stress and the rate of myocardial infarction were greater in women than in men, and that the effects were greatest during the nighttime hours. The data are also consistent with other findings that acute stressors of lesser magnitude but more frequent occurrence may trigger cardiovascular events. It is to be expected that the disasters of September 11, 2001 initiated a similar process of changes.

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