Several stress-related situations represent important risk factors for the development of atherosclerotic cardiovascular disease. Results from recent studies conducted experimentally on animals as well as on human have also shown that physical stress induced by prolonged exercise may result in myocardial cell damage and ventricular dysfunction, with release of cardiac biomarkers into the circulation. Similarly, accumulated data indicated that psychological or emotional stress may lead to myocardial dysfunction and injury associated with increases in cardiac marker levels. Furthermore, various clinical conditions other than acute coronary syndromes have been linked to stress-induced myocardial cell damage. The present review focuses on recent data investigating the association of physical and psychological stress-related conditions with myocardial injury and dysfunction, and discusses the potential pathophysiological mechanism of stress-induced cardiac damage as assessed by measuring the novel cardiac marker proteins troponins and natriuretic peptides.

**Physical stress and myocardial damage and dysfunction**

Epidemiological studies have shown that individuals with regular exercise have a lower long-term risk of myocardial events compared with those not on regular exercise. On the other hand, it has been demonstrated that prolonged intense physical exercise may trigger severe cardiac events, especially in persons with a history of low physical activity. Therefore, it is of interest to know, whether the physical stress-induced cardiac injury is associated with release of cardiac marker proteins into the circulation.

In a rat model of cardiac damage, Chen et al. reported that stressful, forced exercise of 5 hours swimming caused an increase in serum cardiac troponin T (cTnT) concentrations. We have conducted a study on race horses with regular training exercise and found a minor but significant increase in cardiac troponin I (cTnl) plasma concentrations in several blood samples obtained 3-4 hours after exercise compared with baseline values before exercise. The result indicated that even a low exercise level may induce myocardial cell damage.

Previous studies on humans using old and non-specific cardiac troponin assays and high cut-off levels reported heterogeneous and conflicting results. Recent trials utilizing high sensitive and specific assays with lower cut-off levels, however, demonstrated that a significant number of individuals showed increased cardiac troponin concentrations after strenuous exercise (triathlon, marathon running, alpine bicycling). Depending on the cut-off values used and the types of exercise events, the frequency of elevated cTnT or cTnl were between 9 and 86 percent (Table 1). In a recent study of 24 marathon runners, Melanson et al. reported that 11 out of 22 (50%) of the participants showed increased cTnT concentrations at or above the cut-off value of 0.03 ng/ml (10% CV) after the race. None of the runners, however, demonstrated a post-race cTnT level exceeding 0.10 ng/ml, a value considered to be indicative of myocardial necrosis at the Massachusetts General Hospital. These results clearly point to the existence of an exertion-related minor myocardial cell damage. In a more recent study of 482 marathon runners, Fortescue et al. reported that 68% (cTnI and cTnl cut-off = 0.01 ng/ml and 0.10 ng/ml, respectively) and 11% (cTnI and cTnl cut-off = 0.075 ng/ml and 0.50 ng/ml, respectively) of the athletes showed increased cardiac troponin levels. Of particular importance was the finding that less running experience and younger age, but not race duration and the presence of traditional cardiovascular risk factors were associated with elevated troponins.

As also indicated in Table 1, the percentage of increased N-terminal pro-brain natriuretic peptide (NT-proBNP), a novel marker of ventricular dysfunction, after exercise events ranged from 54 to 100 percent. Similar to cardiac troponins, the reported increases in natriuretic peptide levels were only moderate and transient, with a decline to baseline values 24 hours after the races. Of interest was the observation that the young and best-trained athletes exhibited the smallest exercise-induced increases in NT-proBNP concentrations.

The pathophysiological mechanism of physical exercise induced myocyte damage is at present not fully understood. As has been reported in all trials demonstrated in Table 1...
TABLE 1. Percentage of elevated biomarkers of myocardial necrosis and ventricular dysfunction after prolonged strenuous exercise.

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Event</th>
<th>Marker</th>
<th>cut-off concentration*</th>
<th>Percent elevation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifai et al.</td>
<td>23</td>
<td>Triathlon</td>
<td>cTnT</td>
<td>0.03 / 0.10</td>
<td>-</td>
</tr>
<tr>
<td>Neumayr et al.</td>
<td>28</td>
<td>Alpine bicycling</td>
<td>cTnI</td>
<td>0.50</td>
<td>-</td>
</tr>
<tr>
<td>Herrmann et al.</td>
<td>46</td>
<td>Marathon</td>
<td>NT-proBNP</td>
<td>26 / 9</td>
<td>9</td>
</tr>
<tr>
<td>Herrmann et al.</td>
<td>105</td>
<td>Marathon,100 km running, mountain biking</td>
<td>cTnT</td>
<td>0.01 / 0.03</td>
<td>-</td>
</tr>
<tr>
<td>Neumayr et al.</td>
<td>29</td>
<td>Radmarathon</td>
<td>cTnI</td>
<td>0.04 / 0.06</td>
<td>88 or 153</td>
</tr>
<tr>
<td>Herrmann et al.</td>
<td>46</td>
<td>Marathon</td>
<td>NT-proBNP</td>
<td>50 / 17</td>
<td>72 / 59</td>
</tr>
<tr>
<td>Herrmann et al.</td>
<td>105</td>
<td>Marathon,100 km running, mountain biking</td>
<td>cTnT</td>
<td>0.01 / 0.03</td>
<td>-</td>
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<tr>
<td>Neumayr et al.</td>
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<td>Neumayr et al.</td>
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</tr>
</tbody>
</table>

* in ng/ml for cardiac troponins and ng/L for natriuretic peptides.

and in others, it is observed that the exercise-mediated release of cardiac troponins is small and transient, unlike that after irreversible myocardial damage. This may indicate the release of troponins from the free cytoplasmic pool (approximately 3-7% of the cellular content). It has been hypothesized that the oxidative stress during prolonged exercise induces an overload of free radicals which, in turn, leads to cardiocyte-membrane leakage and egress of cytosolic troponins into the circulation. Another possible explanation is the presence of transient myocardial ischemia at the sub-endocardial level subsequent to an elevation in circulating catecholamines during exercise causing coronary vasospasm. In this context, Mann et al. have demonstrated a direct cardiotoxic effect of norepinephrine in an experimental model of cardiac injury in laboratory animals. Recently, a rising and falling pattern of cTnT and cTnI concentrations has been reported in 2 beagle dogs after subcutaneous injection of isoproterenol, a sympathomimetic agent and β-adrenergic receptor agonist. Abnormal pathologic alterations, including severe coagulative necrosis of the myocardium were seen in both animals, thus indirectly confirming the toxic effect of catecholamines on cardiomyocytes. The catecholamine induced myocardial ischemia and cardiac arrhythmias may also be responsible for myocardial dysfunction and release of natriuretic peptides into the circulation. The association between acute physical stress and myocardial damage and dysfunction has also been demonstrated in a study of long-distance running which showed parallel increases in levels of cortisol, cTnT and natriuretic peptides.

Psychological stress and myocardial damage and dysfunction

The transient left ventricular apical ballooning syndrome is a recently described novel acute cardiac syndrome. Initially recognized and first reported in the Japanese population as tako-tsubo cardiomyopathy, the syndrome is clinically characterized by the presence of chest pain, ischemic electrocardiographic changes, echocardiographic ventricular dysfunction, and small elevations of cardiac enzyme and troponin levels. Another characteristic finding was that patients with this syndrome usually do not have angiographic evidence of atherosclerotic obstructive coronary artery disease. An episode of psychological or emotional stress frequently precedes the onset of the syndrome. Other precipitating factors include physical stress, medical illness and cocaine use.

Previous studies on patients with tako-tsubo cardiomyopathy have used the enzyme creatine kinase (CK) as a biochemical parameter for the assessment of myocardial cell damage. This enzyme lacks, however, cardiac specificity due to its presence in significant amounts in skeletal muscle. Table 2 summarized recent clinical trials of the syndrome utilizing the cardiac specific troponins as biochemical markers. Only series with more than 10 cases of tako-tsubo cardiomyopathy were included in the present review. Two series reported a 100% incidence of increased cardiac troponin levels. The extent of myocardial damage varied considerably, depending on the type of troponin assays used. Nevertheless, mildly elevated

TABLE 2. Clinical trials of tako-tsubo cardiomyopathy reporting novel cardiac marker protein levels.

<table>
<thead>
<tr>
<th>Author</th>
<th>N (Female/Male)</th>
<th>Age (Year)</th>
<th>Chest pain (%)</th>
<th>Ischemic*</th>
<th>Mean**</th>
<th>Maximum cardiac marker level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desmet et al.</td>
<td>13 (12/1)</td>
<td>45 - 81</td>
<td>62</td>
<td>100</td>
<td>NR</td>
<td>5.2 - 115.7***</td>
</tr>
<tr>
<td>Seth et al.</td>
<td>12 (11/1)</td>
<td>64 ± 14</td>
<td>25</td>
<td>100</td>
<td>32</td>
<td>-</td>
</tr>
<tr>
<td>Bybee et al.</td>
<td>16 (16/0)</td>
<td>71 ± 12</td>
<td>69</td>
<td>100</td>
<td>40</td>
<td>-</td>
</tr>
<tr>
<td>Wittstein et al.</td>
<td>19 (18/1)</td>
<td>27 - 87</td>
<td>95</td>
<td>100</td>
<td>20</td>
<td>5.0 - 14.0****</td>
</tr>
<tr>
<td>Pilliere et al.</td>
<td>12 (11/1)</td>
<td>35 - 84</td>
<td>83</td>
<td>100</td>
<td>35</td>
<td>-</td>
</tr>
<tr>
<td>Abdulla et al.</td>
<td>35 (34/1)</td>
<td>68 ± 13</td>
<td>NR</td>
<td>NR</td>
<td>33</td>
<td>0.8 ± 0.8****</td>
</tr>
</tbody>
</table>

*Including ST elevation, ST depression and T wave inversion. ** LVEF = Left ventricular ejection fraction, *** in µg/ml, **** in ng/ml or µg/L. NR = not reported.

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troponin levels were observed in most of the patients indicative of minor myocardial damage.

At present, there is no consensus of the underlying mechanism of the apical ballooning syndrome. Accumulating evidences, however, indicate that excessive sympathetic activation secondary to the profound psychological or medical stress may play a key pathophysiological role. The syndrome may represent a catecholamine-mediated myocardial stunning that results from a combination of myocardial ischemia related to diffuse microvascular dysfunction and multivessel epicardial spasm. Wittstein et al. have recently reported that plasma levels of catecholamines (i.e. epinephrine, norepinephrine, and dopamine) among patients with stress-induced cardiomyopathy were 2 to 3 times the values among those with Killip class III myocardial infarction, and were markedly higher than the normal values. Endomyocardial biopsy showed mononuclear infiltrates and contraction-band necrosis comparable to that seen in catecholamine-mediated cardiac toxicity.

Of interest was the observation of a strong predominance of females in advanced age in tako-tsubo cardiomyopathy. The explanation may be related to postmenopausal alterations of endothelial function in response to reduced estrogen levels. In a rat model of emotional stress reported by Ueyama et al., transient apical and mid-ventricular wall motion abnormalities have been induced through physical immobilization. The same group of researchers has also demonstrated that estradiol supplementation attenuates emotional stress-induced changes in left ventricular function in ovariec-tomized female rats. The direct protective effects of estrogen on the cardiovascular system may involve the induction of vasodilatation through activation of endothelial nitric oxide synthase (NOS), and inhibition of the response of blood vessels to injury and the development of atherosclerosis.

Other stress-related conditions and myocardial damage

In a recent contemporary review, Tofler and Muller have summarized data on other stress conditions that represent potential triggers of acute cardiovascular disease. These include environmental stress (air pollution, exposure to traffic and associated pollution and emotional stress), anger and anxiety (arguments with family members, conflicts at work, legal problems), disasters (earthquake, World Trade Center event on September 11, 2001), and sporting events (1996 European football championship etc.). All of these situations are known to be related to acute physiological hormonal and biochemical changes that transiently increase the risk of plaque rupture and thrombosis, with subsequent cardiovascular events in high risk individuals.

There are also several physical stress-related illnesses other than acute coronary syndromes that have been reported to be associated with myocardial ischemia and release of cardiac biomarkers into the circulation. These conditions are congestive heart failure and acute neurologic disease such as acute stroke, subarachnoid hemorrhage or epileptic seizure. As with the physical and psychological stress mentioned above, the most likely explanation of myocardial damage and troponin elevation found in these clinical settings is an excess of sympathetic activity and increased catecholamine effect on the myocardial cells.

CONCLUSION

Physical and psychological stress represent integral parts of our everyday life, and recognition of these two stress-related situations as triggering factors of acute cardiac events is essential. Although the myocardial cell damage and ventricular dysfunction induced by endurance and prolonged exercise in healthy and trained persons is usually minimal and has no clinical significance, individuals with a family history of cardiovascular disease should undergo cardiac testing procedures including blood tests before exercise events. Similarly, even though rarely encountered, the apical ballooning syndrome should now be considered in the differential diagnosis of acute coronary syndromes, especially in women. The two stress conditions possibly share analogous pathophysiological mechanisms that involves overactivation of the sympathetic nervous system and endothelial dysfunction leading to coronary vasoconstriction, myocardial ischemia and infarction (Fig 1). Direct toxic effects of catecholamines on cardiac myocytes through calcium overload may also represent another cause of myocardial damage in these conditions. Although much progress has been made in defining the mechanism of stress-related acute coronary events, further studies are needed to better characterize their specific triggers and to better understand the modifiers of risk in both human and animal models.

ACKNOWLEDGEMENTS

The authors thank Miss Apisara Chotipaporn and Miss Supansa Choeyklinnet for their contribution to preparation of the manuscript.

REFERENCES


1. Which of the following proteins represent the most cardiac specific marker?
   A. Cardiac troponins
   B. Creatine kinase
   C. Creatine kinase-MB
   D. B-type natriuretic peptide
   E. N-terminal probrain natriuretic peptide

2. Features of athletes that are associated with a frequent increase in exercise-induced cardiac marker level include
   A. Well trained athletes
   B. Less trained athletes
   C. Race duration
   D. Less running experience
   E. B and D are correct

3. The common triggering factor of the apical ballooning syndrome is
   A. Physical stress
   B. Emotional stress
   C. Medical illness
   D. Drug abuse
   E. Sporting event

4. Which of the following biochemical and clinical characteristics is not a feature of tako-tsubo cardiomyopathy?
   A. Female predominance
   B. Chest pain
   C. Ischemic electrocardiographic changes
   D. Echocardiographic ventricular dysfunction
   E. Strong cardiac marker release

5. Pathophysiological characteristics of stress-related myocardial damage involve
   A. Sympathetic overactivity
   B. Endothelial dysfunction
   C. Atherosclerotic obstructive coronary artery disease
   D. A and B are correct
   E. A, B and C are correct