Introduction

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The pervasive role of behavioral factors in triggering major cardiovascular events, including myocardial ischemia and infarction, cardiac arrhythmias, and sudden death, often intuited by astute physicians, is gaining more widespread appreciation. This realization has been bolstered by evidence from controlled behavioral studies in large populations, standardized clinical behavioral stress testing, and experimental studies in animals[1]. During the past decade, strong associations with cardiovascular events have been demonstrated for the affective states of anger, fear, anxiety, bereavement, and depression. Collectively, emotional stress has been shown to precede both fatal and nonfatal myocardial infarction in approximately 210 000-270 000 (14 to 18%) of cases annually in the United States alone. The relative risk for behavioral factors in cardiac events is summarized in table I[2].

This minisymposium provides three essays focusing on differing approaches to elucidating this association. We have invited authorities in epidemiology, cardiology, and behavioral medicine to capsulize the latest advances in methodology. Each of the authors also describes a blueprint of intriguing studies to investigate the mechanisms of stress-induced cardiac events.

In the discipline of epidemiology, Dr. Mittleman, who has made pioneering contributions with his widely applicable "case-crossover" design, discusses how this and other tools can be employed to identify the role of behavioral factors at several points in the development of coronary artery disease. He underscores the important effects of stress at all phases of the disease process, including acute precipitation of infarction and sudden death, the more intermediate period when the stage is set for plaque vulnerability and future rupture, and the more elusive contribution over the course of decades through, for example, the development of hypertension. New noninvasive imaging technologies and improved understanding of the disease process create rich opportunities to probe the extent and mechanistic basis of the influence of behavioral factors. As Dr. Mittleman discusses, among the most exciting developments are the ongoing randomized clinical trials that explore the potential to validate the therapeutic efficacy of behavioral interventions with the same analytical strength as pharmacologic interventions are tested.

The state-of-the-art of assessment and treatment of depression in patients with coronary artery disease is presented by Drs. Kop and Ader. Their elegant work, along with that of others, reveals that depression is more than 4 times more prevalent in these patients than in the general population. The authors emphasize the multifactorial basis for this affective state, which includes genetic predisposition, history of distressing experiences, and other psychological triggers. Drs. Kop and Ader illustrate how the structured interview has derived insights into cause-and-effect relationship of depression with cardiac disease, the symptomatology characteristic of this patient group, and the reasons for under-diagnosis of depression in cardiac patients, in whom this affective state more than doubles the risk of cardiac events. This practical information includes a presentation of contemporary, promising treatments for depression in coronary artery disease patients.

The third area addresses the application of human laboratory studies in probing the pathophysiologic mechanisms that underlie mental stress-induced provocation of myocardial ischemia and cardiac events. Dr. Krantz, who with his col-

Table I. Behavioral studies on risk of fatal or nonfatal cardiac events.

Behavior	Outcome	Risk ratio
Anger	Nonfatal MI	2.3 for 2 hours
Anger	Fatal or nonfatal MI	3.2
Anxiety	Nonfatal MI	1.6
Anxiety	Fatal MI	1.9
Anxiety	Sudden death (within 24 hours)	4.5
Phobic anxiety	Fatal MI	3.0
Phobic anxiety	Sudden death (within 24 hours)	6.1
Worry	Nonfatal MI	2.4
Daily life stresses (tension, sadness, frustration)	Silent myocardial ischemia in patients with coronary artery disease	2-3 for 1 hour
Major depression in early survivors of MI	Cardiac death	3.64 for 18 months
Depressive symptomatology in early survivors of MI	Cardiac death	7.82
Depressive symptomatology in early survivors of MI	Cardiac death in patients with > 10/hour premature ventricular contractions	29.1

MI = myocardial infarction. From Verrier and Mittleman[2], modified.

leagues has made many seminal contributions to this area, provides unique insights into the types of cardiovascular alterations impacted by mental stressors that set the stage for impaired myocardial perfusion. Their approach has involved administration of a systematic battery of behavioral tests including mental arithmetic, anger recall, Stroop card testing, and others, particularly with comparison to exercise stress testing. An emerging concept in identifying the prognostic significance of mental stress-induced myocardial ischemia is the dual evaluation of the level of underlying ischemia and the concurrent impact on cardiac electrical stability. With respect to the latter, Dr. Krantz and his colleagues review recent data employing T-wave alternans, a beat-to-beat fluctuation in the magnitude of this waveform, to evaluate electrical instability in patients with implantable cardioverter-defibrillators during psychological stress testing. New frontiers include application of newly developed investigative tools to evaluate cardiac function, such as radionuclide ventriculography, positron emission tomography scanning, thallium perfusion imaging, and two-dimensional echocardiography, and also the possibility of improved pharmacologic and nonpharma-cologic approaches for containing lethal mental triggers of cardiac events.

In summary, notable progress has been made in uncovering the relationship between mental stress and cardiovascular morbidity and mortality. We are at the stage where the community of cardiologists can view psychologic stressors as *bona fide* risk factors. Powerful tools have been made available for further study from the disciplines of epidemiology, laboratory testing protocols, and advanced techniques for evaluating alterations in cardiovascular function and status. The opportunity is now available to test emotional and behavioral interventions as stringently as pharmacologic therapy, the contemporary standard of effectiveness.

References

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2. Verrier RL, Mittleman MA. The impact of emotions on the heart. Prog Brain Res 2000; 122: 369-80.