Epidemiologic perspective on the role of psychosocial factors

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The pathophysiology of acute myocardial infarction is complex and includes long-term effects of risk factors leading to the formation of coronary atherosclerosis, intermediate-term effects of risk factors leading to plaque vulnerability, and short-term effects of triggers that precipitate the onset of acute myocardial infarction and other cardiovascular events. Psychosocial factors may play an etiologic role at each of these stages. The purpose of this brief paper is to identify opportunities and challenges that face the cardiology community over the next decade as we continue to evaluate the role of psychological stressors in the etiology of acute myocardial infarction and other acute cardiovascular events.

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Long-term effects: the role of psychosocial factors in atherogenesis

Several lines of evidence have indicated that chronic psychological distress, including depression[1-3], anxiety[4,5], hostility[6,7], social isolation[8,9], and chronic life stress[10,11], can lead to an increase in the level of risk factors for the development of atherosclerosis, including hypertension, dyslipidemia and coagulation factors. Such atherogenic factors are known to mediate in part the association between these psychosocial factors and cardiovascular disease. In addition, several studies have found an independent association between these psychological factors and the occurrence of cardiovascular disease[12].

Future studies to elucidate the importance of psychosocial factors should be undertaken at several levels. For example, experimental, clinical and cross-sectional epidemiologic studies of the associations between psychosocial stress and the prevalence of intermediate cardiovascular endpoints, including markers of subclinical atherosclerosis, must be undertaken. These studies should focus not only on traditional risk factors, but also on novel risk factors, including hemostatic[13] and inflammatory[14] markers, which have recently been shown to be important mediators of myocardial infarction risk. Another productive line of research involves the cross-sectional evaluation of psychosocial distress and subclinical atherosclerosis, measured for example by noninvasive imaging techniques[15], such as carotid artery ultrasound[16] or electron beam computed tomography[17-19] and perhaps cardiac magnetic resonance imaging[20] modalities, which are on the near-term horizon.

An inherent drawback of cross-sectional and retrospective studies is the risk of "reverse causation bias". Such bias arises when patients with prevalent clinical or subclinical disease are evaluated and compared with subjects free of such disease. With this design, it is unclear whether the level of psychosocial stress observed in the patients is a cause or consequence of their underlying disease. Therefore, prospective cohort studies are required to evaluate the association between psychosocial risk factors and the incidence of myocardial infarction and other acute cardiovascular events. A major advantage of such a design is that it is free from the problem of reverse causation bias. A fruitful area of research within this type of study design will be evaluating the progression of atherosclerosis over time, assessed with serial noninvasive imaging of the carotid or coronary arteries at baseline and then after a follow-up period[16].

Finally, and most importantly, well designed randomized clinical trials of potential interventions, aimed at treating patients with specific types of psychological distress will need to be undertaken to determine whether useful therapeutic options are available to prevent clinical cardiovas-

cular outcomes and to improve the quality of life for these patients. Such randomized trials must be held to the same methodological, technical and ethical rigor as clinical trials of pharmacotherapy. Several important trials have been undertaken to intervene in patients with psychological distress and established coronary disease, including the MHART[21] and the ENRICHD[22,23] studies. In developing such randomized trials, there are several challenges, which must be met, for example, identifying a group of patients with a relatively homogeneous therapeutic target (e.g., depression, social isolation, or hostility); developing an intervention strategy that can be reproducibly administered in a multicenter setting; maintaining compliance with the experimental protocol; and maintaining an unbiased, blinded assessment of the outcome events of interest.

Intermediate-term effects: the role of psychosocial factors in plaque vulnerability

To study intermediate-term effects, the evaluation must focus on risk factors for the development of vulnerable atherosclerotic plaques[24-26]. As our understanding of the determinants of plaque vulnerability evolves, the first major challenge is to develop clinical measures of plaque vulnerability and endothelial cell function that can be measured reproducibly and preferably noninvasively. Some of the most promising work in this field is likely to result from noninvasive studies of flow-mediated vasodilation as markers of endothelial cell functioning[15], and perhaps magnetic resonance imaging studies of the aortic arch that can noninvasively evaluate function as well as structure[27]. A related area is the noninvasive evaluation of measures of vulnerability to ventricular arrhythmias[28], including heart rate variability, T-wave alternans[29], and QT dispersion, which may also be applied in prospective cohort studies that also measure psychosocial risk factors such as depression, hostility, social isolation, and job strain.

Just as for the assessment of more long-term effects, a major challenge to the research community is the development and/or selection of appropriate reproducible and valid exposure assessment tools that can measure psychosocial risk factors with a high level of sensitivity and specificity for classifying individuals with respect to their level of psychosocial risk factors.

Short-term effects: the role of psychosocial factors in triggering the onset of acute cardiovascular events

Over the past decade, mounting evidence has indicated that the majority of nonfatal myocardial infarctions and sudden cardiac deaths result from the disruption of vulnerable but not necessarily tightly stenotic atherosclerotic lesions within the coronary arteries[26,30,31]. The natural history of such lesions is that a thrombus typically forms at the site of a disrupted plaque. Whether the subsequent thrombus becomes completely occlusive is determined by the relative balance between thrombotic and fibrinolytic factors, as well as the balance between vasoconstrictive and vasodilatory forces at the site of a disrupted plaque[24]. There is now evidence that such plaque disruption-thrombosis events are often triggered by physical, psychological and chemical stressors that initiate the onset of acute myocardial infarction[32-35] and sudden cardiac death[36].

A major advance in searching for psychosocial factors as triggers of acute cardiovascular events has been the development of the case-crossover design[37]. This approach compares the risk of acute cardiovascular event onset during periods of exposure to transient psychological states, such as outbursts of anger, discreet episodes of anxiety, or during periods of extreme grief, to the risk of such events during other time periods. The key distinguishing feature of this study design is that each patient serves as his or her own control, thereby eliminating the epidemiological problem of confounding by differences among individuals that otherwise plague standard epidemiologic study designs.

Over the next decade, we will learn even more about these triggers by conducting case-crossover studies nested inside prospective cohort studies. This approach will reduce the problem of recall bias that may have arisen in earlier retrospective studies of triggering events and activities. Furthermore, it is not sufficient merely to identify the existence of such triggers, but it is crucial also to understand factors that alter the risk of myocardial infarction associated with such exposures. For example, aspirin use, which inhibits platelet aggregability, appears to decrease the risk of myocardial infarction onset associated with discreet outbursts of anger[33]. In addition, laboratory, clinical and pathology based studies will be needed to evaluate the acute physiologic sequelae of psychological stressors, such as outbursts of anger, that lead to the disruption of atherosclerotic plaques. For example, the morphology of the culprit lesion in cases of fatal myocardial infarction associated with psychological or physical stress differs from that of the culprit lesions of patients whose infarcts appear to have begun at rest[31].

Conclusion

In summary, the search for the psychosocial factors that may be component causes of acute myocardial infarction is rapidly evolving. New tools that are now available to the cardiology community will lead to new lines of evidence and may refute some existing theories but nonetheless advance the field.

Key challenges that must be addressed for the field to continue to progress are: better and easier-to-use

measures of psychological stressors; a careful choice of valid and relevant outcome measures; and ultimately the development of randomized clinical trials to determine whether interventions can be developed to sever the link between psychological stress, which in some cases may be unavoidable, and the occurrence of acute myocardial infarction and other acute cardiovascular events.

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