Psychosocial Risk Factors for Cardiovascular Disease

More Than One Culprit at Work

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SOLID SCIENTIFIC EVIDENCE SUPPORTING THE ADVERSE effects of stress on health began to emerge nearly 30 years ago with the report by Rosenman et al[1] showing that men with type A behavior (time urgency, hostility, achievement striving) were twice as likely as their counterparts with type B behavior (lacking type A characteristics) to develop coronary heart disease (CHD) over an 8-½ year period.[1] Failure to replicate this finding in another large-scale prospective study[2] raised questions about the validity of type A behavior as a CHD risk factor. However, subsequent research makes a strong case that of the 3 components of the global type A behavior pattern, hostility is the one most reliably associated with increased CHD risk.[3-5]

In this issue of THE JOURNAL, the article by Yan et al[6] provides credible evidence that not only hostility, but another type A component, time urgency/impatience (TUI), are both independently associated with a nearly 2-fold increase in hypertension incidence in a large population-based prospective sample of young adults balanced on sex, ethnicity (black and white), and education (more or less than high school). How do these results fit within the context of current knowledge about psychosocial risk factors for cardiovascular disease (CVD)? Can psychosocial risk factors like TUI and hostility be reduced? And, if so, will there be a corresponding reduction in the incidence of hard CVD end points?

Thirty years ago, turf wars interfered with progress in documenting the role of psychosocial risk factors. Those studying type A behavior had to defend their turf from other researchers who thought that it was really social isolation that increased CVD risk, or others who championed depression as the key psychosocial risk factor. During the past decade, a more enlightened and heuristic approach has emerged that views psychosocial risk factors not as competitors vying for the title of most important risk factor, but as elements of the same group of adverse factors that tend to cluster in the same persons and groups. Thus, women who report high job strain also exhibit higher levels of hostility, anger, depression, anxiety, and social isolation.[7] Hostility, depression, and social isolation are all increased in lower socioeconomic groups.[8,9] As with physical risk factors, when psychosocial risk factors co-occur in the same persons or groups, their impact on CVD risk is compounded. In the Kuopio Study,[10] for example, persons with 1 or 2 psychosocial risk factors were twice as likely to die as those with none during the follow-up period, but those with 3 psychosocial risk factors were 4 times more likely to die.

Following the standard practice in prospective studies to identify risk factors, Yan et al[6] used multivariable statistical approaches that evaluated the impact of each psychosocial factor on hypertension risk with adjustment for demographic, lifestyle, and the other psychosocial factors. This enables the authors to make the case that the contributions of TUI and hostility to hypertension risk are "independent" of each other as well as of the other factors that were controlled, but it does not address the question of their joint effects on risk. Given the independence of the effects of TUI and hostility on risk, it is likely that persons with high TUI and high levels of hostility would show an even larger increase in hypertension incidence than the 84% increase seen in those in the groups with the highest levels of TUI or hostility. If so, it would suggest that interventions to reduce psychosocial risk factors would have a larger impact on hypertension risk if these interventions would target persons with high levels of both TUI and hostility.

Psychosocial risk factors such as TUI, hostility, and others do not, by themselves, have any direct effects on disease processes. These risk factors affect disease processes only via 2 biobehavioral pathways: (1) unhealthy behaviors like smoking, increased caloric intake, increased alcohol intake[11,12] and (2) biological characteristics like increased cardiovascular/neuroendocrine reactivity to stress,[13] increased platelet activation,[14] increased inflammatory cytokines,[15,16] or increased expression of the metabolic syndrome in nondiabetic persons.[17,18] Elevated cardiovascular

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reactivity (CVR) to stress predicts more rapid progression of carotid athersosclerosis[19-21] and increased stroke incidence.[22] Controlling for indicators of these biobehavioral mechanisms in studies to identify psychosocial risk factors misses the point that rather than being independent of these biobehavioral factors, psychosocial factors are most likely acting through them to influence the pathogenesis and course of disease. If both hostility and CVR to stress are associated with hypertension incidence and control for CVR renders the effect of hostility nonsignificant, it may be more useful to view enhanced CVR to stress as mediating the pathogenic effect of hostility rather than concluding that hostility is not an independent risk factor for CVD. Under this scenario, the relationship of CVR to stress should be assessed in behavioral trials that target hostility to ensure that the treatment is ameliorating the pathogenic mechanism.

Consideration of gene-environment interactions that foster the clustering of behavioral, psychological, and biological characteristics that increase CVD risk will enhance the ability to develop effective prevention and treatment approaches. Because the serotonergic system regulates many of these characteristics,[23] much early research in this area has focused on variants in genes that encode for proteins involved in regulation of serotonin function. A functional polymorphism of the serotonin transporter gene promoter has been shown to be associated with psychosocial risk factors like hostility and depression,[24] increased CVR to stress,[25] altered central nervous system serotonin turnover,[26] and increased risk of myocardial infarction (MI).[27,28] Among persons experiencing high levels of life stress, those with the less active short allele of this polymorphism are most likely to become depressed.[29] Use of genetic criteria, therefore, should enhance the sensitivity and specificity with which clinicians can identify persons who are at highest risk and hence most likely to benefit from behavioral interventions.

There is probably no single biobehavioral pathway whereby psychosocial factors always influence the development and course of cardiovascular and other major diseases. A more accurate conceptualization may be one that considers gene-environment interactions as influencing, which among the many potential biobehavioral pathways link psychosocial factors with disease processes in any particular instance. Thus, in one person with high levels of hostility and depression, increased caloric intake and CVR to stress may play the key roles in the occurrence of an MI at age 45 years, whereas in another individual, smoking and elevated inflammatory cytokines may be the underlying predisposing factors.

It is not necessary to wait for a complete understanding of the gene-environment interactions and their influence on biobehavioral pathways that translate psychosocial factors into disease to begin the important task of developing and testing ways to ameliorate their health-damaging impact. Even though much work remains to be done, behavioral and pharmacological interventions targeting psychosocial risk factors and the intervening biobehavioral mechanisms already have shown considerable promise for reducing disease and improving health and well-being.

Several randomized clinical trials have shown benefits of behavioral approaches for secondary prevention in patients with CVD. Meditation techniques produce blood pressure reductions that are associated with decreased carotid artery intimal thickness in older black patients with hypertension.[30,31] The Recurrent Coronary Prevention Project (RCPP) showed that it is possible to reduce type A behavior and that such changes are associated with a 44% reduction of cardiac events following MI compared with usual care.[32] In targeting the multidimensional type A behavior pattern, the RCPP intervention produced lower hostility, anger, and depression as well as enhanced self-efficacy and well-being.[33] This finding shows that multiple psychosocial risk factors can be improved by a behavioral intervention, consistent with the concept that psychosocial risk factors tend to cluster in the same individuals and groups. Another clinical trial of an intervention to reduce hostility in post-MI patients reported significant decreases in hostility as well as in depression and diastolic blood pressure, which were maintained 2 months after the intervention ended.[34] The Enhancing Recovery in Coronary Heart Disease (ENRICHD) trial[35] found that behavioral treatment reduced depression and social isolation in post-MI patients, but clinical end points did not differ from those in the control group, perhaps because controls also showed significant, but smaller, decreases in depression and social isolation.

Other clinical trials used a more general approach, teaching patients coping skills with the goal of helping them manage stress better. One such trial in CHD patients with documented myocardial ischemia and ventricular wall motion abnormalities found that stress management training was associated with both decreased CHD recurrences and improved wall motion function.[36] Coping skills training in patients who had undergone coronary artery bypass graft surgery produced improvements in both psychosocial risk factors and CVR to mental stress testing in those randomized to coping skills training compared with usual care.[37]

There is also evidence that pharmacological interventions that target depression may improve medical prognosis in CHD patients. An observational study in a large insurance sample found that patients treated with selective serotonin reuptake inhibitors had reduced CHD incidence.[38] A randomized trial evaluating a selective serotonin reuptake inhibitor in the treatment of depressed post-MI patients found encouraging evidence that such treatment can improve prognosis in this patient group.[39] Patients in the ENRICHD trial who were treated, albeit nonrandomly, with selective serotonin reuptake inhibitors also showed significant decreases in rates of recurrent coronary events and mortality.[35]

Much more work will be required before behavioral treatments to reduce the harmful effects of psychosocial risk fac-

tors and the accompanying biobehavioral mechanisms are standard practice. The current state of affairs regarding behavioral interventions targeting psychosocial risk factors may be similar to that surrounding the use of β-blocker therapy in the 1970s for patients who had MI: some clinical trials showed a benefit, but others did not. It was not until data were available from the Beta-Blocker Heart Attack Trial[40] and pooled analyses of multiple trials[41,42] that it became clear that highly reliable reductions of 23% to 28% in various clinical end points were obtained. Now β-blocker therapy is standard therapy following MI.

The study by Yan at al,[6] showing that psychosocial risk factors increase risk of CVD, the current evidence regarding biologically plausible mechanisms that are likely to mediate associations between psychosocial risk factors and CVD risk, and the evidence from clinical trials of behavioral and pharmacological treatments targeting psychosocial factors support the need for increased research to develop, implement, and test behavioral and pharmacological interventions aimed at reducing the impact of psychosocial factors on the development and prognosis of CVD. As the state of knowledge continues to expand, it will be important to include assessment of genetic factors that may moderate the impact of such interventions as well as the biobehavioral mechanisms that mediate their benefits.

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