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## Heart Rate Variability in the Prediction of Risk for Posttraumatic Stress Disorder

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Posttraumatic stress disorder (PTSD) is a relatively common condition, with a 7% to 9% lifetime prevalence in US civilians and a 15 % to 19 % lifetime prevalence in combat veterans.<sup>1</sup> Neurobiological dysregulation of autonomic nervous system pathways involved in the stress response has long been considered a hallmark of the abnormal physiologic processes and clinical presentation of PTSD. Common symptoms of PTSD, such as intrusions and hyperarousal, are likely mediated by the autonomic nervous system. Furthermore, autonomic dysregulation, indexed by low heart rate variability (HRV), is a consistent correlate of PTSD symptoms and may improve when PTSD is in remission.<sup>2</sup>

Although PTSD by definition is a consequence of a traumatic event, not every person exposed to trauma develops the condition.<sup>3</sup> However, our ability to predict vulnerability to PTSD is limited, and this issue remains an important topic of exploration. If we knew how to identify at-risk individuals, then we could devise preventive interventions for such people in the armed services before deployment that might prevent PTSD or ameliorate its clinical course. Treatment with 2 main classes of pharmacologic therapies potentially influencing stress systems response ( $\beta$ -blockers and systemic corticosteroids) has been attempted immediately after trauma exposure. However, a recent Cochrane review<sup>4</sup> found that only hydrocortisone administration immediately after trauma had sufficient evidence to protect individuals from the development of PTSD, with a number needed to treat ranging from 7 to 13. Decisions to administer such agents should be based on careful evaluation of risks and benefits given possible adverse effects, such as immunosuppression. Behavioral interventions, such as cognitive therapy, would also be applicable and are low risk, but they are costly and time consuming; thus, careful risk stratification would again be necessary.

Previous studies<sup>3</sup> have shown that higher heart rate and cortisol sensitivity in individuals who experience trauma, measured immediately after exposure, predict subsequent PTSD development. Unfortunately, to our knowledge, no previous studies have evaluated

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autonomic factors prior to trauma exposure as predictors of PTSD. In this issue of *JAMA Psychiatry*, Minassian et al<sup>5</sup> present a timely, prospective evaluation of autonomic biomarkers of risk for PTSD. In a longitudinal cohort of 2160 combat troops in the 2-phase Marine Resiliency Study (MRS), they examined whether predeployment HRV predicts postdeployment PTSD among US Marines being deployed for combat. The investigators found that the low- to high-frequency (LF:HF) HRV ratio predicted postdeployment PTSD, even after adjusting for differences in deployment-related stressors.

Many studies<sup>6</sup> have suggested that the LF:HF HRV ratio represents sympathovagal balance, although this hypothesis has been subject to criticism. Despite this controversy, the conclusions of Minassian and colleagues<sup>5</sup> that increased sympathovagal balance predicts vulnerability to PTSD makes empirical sense, considering the known role of autonomic mechanisms in PTSD. Preventive clinical trials may be suggested based on this finding. For example,  $\beta$ -blockers have been found<sup>7</sup> to reduce the daytime LF:HF ratio compared with placebo and might be considered for clinical trials of PTSD prevention among combat veterans who have high baseline values.

The study by Minassian et al,<sup>5</sup> however, has several weaknesses that limit its ability to infer a causal association between a higher LF:HF HRV ratio and the incidence of postdeployment PTSD. The magnitude of the association was modest in the MRS-I group and even more modest in the MRS-II cohort, and there was no correlation with PTSD symptom severity. Almost half of the sample with HRV data before deployment did not have a postdeployment visit for evaluation, and we are not told what happened to these service members. Thus, the validity of the results may be compromised by selection bias. Furthermore, important correlates of both PTSD and autonomic function were not considered in the analysis, such as depression, previous trauma exposure, medical history, and health behaviors. In the absence of these data, the LF:HF ratio may only be a correlate of other vulnerability factors rather than an index of a biological phenomenon that is etiologically implicated in PTSD. Although these authors should be commended for conducting what we believe to be the first prospective evaluation of HRV as a risk biomarker of PTSD susceptibility, more prospective, rigorous studies are needed to clarify this potential etiologic pathway.

A report from the RAND Corporation<sup>8</sup> estimated that PTSD costs society up to \$10 000 per case in lost productivity alone. With continued conflicts around the world, in addition to the high prevalence of domestic traumatic events and PTSD in civilians, risk stratification and prevention efforts should be worthwhile investments. More research should be invested toward prevention and prediction of PTSD with prospective designs that combine physiologic measures of autonomic dysregulation with inflammatory, genetic, and epigenetic markers of PTSD risk. Data-driven approaches could be incorporated in research designs to discover novel biomarkers of risk as well as elucidate pathophysiologic pathways. In the future, accurate risk stratification with a PTSD risk score would be of particular usefulness for individuals at high risk of trauma exposure, such as combat troops. This risk stratification may ultimately reduce both the cost and health burden of PTSD to society.

The study by Minassian et al,<sup>5</sup> along with other studies<sup>9</sup> from the MRS cohort, provide important initial data to help identify key determinants and prognostic indicators of PTSD after a major trauma. Although the LF:HF HRV ratio alone is not likely to be a sufficient biomarker of risk for PTSD prediction, it is a first step to suggest that PTSD risk can ultimately be targeted and, with the right intervention, prevented in high-risk individuals.

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