Stressed brain, stressed heart?

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In the past decade, more and more individuals experience psychosocial stress on a daily basis. Heavy workloads, job insecurity, or living in poverty are circumstances that can result in chronically increased stress, which in turn can lead to chronic psychological disorders such as depression. Besides the heavy psychological burden, chronic stress is also associated with an increased risk of cardiovascular disease.[1,2] Individuals with increased stress perception have a substantially higher prevalence of myocardial infarction than controls, as was reported by Rosengren and colleagues in 2004.[2] However, these association studies have thus far not established whether increased stress is causally related to the incidence of cardiovascular disease, and neither have they provided mechanistic insight into the pathways involved. This lack of mechanistic insight might be at least partly due to difficulties measuring personal stress levels—which can vary between individuals as stress perception differs from person to person—at the time of the stressor. Experimental work in animal models has established that both acute and chronic stress contribute to the underlying cause of cardiovascular disease[3]—ie, development of atherosclerosis, which is generally mediated by an increased inflammatory response to a stressor. However, direct clinical evidence in human beings was lacking.

In *The Lancet*, Ahmed Tawakol and colleagues[4] report that the activity of the amygdala, a key component of the brain involved in emotion and stress, is of predictive value for the incidence of acute cardiovascular events. Their main study included 293 individuals without previous history of cardiovascular disease who underwent ^{18}F fluorodeoxyglucose (^{18}F-FDG) PET or CT to visualise amygdalar activity as a measure for underlying stress. After median follow-up of 3·7 years, amygdalar activity was significantly associated with the incidence of cardiovascular events, including myocardial infarction, heart failure, and cerebrovascular events, even after multivariate adjustments. ^{18}FDG PET or CT also allows visualisation of haemopoietic tissue activity and the activity of inflammatory cells within the vessel wall. Statistical mediation analysis showed that bone-marrow activity, followed by vascular inflammation, was a significant mediator in the association between amygdalar activity and the incidence of cardiovascular events. Although these mediation analyses do not provide evidence of causality, the data are in line with data from an animal study,[5] in which stress induced an inflammatory response via activation of the bone marrow. Additionally, interleukin 6 derived from bone-marrow-derived leucocytes has been implicated as one of the causal mediators of the stress response in mice.[6] How the reported increase in the inflammatory response directly relates to the rise in acute cardiovascular syndromes caused by atherosclerotic plaque rupture or erosion[7] remains to be investigated.

Of clinical relevance is the perceived stress study that Takawol and colleagues also did,[4] which included patients with a history of post-traumatic stress disorder (PTSD). In these patients, perceived stress was associated with amygdalar activity, vascular inflammation, and circulating c-reactive protein (CRP) concentrations. The association between stress and CRP concentrations is in line with data obtained from other cohorts containing patients with PTSD, depression, and other diseases that are associated with chronic stress, in whom increased circulating CRP, interleukin 6, and tumour necrosis factor α concentrations were noted.[8–10] The findings of these studies[8–10] suggest that individuals with high perceived stress levels—whether patients with PTSD, depression, or anxiety, or other individuals experiencing chronic stress—are at higher risk of having a cardiovascular disease event.

Although only 13 patients with PTSD were included in the perceived stress study (and no healthy controls with basal amygdalar activity), this study provides important evidence justifying the initiation of new studies of larger populations and with longer follow-up to assess cardiovascular disease risk directly in patients with PTSD. Because interleukin 6 is repeatedly increased in stress in both human beings and rodents, analysis of circulating interleukin 6 concentrations, next to CRP, might provide more insight into the underlying inflammatory mechanisms. In Takawol and colleagues' outcomes study,[4] the association between amygdalar activity and the incidence of cardiovascular disease still remains after correction for history of depression or anxiety, which suggests that these data are not only applicable to patients with severe psychological disorders, but

also to individuals without previous history of these conditions. Together, these clinical data establish a connection between stress and cardiovascular disease, thus identifying chronic stress as a true risk factor for acute cardiovascular syndromes, which could, given the increasing number of individuals with chronic stress, be included in risk assessments of cardiovascular disease in daily clinical practice.

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