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Review article

Mental stress and human cardiovascular disease

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ABSTRACT

The London physician and neuroanatomist Thomas Willis in the 17th century correctly attributed the source of emotions to the brain, not the heart as believed in antiquity. Contemporary research documents the phenomenon of "triggered" heart disease, when the autonomic nervous system control of the heart by the brain goes awry, producing heart disease of sudden onset, precipitated by acute emotional upheaval. This can take the form of, variously, cardiac arrhythmias, myocardial infarction, Takotsubo cardiomyopathy and sudden death. Chronic psychological distress also can have adverse cardiovascular consequences, in the causal linkage of depressive illness to heart disease, and in the probable causation of atherosclerosis and hypertension by chronic mental stress. In patients with essential hypertension, stress biomarkers are present. The sympathetic nervous system is the usual mediator between these acute and chronic psychological substrates and cardiovascular disease.

Contents

1. Introduction

There has been a strong resurgence of support for the idea, often in the past banished to the realm of medical folklore, that mental stress and psychological illness is a cause of cardiovascular disease (Table 1). This acceptance, however, was won in the face of a high level of scepticism, very explicitly illustrated in the deliberations of a panel charged with reviewing the topic for an Australian national health body on which I served. The opening address of the Chair included the opinion, "there is no evidence that stress causes heart disease, nor will there ever be". That was 30 years ago, and times have changed.

War has been a fertile field for the development of psychogenic heart disease, with identification and nomenclature being dependent on the era and the level of sophistication in the psychiatric

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Table 1
"Psychogenic Cardiovascular Disease".

Acute mental stress as a trigger:
• myocardial infarction, cardiac arrhythmias • Takotsubo cardiomyopathy • in panic disorder
Major depressive illness
Chronic mental stress
• causing atherosclerosis? • causing hypertension?

formulation. *Soldiers Heart* and *Irritable Heart* are wartime disorders which have morphed post-DSM III into the rubric of Post Traumatic Stress Disorder. In civilian life, the contemporary evidence supporting the existence of psychogenic cardiovascular disease (Table 1) is perhaps strongest for the precipitation ("triggering") by acute mental stress of myocardial infarction, sudden death and Takotsubo Cardiomyopathy (stress cardiomyopathy) (Sato et al., 1990; Rozanski et al., 1999).

Patients with *major depressive disorder*, also, are at increased risk of developing coronary heart disease (Frasure-Smith et al., 1993; Bunker et al., 2003). Perhaps less compelling, but gathering strong support, is the case for participation of chronic mental stress in the origins of essential hypertension and coronary atherogenesis (Table 1).

2. Human sympathetic nervous responses to stress

Neural mechanisms are critical in the linkage of these psychological substrates to cardiovascular disease. Participation of the sympathetic nervous system in human stress responses can be demonstrated with methods for studying regional sympathetic activity, in the sympathetic outflows to different organs (Fig. 1). These techniques are clinical microneurography, which measures postganglionic sympathetic fibre firing rates in the nerves passing to the skeletal muscle vasculature (Hagbarth and Vallbo, 1968; Lambert et al., 2007), and the isotope dilution technique for measurement of the overflow of the sympathetic neurotransmitter to plasma, regional noradrenaline spillover (Esler et al., 1989, 1990) (Fig. 1).

2.1. Clinical microneurography

This technique provides a method for studying nerve firing rates, in subcutaneous sympathetic nerves distributed to skin and skeletal muscle. The technique involves the insertion of a fine tungsten electrode through the skin, with positioning of the electrode tip in sympathetic fibres of, most commonly, the common peroneal nerve near the head of the fibula. Multifiber recordings of "bursts" of nerve activity synchronous with the heart beat (Hagbarth and Vallbo, 1968), and more recently single fibre traces (Macefield et al., 1994; Lambert et al., 2007), are generated. One application of these methods has been in patients with panic disorder. Panic attacks occurring in patients monitored in the research laboratory are accompanied by sympathetic nervous activation, evident in high-level augmentation of the amplitude of multi-unit sympathetic nerve bursts (Fig. 1).

2.2. Organ-specific noradrenaline spillover rate measurements

Sympathetic nerve neurotransmitter release can be studied clinically using radiotracer-derived measurements of the overflow

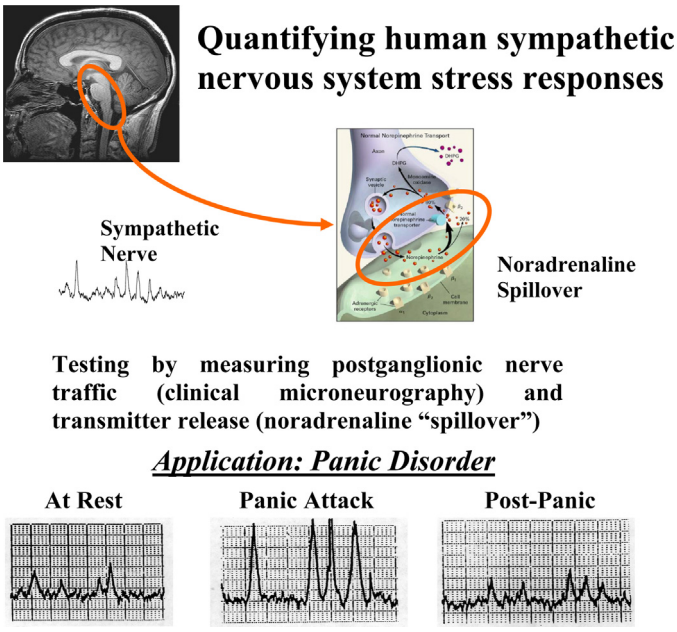

Fig. 1. The principal methods for testing sympathetic nervous system responses to mental stress are sympathetic nerve recording using clinical microneurography and quantification of sympathetic nerve release of noradrenaline to plasma. The lower panels show sympathetic neurograms in a patient with panic disorder, with large-scale increase in amplitude of multiunit sympathetic nerve "bursts" during a panic attack.

of noradrenaline to plasma from individual organs (Esler et al., 1989, 1990). Microneurographic methods do not give access to sympathetic nerves of internal organs. With infusion of tritiated noradrenaline and regional blood sampling from the coronary sinus, the release of the neurotransmitter from the heart can be measured. Cardiac sympathetic activation can be pivotal in the genesis of psychogenic cardiovascular disease.

2.3. Changes with laboratory mental stress

In the laboratory forced mental arithmetic, used as a cognitive challenge to simulate acute mental stress induces a pronounced increase in the adrenal medullary secretion of adrenaline, accompanied by sympathetic nervous system activation (Esler et al., 1989, 1990). The sympathetic nervous stimulation is regionally differentiated, preferentially involving the sympathetic outflow to the heart, where 2–6 fold increase in cardiac noradrenaline spillover is seen (Esler et al., 1989). This preferential activation of the sympathetic nerves of the heart gives biological credence to the empirical evidence that acute mental stress can trigger cardiac arrhythmias and myocardial infarction.

3. "Triggered" heart disease

It has always seemed plausible that short-term mental stress could act as an immediate precipitant ("trigger") for the development of abnormal heart rhythm and sudden death in patients with existing heart disease. For many years this claimed relation of acute mental stress to heart attacks was largely based on individual anecdotes, such as the celebrated case of the famous 18th century English surgeon, John Hunter, who wrote that he was at the mercy of any scoundrel who aggravated him, then proved the point by dying suddenly in the middle of a stormy meeting of the board of his hospital.

Systematic evidence has now been gathered at times of disasters, including war, missile attacks on civilians and earthquakes,